

factor modification, including high-potency statins, may be as valuable as surgical intervention in these patients; the large NIH-sponsored CREST2 study is examining this issue.

Mild to moderate disease (30–50% stenosis) indicates the need for ongoing monitoring and aggressive risk factor modification. Patients with carotid stenosis that suddenly worsens are thought to have an unstable plaque and are at particularly high risk for embolic stroke.

B. Symptomatic Patients

Large randomized trials have shown that patients with TIAs or strokes from which they have completely or nearly completely recovered will benefit from carotid intervention if the ipsilateral carotid artery has a stenosis of more than 70% (Figure 12-1), and they are likely to benefit if the artery has a stenosis of 50–69%. In these situations, carotid endarterectomy (CEA) and, in selected cases, CAS have been shown to have a durable effect in preventing further events. In symptomatic patients, intervention should ideally be planned within 2 weeks since delays increase the risk of a second event.

► Complications

The most common complication from carotid intervention is cranial nerve injury, while the most dreaded complication is stroke from embolization or carotid occlusion. The American Heart Association's recommendations for upper limits of acceptable combined morbidity and mortality for these interventions is 3% for patients with asymptomatic carotid stenosis, 5% for those with TIAs, and 7% for patients with previous stroke. Higher rates of morbidity

and mortality negate the therapeutic benefit of carotid intervention.

A. Carotid Endarterectomy

In the 2010 CREST study the stroke risk for CEA was 2.3%. CEA also carries a 1–2% risk of permanent cranial nerve injury (usually the vagus nerve). There is also the risk of postoperative neck hematoma, which can cause acute airway compromise. Coronary artery disease is a comorbidity in most of these patients. Myocardial infarction rates after CEA are approximately 2–6%.

B. Carotid Angioplasty and Stenting

CAS had a stroke risk of 4.1% in the 2010 CREST study; patients over 70 years of age as well as women had higher stroke rates with CAS than with CEA. However, the risk of myocardial infarction was lower with CAS compared to CEA (1.1% vs 2.3%). CAS is indicated for reoperative cases, prior neck radiation, and high carotid bifurcations not otherwise accessible surgically. Nonetheless, emboli are more common during transfemoral CAS in spite of embolic protection devices, especially when the carotid artery is tortuous and heavily calcified. Transcervical carotid stenting, performed through a small incision at the base of the neck, avoids artery tortuosity and has lower embolization rates than transfemoral carotid stenting.

► Prognosis

Twenty-five percent of patients presenting with carotid stenosis and a TIA or small stroke will have further brain ischemia within 18 months with most of the events occurring within the first 6 months. Historically, patients with asymptomatic carotid stenosis are believed to have an annual stroke rate of just over 2% but this may be lower in the statin era. Prospective ultrasound screening at least annually is recommended in asymptomatic patients with known carotid stenosis to identify those who have evidence of plaque progression, which increases stroke risk. Comitant coronary artery disease is common and is an important factor in these patients both for perioperative risk and long-term prognosis. Aggressive risk factor modification should be prescribed for patients with cerebrovascular disease regardless of planned intervention.

► When to Refer

Asymptomatic or symptomatic patients with a carotid stenosis of more than 70% and patients with carotid stenosis of less than 70% with symptoms of a TIA or stroke should be referred to a vascular specialist for consultation.



▲ Figure 12-1. Digital subtraction angiography of a high-grade (90%) stenosis of the internal carotid artery with ulceration (arrow). (Used, with permission, from Dean SM, Satianni B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases*. McGraw-Hill, 2014.)

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VISCERAL ARTERY INSUFFICIENCY (Intestinal Angina)



ESSENTIALS OF DIAGNOSIS

- ▶ Severe postprandial abdominal pain.
- ▶ Weight loss with a “fear of eating.”
- ▶ **Acute mesenteric ischemia:** severe abdominal pain yet minimal findings on physical examination.

► General Considerations

Acute mesenteric ischemia results from occlusive mesenteric arterial disease, either embolic occlusion or primary thrombosis of at least one major mesenteric artery. Ischemia can also result from **nonocclusive mesenteric ischemia**, which is generally seen in patients with low flow states, such as severe heart failure, sepsis, or hypotension. **Chronic mesenteric ischemia**, also called intestinal angina, occurs when increased flow demands during feeding are not met resulting in abdominal pain. Because of the rich collateral mesenteric network, generally at least two of the three major visceral vessels (celiac, superior mesenteric, inferior mesenteric arteries) are affected before symptoms develop. **Ischemic colitis**, a variant of mesenteric ischemia, usually occurs in the distribution of the inferior mesenteric artery. The intestinal mucosa is the most sensitive to ischemia and will slough if underperfused.

► Clinical Findings

A. Symptoms and Signs

1. Acute mesenteric ischemia—Visceral arterial embolism presents acutely with severe abdominal pain. In contrast, patients with primary visceral arterial thrombosis often give an antecedent history consistent with chronic mesenteric ischemia. The key finding with acute mesenteric ischemia is severe, steady, diffuse abdominal pain with an absence of focal tenderness or distention. This “pain out of proportion” to physical examination findings occurs because ischemia initially is mucosal and does not impact the peritoneum until transmural ischemia inflames the peritoneal lining. A high white blood cell count, lactic acidosis, hypotension, and abdominal distention may aid in the diagnosis.

2. Chronic mesenteric ischemia—Patients are generally over 45 years of age and may have evidence of atherosclerosis in other vascular beds. Symptoms consist of epigastric or periumbilical postprandial pain lasting 1–3 hours. To avoid the pain, patients limit food intake and may develop a fear of eating. Weight loss is universal.

3. Ischemic colitis—Characteristic symptoms are left lower quadrant pain and tenderness, abdominal cramping, and mild diarrhea. Rectal discharge will appear mucus-like or bloody and should prompt further evaluation.

B. Imaging and Colonoscopy

Contrast-enhanced CT is highly accurate at determining the presence of ischemic intestine. In patients with acute or chronic mesenteric ischemia, a CTA or MRA can demonstrate narrowing of the proximal visceral vessels. In acute mesenteric ischemia from a nonocclusive low flow state, angiography is needed to display the typical “pruned tree” appearance of the distal visceral vascular bed. Ultrasound scanning of the mesenteric vessels may show proximal obstructing lesions.

In patients with ischemic colitis, flexible sigmoidoscopy should be performed to assess the grade of ischemia that occurs most often in watershed areas, such as the rectal sigmoid and splenic flexure.

► Treatment

A high suspicion of acute mesenteric ischemia dictates immediate exploration to assess bowel viability. If the bowel remains viable, arterial bypass using a prosthetic conduit can be done either from the supra-celiac aorta or common iliac artery to the celiac and the superior mesenteric artery. In cases where bowel viability is questionable or bowel resection will be required, the bypass can be done with autologous vein to avoid the use of prosthetic conduits in a potentially contaminated field. Angioplasty and stenting of the arteries can be used but does not avoid a surgical evaluation of bowel viability.

In chronic mesenteric ischemia, angioplasty and stenting of the proximal vessel may be beneficial depending on the anatomy of the stenosis. Should an endovascular solution not be available, an aorto-visceral artery bypass is the preferred management. The long-term results are highly durable. Visceral arteryendarterectomy is reserved for cases with multiple lesions where bypass would be difficult.

The mainstay of treatment of ischemic colitis is maintenance of blood pressure and perfusion until collateral circulation becomes well established. The patient must be monitored closely for evidence of perforation necessitating resection.

► Prognosis

The combined morbidity and mortality rates are 10–15% from surgical intervention in part due to malnutrition and frailty in patients preceding chronic mesenteric ischemia. However, without intervention both conditions are uniformly fatal. Adequate collateral circulation usually develops in those who have ischemic colitis, and the prognosis for this entity is better than chronic mesenteric ischemia.

► When to Refer

Any patient in whom there is a suspicion of mesenteric ischemia should be urgently referred for imaging and possible intervention.

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ACUTE MESENTERIC VEIN OCCLUSION

The hallmarks of acute mesenteric vein occlusion are post-prandial pain and evidence of a hypercoagulable state. Acute mesenteric vein occlusion presents similarly to the arterial occlusive syndromes but is much less common. Patients at risk include those with paroxysmal nocturnal hemoglobinuria; protein C, protein S, or antithrombin deficiencies; or the *JAK2* mutation. These lesions are difficult to treat surgically, and thrombolysis is the mainstay of therapy. Aggressive long-term anticoagulation is required for these patients.

NONATHEROSCLEROTIC VASCULAR DISEASE

THROMBOANGIITIS OBLITERANS (Buerger Disease)



ESSENTIALS OF DIAGNOSIS

- ▶ Typically occurs in male cigarette smokers.
- ▶ Distal extremities involved with severe ischemia, progressing to tissue loss.
- ▶ Thrombosis of the superficial veins may occur.
- ▶ Smoking cessation is essential to stop disease progression.

General Considerations

Buerger disease is a segmental, inflammatory, and thrombotic process of the distal-most arteries and occasionally veins of the extremities. Pathologic examination reveals arteritis in the affected vessels. The cause is not known but it is rarely seen in patients who do not smoke cigarettes. Arteries most commonly affected are the plantar and digital vessels of the foot and lower leg. In advanced stages, the fingers and hands may become involved. The incidence of Buerger disease has decreased dramatically.

Clinical Findings

A. Symptoms and Signs

Buerger disease may be initially difficult to differentiate from routine peripheral vascular disease, but in most cases, the lesions are on the toes and the patient is younger than 40 years of age. The observation of superficial thrombophlebitis may aid the diagnosis. Because the distal vessels are usually affected, intermittent claudication is not common with Buerger disease, but rest pain, particularly pain

in the distal most extremity (ie, toes), is frequent. This pain often progresses to tissue loss and amputation, unless the patient stops smoking. The progression of the disease seems to be intermittent with acute and dramatic episodes followed by some periods of remission.

B. Imaging

MRA or invasive angiography can demonstrate the obliteration of the distal arterial tree typical of Buerger disease.

Differential Diagnosis

In atherosclerotic peripheral vascular disease, the onset of tissue ischemia tends to be less dramatic than in Buerger disease, and symptoms of proximal arterial involvement, such as claudication, predominate.

Symptoms of Raynaud disease may be difficult to differentiate from Buerger disease and are often coexistent in 40% of patients. Repetitive atheroemboli may also mimic Buerger disease and may be difficult to differentiate. It may be necessary to image the proximal arterial tree to rule out sources of arterial microemboli.

Treatment

Smoking cessation is the mainstay of therapy and will halt the disease in most cases. As the distal arterial tree is occluded, revascularization is often not possible. Sympathectomy is rarely effective.

Prognosis

If smoking cessation can be achieved, the outlook for Buerger disease may be better than in patients with premature peripheral vascular disease. If smoking cessation is not achieved, then the prognosis is generally poor, with amputation of both lower and upper extremities a possible outcome.

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ARTERIAL ANEURYSMS

ABDOMINAL AORTIC ANEURYSM



ESSENTIALS OF DIAGNOSIS

- ▶ Most aortic aneurysms are asymptomatic until rupture.
- ▶ 80% of abdominal aortic aneurysms measuring 5 cm are palpable; the usual threshold for treatment is 5.5 cm.
- ▶ Back or abdominal pain with aneurysmal tenderness may precede rupture.
- ▶ Rupture is catastrophic: excruciating abdominal pain that radiates to the back; hypotension.

► General Considerations

Dilatation of the infrarenal aorta is a normal part of aging. The aorta of a healthy young man measures approximately 2 cm. An aneurysm is considered present when the aortic diameter exceeds 3 cm, but aneurysms rarely rupture until their diameter exceeds 5 cm. Abdominal aortic aneurysms are found in 2% of men over 55 years of age; the male to female ratio is 4:1. Ninety percent of abdominal atherosclerotic aneurysms originate below the renal arteries. The aneurysms usually involve the aortic bifurcation and often involve the common iliac arteries.

Inflammatory aneurysms are an unusual variant. These have an inflammatory peel (similar to the inflammation seen with retroperitoneal fibrosis) that surrounds the aneurysm and encases adjacent retroperitoneal structures, such as the duodenum and, occasionally, the ureters.

► Clinical Findings

A. Symptoms and Signs

1. Asymptomatic—Although 80% of 5-cm infrarenal aneurysms are palpable on routine physical examination, most aneurysms are discovered on ultrasound or CT imaging as part of a screening program or during the evaluation of unrelated abdominal symptoms.

2. Symptomatic

A. PAIN—Aneurysmal expansion may be accompanied by pain that is mild to severe midabdominal discomfort often radiating to the lower back. The pain may be constant or intermittent and is exacerbated by even gentle pressure on the aneurysm sack. Pain may also accompany inflammatory aneurysms. Most aneurysms have a thick layer of thrombus lining the aneurysmal sac, but embolization to the lower extremities is rarely seen.

B. RUPTURE—The sudden escape of blood into the retroperitoneal space causes severe pain and hypotension. Free rupture into the peritoneal cavity is a lethal event.

B. Laboratory Findings

In acute cases of a contained rupture, the hematocrit may be normal, since there has been no opportunity for hemodilution.

Patients with aneurysms may also have coronary artery disease, carotid disease, kidney impairment, and emphysema, which are typically seen in elderly men who smoke cigarettes. Preoperative testing may indicate the presence of these comorbid conditions, which increase the risk of intervention.

C. Imaging

Abdominal ultrasonography is the diagnostic study of choice for initial screening for the presence of an aneurysm. In approximately three-quarters of patients with aneurysms, curvilinear calcifications outlining portions of the aneurysm wall may be visible on plain radiographs of the abdomen or back. CT scans provide a more reliable assessment of aneurysm diameter and should be done when the aneurysm nears the diameter threshold (5.5 cm)

for treatment. Contrast-enhanced CT scans show the arteries above and below the aneurysm. The visualization of this vasculature is essential for planning repair. CT imaging will often demonstrate mural thrombus within the aneurysm and is not an indication for anticoagulation.

Once an aneurysm is identified, routine follow-up with ultrasound will determine size and growth rate. The frequency of imaging depends on aneurysm size ranging from every 2 years for aneurysms smaller than 4 cm to every 6 months for aneurysms at or approaching 5 cm. When an aneurysm measures approximately 5 cm, a CTA with contrast should be done to more accurately assess the size of the aneurysm and define the anatomy.

► Screening

Guidelines recommend abdominal ultrasound screening in men 65–75 years old with exposure to 100 or more lifetime cigarettes but conflict on whether women with the same exposure should be screened. Guidelines do not recommend repeated screening if the aorta shows no enlargement. While patients are monitored, smoking cessation and treatment of underlying hypertension, hyperlipidemia, and diabetes should be considered.

► Treatment

A. Elective Repair

The risk of rupture increases with aneurysm diameter. In general, elective repair is indicated for aortic aneurysms 5.5 cm or larger in diameter or aneurysms that demonstrate rapid expansion (more than 0.5 cm in 6 months). Symptoms such as pain or tenderness may indicate impending rupture and require urgent repair regardless of the aneurysm's diameter.

B. Aneurysmal Rupture

A ruptured aneurysm is a lethal event. Approximately half the patients exsanguinate prior to reaching a hospital. In the remainder, bleeding may be temporarily contained in the retroperitoneum (contained rupture), allowing the patient to undergo emergent surgery. However, only half of those patients will survive. Endovascular repair is available for ruptured aneurysm treatment in most major vascular centers, with the results offering some improvement over open repair for these critically ill patients.

C. Inflammatory Aneurysm

The presence of periaortic inflammation (inflammatory aneurysm) is not an indication for surgical treatment, unless there is associated compression of retroperitoneal structures, such as the ureter or pain upon palpation of the aneurysm. Interestingly, the inflammation that encases an inflammatory aneurysm recedes after either endovascular or open surgical aneurysm repair.

D. Assessment of Operative Risk

Aneurysms appear to be a variant of systemic atherosclerosis. Patients with aneurysms have a high rate of coronary disease but a 2004 trial demonstrated minimal value in

addressing stable coronary artery disease prior to aneurysm resection. However, in patients with significant symptoms of coronary disease, the coronary disease should be treated first. Aneurysm repair should follow shortly thereafter because there is a slightly increased risk of aneurysm rupture after the coronary procedures.

E. Open Surgical Resection Versus Endovascular Repair

In open surgical aneurysm repair, a graft is sutured to the non-dilated vessels above and below the aneurysm. This involves an abdominal incision, extensive dissection, and interruption of aortic blood flow. The mortality rate is low (2–5%) in centers that have a high volume for this procedure and when it is performed in good-risk patients. Older, sicker patients may not tolerate the cardiopulmonary stresses of the operation. With endovascular aortic repair, a stent-graft is introduced through small incisions over the femoral arteries and positioned within the aorta under fluoroscopic guidance. The stent must be able to seal securely against the wall of the aorta above and below the aneurysm, thereby excluding blood from flowing into the aneurysm sac. To successfully treat an aneurysm, the anatomic requirements for endovascular repairs are more precise than for open repairs. Most studies have found that endovascular aortic repair offers patients reduced operative morbidity and mortality as well as shorter recovery periods. Long-term survival is equivalent between the two techniques. Patients who undergo endovascular repair, however, likely need additional interventions and need lifelong monitoring, since there is a 10–15% incidence of continued aneurysm growth after endovascular repair.

Complications

Myocardial infarction, the most common complication, occurs in up to 10% of patients who undergo open aneurysm repair. The incidence of myocardial infarction is substantially lower with endovascular repair. For routine infrarenal aneurysms, renal injury is unusual; however, when it does occur, or if the baseline creatinine is elevated, it is a significant complicating factor in the postoperative period. Respiratory complications are similar to those seen in most major abdominal surgery. Gastrointestinal hemorrhage, even years after aortic surgeries, suggests the possibility of **graft enteric fistula**, most commonly between the aorta and the distal duodenum; the incidence of this complication is higher when the initial surgery is performed on an emergency basis.

Prognosis

The mortality rate for an open elective surgical resection is 1–5%, and the mortality rate for endovascular therapy is 0.5–2%. Of those who survive surgery, approximately 60% are alive at 5 years; myocardial infarction is the leading cause of death. The long-term survival (5 years or more) after open and endovascular repairs is equivalent.

Mortality rates of untreated aneurysms vary with aneurysm diameter. The mortality rate among patients with large aneurysms has been defined as follows: 12% annual risk of rupture with an aneurysm larger than 6 cm in

diameter and a 25% annual risk of rupture in aneurysms of more than 7 cm diameter. In general, a patient with an aortic aneurysm larger than 5.5 cm has a threefold greater chance of dying of a consequence of rupture of the aneurysm than of dying of the surgical resection.

At present, endovascular aneurysm repair may be less definitive than open surgical repair and requires close follow up with an imaging procedure. Device migration, component separation, and graft limb thrombosis or kinking are common reasons for repeat intervention. With complete exclusion of blood from the aneurysm sac, the pressure is lowered, which causes the aneurysm to shrink. An “endoleak” from the top or bottom seal zones (type 1) or through a graft defect (type 3) is associated with a persistent risk of rupture. Indirect leakage of blood through lumbar and inferior mesenteric branches of the aneurysm (type-2 endoleak) produces an intermediate picture with somewhat reduced pressure in the sac, slow shrinkage, and low rupture risk. However, type-2 endoleak warrants close observation as aneurysm dilatation can change aneurysm morphology leading to type-1 endoleak and rupture.

When to Refer

- Any patient with a 4.5-cm or larger aortic aneurysm should be referred to a vascular specialist for observation and assessment.
- Urgent referrals should be made if the patient complains of pain and gentle palpation of the aneurysm confirms that it is the source, regardless of the aneurysmal size.

When to Admit

- Patients with a tender aneurysm to palpation or signs of aortic rupture require emergent hospital admission.
- Evidence of infection after repair.

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THORACIC AORTIC ANEURYSMS

ESSENTIALS OF DIAGNOSIS

- Widened mediastinum on chest radiograph.
- With rupture, sudden onset of chest pain radiating to the back.

► General Considerations

Most thoracic aortic aneurysms are due to atherosclerosis; syphilis is a rare cause. Disorders of connective tissue and Ehlers-Danlos and Marfan syndromes also are rare causes but have important therapeutic implications. Traumatic, false aneurysms, caused by partial tearing of the aortic wall with deceleration injuries, may occur just beyond the origin of the left subclavian artery. Less than 10% of aortic aneurysms occur in the thoracic aorta.

► Clinical Findings

A. Symptoms and Signs

Most thoracic aneurysms are asymptomatic. When symptoms occur, they depend largely on the size and the position of the aneurysm and its rate of growth. Substernal back or neck pain may occur. Pressure on the trachea, esophagus, or superior vena cava can result in the following symptoms and signs: dyspnea, stridor or brassy cough, dysphagia, and edema in the neck and arms as well as distended neck veins. Stretching of the left recurrent laryngeal nerve causes hoarseness. With aneurysms of the ascending aorta, aortic regurgitation may be present due to dilation of the aortic valve annulus. Rupture of a thoracic aneurysm is catastrophic because bleeding is rarely contained, allowing no time for emergent repair.

B. Imaging

The aneurysm may be diagnosed on chest radiograph by the calcified outline of the dilated aorta. CT scanning with contrast enhancement is the modality of choice, but MRA can be used to demonstrate the anatomy and aneurysmal size and to exclude lesions that can mimic aneurysms, such as neoplasms or substernal goiter. There is no low-cost alternative (eg, ultrasonography) for screening or surveillance. Cardiac catheterization and echocardiography may be required to describe the relationship of the coronary vessels to an aneurysm of the ascending aorta.

► Treatment

Indications for repair depend on the location of dilation, rate of growth, associated symptoms, and overall condition of the patient. Descending thoracic aneurysms measuring 6 cm or larger may be considered for repair, since there is a 5-year survival of 54% in these patients. Aneurysms of the descending thoracic aorta are treated routinely by endovascular grafting. Repair of arch aneurysms should be undertaken only if there is a skilled surgical team with an acceptable record of outcomes for these complex procedures. The availability of thoracic aortic endograft technique using complex branched endovascular reconstructions for aneurysms involving the arch or visceral aorta (custom-made grafts with branches to the vessels involved in the aneurysm) does not change the indications for aneurysm repair. Aneurysms that involve the proximal aortic arch or ascending aorta represent particularly challenging problems and may be considered for repair when they measure 5.5 cm. Open surgery is usually required, carrying substantial risk of morbidity (including stroke, diffuse neurologic injury, and intellectual

impairment) because interruption of arch blood flow is required.

► Complications

With the exception of endovascular repair for discrete saccular aneurysms of the descending thoracic aorta, the morbidity and mortality of thoracic aneurysm repair is higher than for infra-renal abdominal aortic aneurysm repair. Paraplegia remains a devastating complication. Most large series report approximately 4–10% rate of paraplegia following endovascular repair of thoracic aortic aneurysms. The spinal arterial supply is segmental through intercostal branches of the aorta with variable degrees of intersegmental connection. Therefore, the more extensive the aneurysm, the greater is the risk of paraplegia with repair. Prior infrarenal abdominal aortic surgery, subclavian or internal iliac artery occlusion, and hypotension all increase the paraplegia risk. Involvement of the aortic arch also increases the risk of stroke, even when the aneurysm does not directly affect the carotid artery.

► Prognosis

Generally, degenerative aneurysms of the thoracic aorta will enlarge (on average 0.1 cm/y) and require repair to prevent death from rupture. Saccular aneurysms, particularly those distal to the left subclavian artery and the descending thoracic aorta, have good results with endovascular repair. Resection of aneurysms of the aortic arch requires a skilled surgical team and should be attempted only in low-risk patients. Branched or fenestrated endovascular grafting technology has demonstrated reduced morbidity and mortality.

► When to Refer

- Ascending aortic aneurysms larger than 4.5 cm should be referred to a cardiac surgeon for observation and assessment and considered for repair at 5.5 cm.
- Descending thoracic aortic aneurysm should be referred to a vascular specialist when they reach 5 cm for observation and assessment and considered for repair at 6 cm.

► When to Admit

- Any patient with chest or back pain with a known or suspected thoracic aorta aneurysm must be brought to the hospital and undergo urgent imaging studies to rule out the aneurysm as a cause of the pain.

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Upchurch GR et al. Society for Vascular Surgery clinical practice guidelines of thoracic endovascular aortic repair for descending thoracic aortic aneurysms. *J Vasc Surg.* 2021;73:55S. [PMID: 32628988]

Werlin EC et al. Multibranched endovascular aortic aneurysm repair in patients with and without chronic aortic dissections. *J Vasc Surg.* 2019;70:1419. [PMID: 31327618]

PERIPHERAL ARTERY ANEURYSMS



ESSENTIALS OF DIAGNOSIS

- ▶ Widened, prominent pulses.
- ▶ Acute leg or foot pain and paresthesias with loss of distal pulses.
- ▶ High association of popliteal aneurysms with abdominal aortic aneurysms.

General Considerations

Like aortic aneurysms, peripheral artery aneurysms are silent until critically symptomatic. However, unlike aortic aneurysms, the presenting manifestations are due to peripheral embolization and thrombosis. Popliteal artery aneurysms account for 70% of peripheral arterial aneurysms. Popliteal aneurysms may embolize repetitively over time and occlude distal arteries. Due to the redundant parallel arterial supply to the foot, ischemia does not occur until a final embolus occludes flow.

Primary femoral artery aneurysms are much less common. However, pseudoaneurysms of the femoral artery following arterial punctures for arteriography and cardiac catheterization occur with an incidence ranging from 0.05% to 6% of arterial punctures.

Clinical Findings

A. Symptoms and Signs

The patient may be aware of a pulsatile mass when the aneurysm is in the groin, but popliteal aneurysms are often undetected by the patient and clinician. Rarely, peripheral aneurysms may produce symptoms by compressing the local vein or nerve. The first symptom may be due to ischemia of acute arterial occlusion. The symptoms range from sudden-onset pain and paralysis to short-distance claudication that slowly lessens as collateral circulation develops. Symptoms from recurrent embolization to the leg are often transient, if they occur at all. Sudden ischemia may appear in a toe or part of the foot, followed by slow resolution, and the true diagnosis may be elusive. The onset of recurrent episodes of pain in the foot, particularly if accompanied by cyanosis, suggests embolization and requires investigation of the heart and proximal arterial tree.

Because popliteal pulses are somewhat difficult to palpate even in normal individuals, a particularly prominent or easily felt pulse is suggestive of aneurysm and should be investigated by ultrasound. Since popliteal aneurysms are bilateral in 60% of cases, the diagnosis of thrombosis of a popliteal aneurysm is often aided by the palpation of a pulsatile aneurysm in the contralateral popliteal space. Approximately 50% of patients with popliteal aneurysms have an aneurysmal abdominal aorta.

B. Imaging Studies

Duplex color ultrasound is the most efficient investigation to confirm the diagnosis of peripheral aneurysm, measure

its size and configuration, and demonstrate mural thrombus. MRA or CTA is required to define the aneurysm and local arterial anatomy for reconstruction. Arteriography is not recommended because mural thrombus reduces the apparent diameter of the lumen on angiography. Patients with popliteal aneurysms should undergo abdominal ultrasonography to determine whether an abdominal aortic aneurysm is also present.

Treatment

To prevent limb loss from thrombosis or embolization, surgery is indicated when an aneurysm is associated with any peripheral embolization, the aneurysm is larger than 2 cm, or a mural thrombus is present. Immediate or urgent surgery is indicated when acute embolization or thrombosis has caused acute ischemia. Open surgical bypass is generally indicated. Endovascular exclusion of the aneurysm can be done but has anatomic constraints and is reserved for high-risk patients. Intra-arterial thrombolysis may be done in the setting of acute ischemia, if examination (light touch) remains intact, suggesting that immediate surgery is not imperative. Acute pseudoaneurysms of the femoral artery due to arterial punctures can be successfully treated using ultrasound-guided compression or thrombin injection. Open surgery with prosthetic interposition grafting is preferred for primary aneurysms of the femoral artery.

Prognosis

Approximately one-third of untreated patients will require an amputation. The long-term patency of bypass grafts for femoral and popliteal aneurysms is generally excellent but depends on the adequacy of the outflow tract. Late graft occlusion is less common than in similar surgeries for occlusive disease.

When to Refer

- Peripheral arterial aneurysms measuring 2 cm or with ultrasound evidence of thrombus within the aneurysm should be referred to prevent progression to limb-threatening ischemia.

When to Admit

- Patients with symptoms of ischemia or any signs of embolization should be admitted and referred to a vascular specialist.

AORTIC DISSECTION



ESSENTIALS OF DIAGNOSIS

- ▶ Sudden searing chest pain with radiation to the back, abdomen, or neck in a hypertensive patient.
- ▶ Widened mediastinum on chest radiograph.
- ▶ Pulse discrepancy in the extremities.
- ▶ Acute aortic regurgitation may develop.

► General Considerations

Aortic dissection occurs when a spontaneous intimal tear develops and blood dissects into the media of the aorta. The tear can result from repetitive torque applied to the ascending and proximal descending aorta during the cardiac cycle; hypertension is an important component of this disease process. Dissections are classified by the entry point and distal extent. **Type A dissection** involves the arch proximal to the left subclavian artery, and **type B dissection** occurs in the proximal descending thoracic aorta typically just beyond the left subclavian artery. Dissections may occur in the absence of hypertension but abnormalities of smooth muscle, elastic tissue, or collagen are more common in these patients. Pregnancy, bicuspid aortic valve, and coarctation also are associated with increased risk of dissection.

Blood entering the intimal tear may extend the dissection into the abdominal aorta, the lower extremities, the carotid arteries, or less commonly, the subclavian arteries. Both absolute pressure levels and the pulse pressure are important in propagation of dissection. *Aortic dissection is a true emergency and requires immediate control of blood pressure to limit the extent of the dissection.* With type A dissection, which has the worse prognosis, death may occur within hours due to rupture of the dissection into the pericardial sac or dissection into the coronary arteries, resulting in myocardial infarction. Rupture into the pleural cavity is also possible. The intimal/medial flap of the aortic wall created by the dissection may occlude major aortic branches, resulting in ischemia of the brain, intestines, kidney, or extremities.

► Clinical Findings

A. Symptoms and Signs

Severe persistent chest pain of sudden onset radiating down the back or possibly into the anterior chest is characteristic. Radiation of the pain into the neck may also occur. The patient is usually hypertensive. Syncope, hemiplegia, or paralysis of the lower extremities may occur. Mesenteric ischemia or kidney injury may develop. Peripheral pulses may be diminished or unequal. A diastolic murmur may develop as a result of a dissection in the ascending aorta close to the aortic valve, causing valvular regurgitation, heart failure, and cardiac tamponade.

B. Electrocardiographic Findings

Left ventricular hypertrophy from long-standing hypertension is often present. Acute changes suggesting myocardial ischemia do not develop unless dissection involves the coronary artery ostium. Classically, inferior wall abnormalities predominate since dissection leads to compromise of the right rather than the left coronary artery. In some patients, the ECG may be completely normal.

C. Imaging

A multiplanar CT scan with contrast enhancement is the immediate diagnostic imaging modality of choice; clinicians should have a low threshold for obtaining a CT scan in any hypertensive patient with chest pain and equivocal findings on ECG. The CT scan should include both the chest and abdomen to fully delineate the extent of the

dissected aorta. MRA is an excellent imaging modality for chronic dissections, but in the acute situation, the longer imaging time and the difficulty of monitoring patients in the MRI scanner make the CT scan preferable. Chest radiographs may reveal an abnormal aortic contour or widened superior mediastinum. Although transesophageal echocardiography (TEE) is an excellent diagnostic imaging method, it is generally not readily available in the acute setting.

► Differential Diagnosis

Aortic dissection is most commonly misdiagnosed as myocardial infarction or other causes of chest pain such as pulmonary embolization. Dissections may occur with minimal pain; branch vessel occlusion of the lower extremity can mimic arterial embolus.

► Treatment

A. Medical

Aggressive measures to lower blood pressure should occur when an aortic dissection is suspected, even before the diagnostic studies have been completed. Treatment requires a simultaneous reduction of the systolic blood pressure to 100–120 mm Hg and pulse pressure. Beta-blockers have the most desirable effect of reducing the left ventricular ejection force that continues to weaken the arterial wall and should be first-line therapy. Labetalol, both an alpha- and beta-blocker, lowers pulse pressure and achieves rapid blood pressure control. Give 20 mg over 2 minutes by intravenous injection. Additional doses of 40–80 mg intravenously can be given every 10 minutes (maximum dose 300 mg) until the desired blood pressure has been reached. Alternatively, 2 mg/min may be given by intravenous infusion, titrated to desired effect. In patients who have asthma, bradycardia, or other conditions that necessitate the patient's reaction to beta-blockers to be tested, esmolol is a reasonable choice because of its short half-life. Give a loading dose of esmolol, 0.5 mg/kg intravenously over 1 minute, followed by an infusion of 0.0025–0.02 mg/kg/min. Titrate the infusion to a goal heart rate of 60–70 beats/min. If beta-blockade alone does not control the hypertension, nitroprusside may be added as follows: 50 mg of nitroprusside in 1000 mL of 5% dextrose and water, infused at a rate of 0.5 mL/min for a 70-kg person (0.3 mcg/kg/min); the infusion rate is increased by 0.5 mL every 5 minutes until adequate control of the pressure has been achieved. In patients with asthma, while there are no data supporting the use of the calcium channel antagonists, diltiazem and verapamil are potential alternatives to treatment with beta-blocking drugs. Morphine sulfate is the appropriate drug to use for pain relief. Long-term medical care of patients should include beta-blockers in their antihypertensive regimen.

B. Surgical Intervention

1. Type A dissection—*Urgent surgical intervention is required for all type A dissections.* If a skilled cardiovascular team is not available, the patient should be transferred to an appropriate facility. The procedure involves grafting and replacing the diseased portion of the arch and brachiocephalic vessels as necessary. Replacement of the aortic valve may be required with reattachment of the coronary arteries.

2. Type B dissection with malperfusion—Urgent surgery is required for type B dissections if there is aortic branch compromise resulting in malperfusion of the renal, visceral, or extremity vessels. The immediate goal of surgery is to restore flow to the ischemic tissue. Endovascular stenting of the entry tear at the level of the subclavian artery may result in obliteration of the false lumen and restore flow into the branch vessel from the true lumen. The results, however, are unpredictable and should only be attempted by an experienced team.

3. Type B dissection without malperfusion—For acute type B dissections without malperfusion, blood pressure control is the primary treatment. Long-term aortic-specific survival and late aneurysm formation rates are improved with early thoracic stent graft repair, especially in healthy patients with high-risk anatomic features (aortic diameter greater than 4 cm or partial false lumen thrombosis).

► Prognosis & Follow-Up

The mortality rate for untreated type A dissections is approximately 1% per hour for 72 hours and over 90% at 3 months. Mortality is also extremely high for untreated type B dissections with malperfusion or rupture. The surgical and endovascular therapies for these patients are technically demanding and require an experienced team to achieve perioperative mortalities of less than 10%. Aneurysmal enlargement of the residual false lumen may develop despite adequate antihypertensive therapy. Yearly CT scans are required to monitor for aneurysm development. Indications for late aneurysm repair are determined by aneurysm size (6 cm or larger), similar to undissected thoracic aneurysms.

► When to Admit

- All patients with an acute dissection should be hospitalized for blood pressure management and observation.
- Urgent surgical repair is indicated for all type A dissections and for type B dissections with malperfusion, rupture, or persistent symptoms.

Bossone E et al. Acute aortic syndromes: diagnosis and management, an update. Eur Heart J. 2018;39:739. [PMID: 29106452]
 Evangelista A et al; IRAD Investigators. Insights from the International Registry of Acute Aortic Dissection: a 20-year experience of collaborative clinical research. Circulation. 2018;137:1846. [PMID: 29685932]

VENOUS DISEASES

VARICOSE VEINS



ESSENTIALS OF DIAGNOSIS

- ▶ Dilated, tortuous superficial veins in the legs.
- ▶ Asymptomatic or there may be aching discomfort or pain.
- ▶ Often hereditary.
- ▶ Increased frequency after pregnancy.

► General Considerations

Varicose veins develop in the lower extremities. Periods of high venous pressure related to prolonged standing or heavy lifting are contributing factors, but the highest incidence occurs in women after pregnancy. Varicosities develop in over 20% of all adults.

The combination of progressive venous reflux and venous hypertension is the hallmark of chronic venous disease. The superficial veins are involved, typically the great saphenous vein and its tributaries, but the short saphenous vein (posterior lower leg) may also be affected. Distention of the vein prevents the valve leaflets from coaptation, creating incompetence and reflux of blood toward the foot. Focal venous dilation and reflux leads to increased pressure and distention of the vein segment below that valve, which in turn causes progressive failure of the next lower valve. Perforating veins that connect the deep and superficial systems may become incompetent, allowing blood to reflux into the superficial veins from the deep system, increasing venous pressure and distention.

Secondary varicosities can develop as a result of obstructive changes and valve damage in the deep venous system following thrombophlebitis, or rarely as a result of proximal venous occlusion due to neoplasm or fibrosis. Congenital or acquired arteriovenous fistulas or venous malformations are also associated with varicosities and should be considered in young patients with varicosities.

► Clinical Findings

A. Symptoms and Signs

Symptom severity is not correlated with the number and size of the varicosities; extensive varicose veins may produce no subjective symptoms, whereas minimal varicosities may produce many symptoms. Dull, aching heaviness or a feeling of fatigue of the legs brought on by periods of standing is the most common complaint. Itching from venous eczema may occur either above the ankle or directly overlying large varicosities.

Dilated, tortuous veins of the thigh and calf are visible and palpable when the patient is standing. Longstanding varicose veins may progress to chronic venous insufficiency with associated ankle edema, brownish skin hyperpigmentation, and chronic skin induration or fibrosis. A bruit or thrill is never found with primary varicose veins and, when found, alerts the clinician to the presence of an arteriovenous fistula or malformation.

B. Imaging

The identification of the source of venous reflux that feeds the symptomatic veins is necessary for effective surgical treatment. Duplex ultrasonography by a technician experienced in the diagnosis and localization of venous reflux is the test of choice for planning therapy. In most cases, reflux will arise from the greater saphenous vein.

► Differential Diagnosis

Varicose veins due to primary superficial venous reflux should be differentiated from those secondary to previous

or ongoing obstruction of the deep veins (post-thrombotic syndrome). Pain or discomfort secondary to neuropathy should be distinguished from symptoms associated with coexistent varicose veins. Similarly, vein symptoms should be distinguished from pain due to intermittent claudication, which occurs after a predictable amount of exercise and resolves with rest. In adolescent patients with varicose veins, imaging of the deep venous system is obligatory to exclude a congenital malformation or atresia of the deep veins. *Surgical treatment of varicose veins in these patients is contraindicated because the varicosities may play a significant role in venous drainage of the limb.*

► Complications

Superficial thrombophlebitis of varicose veins is uncommon. The typical presentation is acute localized pain with tender, firm veins. The process is usually self-limiting, resolving within several weeks. The risk of deep venous thrombosis (DVT) or embolization is very low unless the thrombophlebitis extends into the great saphenous vein in the upper medial thigh. Predisposing conditions include pregnancy, local trauma, or prolonged periods of sitting.

In older patients, superficial varicosities may bleed with even minor trauma. The amount of bleeding can be alarming as the pressure in the varicosity is high.

► Treatment

A. Nonsurgical Measures

Nonsurgical treatment is effective. Elastic graduated compression stockings (20–30 mm Hg pressure) reduce the venous pressure in the leg and may prevent the progression of disease. Good control of symptoms can be achieved when stockings are worn daily during waking hours and legs are elevated, especially at night. Compression stockings are well-suited for elderly patients or patients who do not want surgery.

B. Varicose Vein Sclerotherapy

Direct injection of a sclerosing agent induces permanent fibrosis and obliteration of the target veins. Chemical irritants (eg, glycerin) or hypertonic saline are often used for small, less-than-4-mm reticular veins or telangiectasias. Foam sclerotherapy is used to treat the great saphenous vein, varicose veins larger than 4 mm, and perforating veins. Sclerotherapy of varicose veins without treatment of underlying saphenous vein reflux is associated with varicosity recurrence rates over 50% as uncorrected reflux progressively dilates adjacent veins. Complications such as phlebitis, tissue necrosis, or infection may occur with any sclerosing agent.

C. Surgical Reflux Treatment

Treatment options for reflux arising from the great saphenous vein include surgical vein stripping (removal) or endovenous treatments using thermal devices (laser or radiofrequency catheter), cyanoacrylate glue injection, or foam sclerosant injection. Endovenous treatments can often be performed with local anesthesia alone and the

early success is equal to vein stripping. Long-term success is highest with vein stripping and thermal treatments while the long-term durability of cyanoacrylate glue and foam is unknown. One major complication of thermal treatments includes endothermal heat-induced thrombosis of the deep vein and may require prolonged anticoagulation. Less common sources of reflux include the small saphenous vein (for varicosities in the posterior calf) and incompetent perforator veins arising directly from the deep venous system. Correction of reflux is performed at the same time as excision of the symptomatic varicose veins. When superficial venous reflux is present, concomitant reflux in the deep venous system is often secondary to volume overload, which will resolve with correction of the superficial reflux.

► Prognosis

Surgical treatment of superficial vein reflux and excision of varicose veins provide excellent results. The 5-year success rate (as defined as lack of pain and recurrent varicosities) is 85–90%. Simple excision (phlebectomy) or injection sclerotherapy without correction of reflux is associated with recurrence rates over 50%. Even after adequate treatment, secondary tissue changes may persist.

► When to Refer

- Absolute indications for referral for saphenous ablation include thrombophlebitis and bleeding.
- Pain and cosmetic concerns are responsible for the majority of referrals for ablation.

Kabnick LS et al. Classification and treatment of endothermal heat-induced thrombosis: recommendations from the American Venous Forum and the Society for Vascular Surgery. *J Vasc Surg Venous Lymphat Disord.* 2021;9:6. [PMID: 33012690]

DePopas E et al. Varicose veins and lower extremity venous insufficiency. *Semin Intervent Radiol.* 2018;35:56. [PMID: 29628617]

SUPERFICIAL VENOUS THROMBOPHLEBITIS

► ESSENTIALS OF DIAGNOSIS

- Red, painful induration along a superficial vein, usually at the site of a recent intravenous line.
- Marked swelling of the extremity may not occur.

► General Considerations

Short-term venous catheterization of superficial arm veins as well as the use of longer-term peripherally inserted central catheter (PICC) lines are the most common cause of superficial thrombophlebitis. Intravenous catheter sites should be observed daily for signs of local inflammation and should be removed if a local reaction develops in the vein. Serious thrombotic or septic complications can occur if this policy is not followed; *S aureus* is the most common

pathogen. Other organisms, including fungi, may also be responsible.

Superficial thrombophlebitis may occur spontaneously, often in pregnant or postpartum women or in individuals with varicose veins, or it may be associated with trauma, as with a blow to the leg or following intravenous therapy with irritating solutions. It also may be a manifestation of systemic hypercoagulability secondary to abdominal cancer such as carcinoma of the pancreas and may be the earliest sign of these conditions. Superficial thrombophlebitis may be associated with occult DVT in about 20% of cases. Pulmonary emboli are exceedingly rare and occur from an associated DVT. (See Chapters 9 and 14 for discussion on deep venous thrombosis.)

► Clinical Findings

In spontaneous superficial thrombophlebitis, the great saphenous vein is most often involved. The patient usually experiences a dull pain in the region of the involved vein. Local findings consist of induration, redness, and tenderness along the course of a vein. The process may be localized, or it may involve most of the great saphenous vein and its tributaries. The inflammatory reaction generally subsides in 1–2 weeks; a firm cord may remain for a much longer period. Edema of the extremity is uncommon.

Localized redness and induration at the site of a recent intravenous line requires urgent attention. Proximal extension of the induration and pain with chills and high fever suggest septic phlebitis and requires urgent treatment.

► Differential Diagnosis

The linear rather than circular nature of the lesion and the distribution along the course of a superficial vein serve to differentiate superficial phlebitis from cellulitis, erythema nodosum, erythema induratum, panniculitis, and fibrosis. Lymphangitis and deep thrombophlebitis must also be considered.

► Treatment

For spontaneous thrombophlebitis if the process is well localized and not near the saphenofemoral junction, local heat and nonsteroidal anti-inflammatory medications are usually effective in limiting the process. If the induration is extensive or is progressing toward the saphenofemoral junction (leg) or cephalo-axillary junction (arm), ligation and division of the vein at the junction of the deep and superficial veins is indicated.

Anticoagulation therapy is usually not required for focal processes. Prophylactic dose low-molecular-weight heparin or fondaparinux is recommended for 5 cm or longer superficial thrombophlebitis of the lower limb veins (Table 14–14) and full anticoagulation is reserved for disease that is rapidly progressing or if there is concern for extension into the deep system (Table 14–16).

Septic superficial thrombophlebitis is an intravascular abscess and requires urgent treatment with heparin or fondaparinux (see Table 14–16) to limit further thrombus formation and removal of the offending catheter in catheter-related infections (see Chapter 30). Treat with antibiotics

(eg, vancomycin, 15 mg/kg intravenously every 12 hours, plus ceftriaxone, 1 g intravenously every 24 hours). If cultures are positive, therapy should be continued for 7–10 days or for 4–6 weeks if complicating endocarditis cannot be excluded. Surgical excision of the involved vein may also be necessary to control the infection.

► Prognosis

With spontaneous thrombophlebitis, the course is generally benign and brief. In patients with phlebitis secondary to varicose veins, recurrent episodes are likely unless correction of the underlying venous reflux and excision of varicosities is done. In contrast, the mortality from septic thrombophlebitis is 20% or higher and requires aggressive treatment. However, if the involvement is localized, the mortality is low and prognosis is excellent with early treatment.

Di Nisio M et al. Treatment for superficial thrombophlebitis of the leg. Cochrane Database Syst Rev. 2018;2:CD004982. [PMID: 29478266]

CHRONIC VENOUS INSUFFICIENCY



ESSENTIALS OF DIAGNOSIS

- History of prior DVT or leg injury.
- Edema, (brawny) skin hyperpigmentation, subcutaneous lipodermosclerosis in the lower leg.
- Venous ulcers: large ulcerations at or above the medial ankle.

► General Considerations

Chronic venous insufficiency is a severe manifestation of venous hypertension. One of the most common etiologies is prior deep venous thrombophlebitis, although about 25% of patients do not have a known history of DVT. In these cases, there may be a history of leg trauma or surgery; obesity is often a complicating factor. Progressive superficial venous reflux is also a common cause. Other causes include congenital or neoplastic obstruction of the pelvic veins or a congenital or acquired arteriovenous fistula.

The basic pathology is caused by valve leaflets that do not coapt because they are either thickened and scarred (post-thrombotic syndrome) or in a dilated vein and are therefore functionally inadequate. Proximal venous obstruction due to chronic thrombus or scarring compounds the problem. With the valves unable to stop venous blood from returning to the foot (venous reflux), the leg develops venous hypertension and an abnormally high hydrostatic force is transmitted to the subcutaneous veins and tissues of the lower leg. The resulting edema results in dramatic and deleterious secondary changes. The stigmata of chronic venous insufficiency include fibrosis of the subcutaneous tissue and skin, pigmentation of skin (hemosiderin taken up by the dermal macrophages), and, later,

ulceration, which is extremely slow to heal. Itching may precipitate the formation of ulceration or local wound cellulitis. Dilation of the superficial veins may occur, leading to varicosities. Although surgical treatment for venous reflux can improve symptoms, controlling edema and the secondary skin changes usually require lifelong compression therapy.

► Clinical Findings

A. Symptoms and Signs

Progressive pitting edema of the leg (particularly the lower leg) is the primary presenting symptom. Secondary changes in the skin and subcutaneous tissues develop over time (Figure 12–2). The usual symptoms are itching, a dull discomfort made worse by periods of standing, and pain if an ulceration is present. The skin at the ankle is usually taut from swelling, shiny, and a brownish pigmentation (hemosiderin) often develops. If the condition is longstanding, the subcutaneous tissues become thick and fibrous. Ulcerations may occur, usually just above the ankle, on the medial or anterior aspect of the leg. Healing results in a thin scar on a fibrotic base that often breaks down with minor trauma or further bouts of leg swelling. Varicosities may appear (Figure 12–3) that are associated with incompetent perforating veins. Cellulitis, which is often difficult to distinguish from the hemosiderin pigmentation, may be diagnosed by blanching erythema with pain.



▲ **Figure 12–2.** Bilateral pretibial edema and erythema consistent with stasis dermatitis (sometimes mimicking cellulitis) in chronic venous insufficiency. (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases*. McGraw-Hill, 2014.)



▲ **Figure 12–3.** Varicose veins, manifested as blue, subcutaneous, tortuous veins more than 3 mm in diameter. (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases*. McGraw-Hill, 2014.)

B. Imaging

Patients with post-thrombotic syndrome or signs of chronic venous insufficiency should undergo duplex ultrasonography to determine whether superficial reflux is present and to evaluate the degree of deep reflux and obstruction.

► Differential Diagnosis

Patients with heart failure, chronic kidney disease, or decompensated liver disease may have bilateral edema of the lower extremities. Many medications can cause edema (eg, calcium channel blockers, nonsteroidal anti-inflammatory agents, thiazolidinediones). Swelling from lymphedema involves the feet and may be unilateral, but varicosities are absent. Edema from these causes pits easily and brawny discoloration is rare. Lipedema is a disorder of adipose tissue that occurs almost exclusively in women, is bilateral and symmetric, and is characterized by stopping at a distinct line just above the ankles.

Primary varicose veins may be difficult to differentiate from the secondary varicosities of post-thrombotic syndrome or venous obstruction.

Other conditions associated with chronic ulcers of the leg include neuropathic ulcers usually from diabetes mellitus, arterial insufficiency (often manifests as painful lateral ankle ulcers with absent pulses; medial ankle ulcers, on

the other hand, are usually due to venous insufficiency), autoimmune diseases (eg, Felty syndrome), sickle cell anemia, erythema induratum (bilateral and usually on the posterior aspect of the lower part of the leg), and fungal infections.

► Prevention

Irreversible tissue changes and associated complications in the lower legs can be reduced through early and aggressive anticoagulation of acute DVT to minimize the valve damages and by prescribing compression stockings if chronic edema develops after the DVT has resolved. Treatment of acute iliofemoral DVT with catheter-directed thrombolysis or mechanical thrombectomy does not reduce post-thrombotic syndrome and chronic venous insufficiency.

► Treatment

A. General Measures

Fitted, graduated compression stockings (20–30 mm Hg pressure or higher) worn from the foot to just below the knee during the day and evening are the mainstays of treatment and are usually sufficient. When they are not, additional measures, such as avoidance of long periods of sitting or standing, intermittent elevations of the involved leg, and sleeping with the legs kept above the level of the heart, may be necessary to control the swelling. Pneumatic compression of the leg, which can pump the fluid out of the leg, is used in refractory cases.

B. Ulceration

As the primary pathology is edema and venous hypertension, healing of the ulcer will not occur until the edema is controlled and compression is applied. Circumferential nonelastic bandages on the lower leg enhance the pumping action of the calf muscles on venous blood flow out of the calf. A lesion can often be treated on an ambulatory basis by means of a semi-rigid gauze boot made with Unna paste (Gelcast, Medicopaste) or a multi-layer compression dressing (eg, Profore). Initially, the ulcer needs to be debrided and the boot changed every 2–3 days to control ulcer drainage. As the edema and drainage subside, optimal healing is achieved when the boot is kept in place for 5–7 days. The ulcer, tendons, and bony prominences must be adequately padded. Alternatively, knee-high graduated compression stockings with an absorbent dressing may be used, if wound drainage is minimal. Home compression therapy with a pneumatic compression device is used in refractory cases, but many patients have severe pain with the “milking” action of the pump device. Some patients will require admission for complete bed rest and leg elevation to achieve ulcer healing. After the ulcer has healed, daily graduated compression stocking therapy is mandatory to prevent ulcer recurrence.

C. Vein Treatment (Reflux or Obstruction)

Treatment of superficial vein reflux (see Varicose Veins section, above) has been shown to decrease the recurrence rate of venous ulcers. Where there is substantial obstruction of

the femoral and popliteal deep venous system, superficial varicosities supply the venous return and they should not be removed.

Venous stents as treatment of chronic iliac deep vein stenosis or obstruction may improve venous ulcer healing and reduce the ulcer recurrence rate in severe cases.

► Prognosis

Individuals with chronic venous insufficiency often have recurrent edema, particularly if they do not consistently wear support stockings that have at least 20–30 mm Hg compression.

► When to Refer

- Patients with significant saphenous reflux should be evaluated for ablation.
- Patients with ulcers should be monitored by an interdisciplinary wound care team so that these challenging wounds receive aggressive care.

Raffetto JD. Pathophysiology of chronic venous disease and venous ulcers. *Surg Clin North Am.* 2018;98:337. [PMID: 29502775]

Vedantham S et al; ATTRACT Trial Investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med.* 2017;377:2240. [PMID: 29211671]

SUPERIOR VENA CAVAL OBSTRUCTION

ESSENTIALS OF DIAGNOSIS

- Swelling of the neck, face, and upper extremities.
- Dilated veins over the upper chest and neck.

► General Considerations

Partial or complete obstruction of the superior vena cava is a relatively rare condition that is usually secondary to neoplastic or inflammatory processes in the superior mediastinum. The most frequent causes are (1) neoplasms, such as lymphomas, primary malignant mediastinal tumors, or carcinoma of the lung with direct extension (over 80%); (2) chronic fibrotic mediastinitis, either of unknown origin or secondary to tuberculosis, histoplasmosis, pyogenic infections, or drugs, especially methysergide; (3) DVT, often by extension of the process from the axillary or subclavian vein into the innominate vein and vena cava associated with catheterization of these veins for dialysis or for hyperalimentation; (4) aneurysm of the aortic arch; and (5) constrictive pericarditis.

► Clinical Findings

A. Symptoms and Signs

The onset of symptoms is acute or subacute. Symptoms include swelling of the neck and face and upper extremities. Symptoms are often perceived as congestion and present as

headache, dizziness, visual disturbances, stupor, syncope, or cough. There is progressive obstruction of the venous drainage of the head, neck, and upper extremities. The cutaneous veins of the upper chest and lower neck become dilated, and flushing of the face and neck develops. Brawny edema of the face, neck, and arms occurs later, and cyanosis of these areas then appears. Cerebral and laryngeal edema ultimately result in impaired function of the brain as well as respiratory insufficiency. Bending over or lying down accentuates the symptoms; sitting quietly is generally preferred. The manifestations are more severe if the obstruction develops rapidly and if the azygos junction or the vena cava between that vein and the heart is obstructed.

B. Laboratory Findings

The venous pressure is elevated (often more than 20 cm of water) in the arm and is normal in the leg. Since lung cancer is a common cause, bronchoscopy is often performed; transbronchial biopsy, however, is relatively contraindicated because of venous hypertension and the risk of bleeding.

C. Imaging

Chest radiographs and a CT scan can define the location and often the nature of the obstructive process, and contrast venography or magnetic resonance venography (MRV) will map out the extent and degree of the venous obstruction and the collateral circulation. Brachial venography or radionuclide scanning following intravenous injection of technetium ($Tc-99m$) pertechnetate demonstrates a block to the flow of contrast material into the right heart and enlarged collateral veins. These techniques also allow estimation of blood flow around the occlusion as well as serial evaluation of the response to therapy.

D. Treatment

Conservative measures, such as elevation of the head of the bed and lifestyle modification to avoid bending over, are useful. Balloon angioplasty of the obstructed caval segment combined with stent placement provides prompt relief of symptoms and is the procedure of choice for all etiologies. Occasionally, anticoagulation is needed, while thrombolysis is rarely needed.

Urgent treatment for neoplasm consists of (1) cautious use of intravenous diuretics and (2) mediastinal irradiation, starting within 24 hours, with a treatment plan designed to give a high daily dose but a short total course of therapy to rapidly shrink the local tumor. Intensive combined therapy will palliate the process in up to 90% of patients. In patients with a subacute presentation, radiation therapy alone usually suffices. Chemotherapy is added if lymphoma or small-cell carcinoma is diagnosed.

Long-term outcome is complicated by risk of re-occlusion from either thrombosis or neoplasm growth. Surgical procedures to bypass the obstruction are complicated by bleeding from high venous pressure. In cases where the thrombosis is secondary to an indwelling catheter, thrombolysis may be attempted. Clinical judgment is required since a long-standing clot may be fibrotic and the risk of bleeding can outweigh the potential benefit.

► Prognosis

The prognosis depends on the nature and degree of obstruction and its speed of onset. Slowly developing forms secondary to fibrosis may be tolerated for years. A high degree of obstruction of rapid onset secondary to cancer is often fatal in a few days or weeks because of increased intracranial pressure and cerebral hemorrhage, but treatment of the tumor with radiation and chemotherapeutic drugs may result in significant palliation. Balloon angioplasty and stenting provide good relief but may require re-treatment for recurrent symptoms secondary to thrombosis or restenosis.

► When to Refer

- Any patient with progressive head and neck swelling should be referred to rule out superior vena cava syndrome.

► When to Admit

- Any patient with acute edema of the head and neck or with signs and symptoms of airway compromise, such as hoarseness or stridor, should be admitted.

Kalra M et al. Endovenous and operative treatment of superior vena cava syndrome. *Surg Clin North Am.* 2018;98:321. [PMID: 29502774]

DISEASES OF THE LYMPHATIC CHANNELS

LYMPHANGITIS & LYMPHADENITIS



ESSENTIALS OF DIAGNOSIS

- Red streak from wound or cellulitis toward regional lymph nodes, which are usually enlarged and tender.
- Chills, fever, and malaise may be present.

► General Considerations

Lymphangitis and lymphadenitis are common manifestations of a bacterial infection that is usually caused by hemolytic streptococci or *S aureus* (or by both organisms) and becomes invasive, generally from an infected wound, cellulitis, or an abscess. The wound may be very small or superficial, or an established abscess may be present, feeding bacteria into the lymphatics. The involvement of the lymphatics is often manifested by a red streak in the skin extending in the direction of the regional lymph nodes.

► Clinical Findings

A. Symptoms and Signs

Throbbing pain is usually present at the site of bacterial invasion from a wound, cellulitis, or abscess. Malaise,

anorexia, sweating, chills, and fever of 38–40°C develop quickly, often with a rapid pulse. The red streak, when present, may be definite or may be faint and easily missed, especially in dark-skinned patients. The involved regional lymph nodes may be significantly enlarged and are usually quite tender. The infection may progress rapidly, often in a matter of hours, and may lead to septicemia and death.

B. Laboratory Findings

Leukocytosis with a left shift is usually present. Blood cultures may be positive, most often for staphylococcal or streptococcal species. Culture and sensitivity studies of the wound exudate or pus may be helpful in treatment of the more severe or refractory infections but are often difficult to interpret because of skin contaminants.

Differential Diagnosis

The erythema and induration of superficial thrombophlebitis are localized in and around the thrombosed vein. Venous thrombosis is not associated with lymphadenitis, and a wound of entrance with secondary cellulitis is generally absent.

Cat-scratch fever (*Bartonella henselae*) is a cause of lymphadenitis; the nodes, though often very large, are relatively nontender. Exposure to cats is common, but the patient may have forgotten about the scratch.

It is extremely important to differentiate cellulitis from acute streptococcal hemolytic gangrene or a necrotizing soft tissue infection. These are deeper infections that may be extensive and are potentially lethal. Patients are more seriously ill; there may be redness due to leakage of red cells, creating a non-blanching erythema; subcutaneous crepitus, a late finding, may be palpated or auscultated; and subcutaneous air may be present on radiography or CT scan. Immediate surgical consultation is needed for wide debridement of all involved deep tissues if a necrotizing infection is suspected.

Treatment

A. General Measures

Prompt treatment should include heat (hot, moist compresses or heating pad), elevation when feasible, and immobilization of the infected area. Analgesics may be prescribed for pain.

B. Specific Measures

Empiric antibiotic therapy for hemolytic streptococci or *S aureus* (or both organisms) should always be instituted. Cephalosporins or extended-spectrum penicillins are commonly used (eg, cephalexin, 0.5 g orally four times daily for 7–10 days; see Table 30–6). Trimethoprim-sulfamethoxazole (two double-strength tablets orally twice daily for 7–10 days) should be considered when there is concern that the pathogen is MRSA (see Tables 30–4 and 30–6).

C. Wound Care

Any wound that is the initiating site of lymphangitis should be treated aggressively. Any necrotic tissue must be debrided and loculated pus drained.

Prognosis

With proper therapy including an antibiotic effective against the invading bacteria, control of the infection can usually be achieved in a few days. Delayed or inadequate therapy can lead to overwhelming infection with septicemia.

When to Admit

- Infections causing lymphangitis should be treated in the hospital with intravenous antibiotics.
- Debridement may be required and prompt surgical consultation is prudent.

LYMPHEDEMA



ESSENTIALS OF DIAGNOSIS

- Painless persistent edema of one or both lower extremities, primarily in young women.
- Pitting edema without ulceration, varicosities, or stasis pigmentation.
- Lymphangitis and cellulitis may occur.

General Considerations

When lymphedema is due to congenital developmental abnormalities consisting of hypoplastic or hyperplastic involvement of the proximal or distal lymphatics, it is referred to as the **primary form**. The obstruction may be in the pelvic or lumbar lymph channels and nodes when the disease is extensive and progressive. The **secondary form** of lymphedema involves inflammatory or mechanical lymphatic obstruction from trauma, regional lymph node resection or irradiation, or extensive involvement of regional nodes by malignant disease or filariasis. Lymphedema may occur following surgical removal of the lymph nodes in the groin or axillae. Secondary dilation of the lymphatics that occurs in both forms leads to incompetence of the valve system, disrupts the orderly flow along the lymph vessels, and results in progressive stasis of a protein-rich fluid. Episodes of acute and chronic inflammation may be superimposed, with further stasis and secondary fibrosis.

Clinical Findings

Hypertrophy of the limb results, with markedly thickened and fibrotic skin and subcutaneous tissue (Figure 12–4) in very advanced cases.

T_2 -weighted MRI has been used to identify lymphatics and proximal obstructing masses. Lymphangiography and radioactive isotope studies may identify focal defects in lymph flow but are of little value in planning therapy.

Treatment

Since there is no effective cure for lymphedema, the treatment strategies are designed to control the problem and



▲ Figure 12–4. Lymphedema with a dorsal pedal hump and exaggerated skin folds near the ankle.
(Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases*. McGraw-Hill, 2014.)

allow normal activity and function. Most patients can be treated with some of the following measures: (1) The flow of lymph out of the extremity can be aided through intermittent elevation of the extremity, especially during the sleeping hours (foot of bed elevated 15–20 degrees, achieved by placing pillows beneath the mattress); the constant use of graduated elastic compression stockings; and massage toward the trunk—either by hand or by means of pneumatic pressure devices designed to milk edema out of an extremity. Wound care centers specializing in the care of patients with lymphedema may be helpful. (2) Secondary cellulitis should be avoided by means of good hygiene and treatment of any trichophytosis of the toes. Once an infection starts, it should be treated by periods of elevation and antibiotic therapy that covers *Staphylococcus* and *Streptococcus* organisms (see Table 30–6). Infections can be a serious and recurring problem and are often difficult to control. Prophylactic antibiotics have not been shown to be of benefit. (3) Intermittent courses of diuretic therapy, especially in those with premenstrual or seasonal exacerbations, are rarely helpful. (4) Amputation is used only for the rare complication of lymphangiosarcoma in the extremity.

► Prognosis

With aggressive treatment, including pneumatic compression devices, good relief of symptoms can be achieved. The long-term outlook is dictated by the associated conditions and avoidance of recurrent cellulitis.

Chen K et al. Surgical management of postmastectomy lymphedema and review of the literature. Ann Plast Surg. 2021;86: S173. [PMID: 33346539]

SHOCK



ESSENTIALS OF DIAGNOSIS

- ▶ Hypotension, tachycardia, oliguria, altered mental status.
- ▶ Peripheral hypoperfusion and impaired oxygen delivery.
- ▶ Four classifications: hypovolemic, cardiogenic, obstructive, or distributive.

► General Considerations

Shock occurs when the rate of arterial blood flow is inadequate to meet tissue metabolic needs. This results in regional hypoxia and subsequent lactic acidosis from anaerobic metabolism in peripheral tissues as well as eventual end-organ damage and failure.

► Classification

Table 12–1 outlines common causes and mechanisms associated with each type of shock.

A. Hypovolemic Shock

Hypovolemic shock results from decreased intravascular volume secondary to loss of blood or fluids and electrolytes. The etiology may be suggested by the clinical setting (eg, trauma) or by signs and symptoms of blood loss (eg, gastrointestinal bleeding) or dehydration (eg, vomiting or diarrhea). Compensatory vasoconstriction may transiently maintain the blood pressure but unreplaced losses of over 15% of the intravascular volume can result in hypotension and progressive tissue hypoxia.

B. Cardiogenic Shock

Cardiogenic shock results from cardiac failure with the resultant inability of the heart to maintain adequate tissue perfusion. The clinical definition of cardiogenic shock is evidence of tissue hypoxia due to decreased cardiac output (cardiac index less than 2.2 L/min/m²) in the presence of adequate intravascular volume. This is most often caused by myocardial infarction but can also be due to cardiomyopathy, myocardial contusion, valvular incompetence or stenosis, or arrhythmias. See Chapter 10.

C. Obstructive Shock

Pericardial tamponade, tension pneumothorax, and massive pulmonary embolism can cause an acute decrease in cardiac output resulting in shock. These are medical emergencies requiring prompt diagnosis and treatment.

D. Distributive Shock

Distributive or vasodilatory shock has many causes including sepsis, anaphylaxis, traumatic spinal cord injury, or

Table 12–1. Classification of shock by mechanism and common causes.

Hypovolemic shock	
Blood loss	
Traumatic hemorrhage	
Exsanguination	
Hemothorax	
Hemoperitoneum	
Fracture (femur and pelvis)	
Nontraumatic hemorrhage	
Gastrointestinal bleed	
AAA rupture	
Ectopic pregnancy rupture	
Volume loss	
Burns	
Skin integrity loss (toxic epidermal necrolysis)	
Vomiting	
Diarrhea	
Hyperosmolar states (diabetic ketoacidosis)	
Third spacing (eg, ascites, pancreatitis)	
Decreased intake	
Cardiogenic shock	
Dysrhythmia	
Bradycardias and blocks	
Tachycardias	
Myocardial disease	
Left or right ventricular infarction	
Dilated cardiomyopathy	
Mechanical	
Valvular	
Aortic regurgitation from dissection	
Papillary muscle rupture from ischemia	
Acute valvular rupture from abscess	
Ventricular aneurysm rupture	
Ventricular septum rupture	
Free wall ventricle rupture	
Obstructive shock	
Tension pneumothorax	
Pericardial disease	
Pericardial tamponade	
Constrictive pericarditis	
High-risk (massive) pulmonary embolism	
Severe pulmonary hypertension	
Auto PEEP from mechanical ventilation	
Distributive (vasodilatory) shock	
Anaphylactic shock	
Septic shock	
Neurogenic shock	
Drug-induced vasodilation	
Adrenal insufficiency	

Modified, with permission, from Stone CK, Humphries RL (editors). *Current Emergency Diagnosis & Treatment*, 7th ed. McGraw-Hill, 2011.

AAA, abdominal aortic aneurysm; PEEP, positive end expiratory pressure.

acute adrenal insufficiency. The reduction in systemic vascular resistance results in inadequate cardiac output and tissue hypoperfusion despite normal circulatory volume.

1. Septic shock—Sepsis is the most common cause of distributive shock and carries a mortality rate of 20–50%. The

Society of Critical Care Medicine and the European Society of Intensive Care Medicine's 2016 definition for **sepsis** is life-threatening organ dysfunction caused by a dysregulated host response to infection from any organism (bacterial, viral, or fungal). **Septic shock** is clinically defined as sepsis with fluid-unresponsive hypotension (systolic blood pressure less than 100 mm Hg), serum lactate level higher than 2 mmol/L, and a need for vasopressors to keep mean arterial pressure (MAP) above 65 mm Hg. The most common cause of septic shock in hospitalized patients is infection with gram-positive or gram-negative organisms, with a growing incidence of infection from multidrug-resistant organisms. Sepsis from viral and fungal organisms is increasing but remain less than that for bacterial infections. Risk factors for septic shock include bacteremia, extremes of age, diabetes, cancer, immunosuppression, and history of a recent invasive procedure.

A. CLINICAL TOOLS TO IDENTIFY SEPSIS AND SEPTIC SHOCK—The Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3) recommend using the Sequential Organ Failure Assessment (SOFA) score to define sepsis (https://en.wikipedia.org/wiki/SOFA_score); an increase of 2 or more SOFA score points in a patient with infection is diagnostic of sepsis with a predicted 10% mortality. The SEPSIS-3 group also introduced the quick SOFA (qSOFA) scoring system (https://en.wikipedia.org/wiki/SOFA_score); 1 point each is assigned for hypotension (systolic blood pressure below 100 mm Hg), altered mental status, or tachypnea (respiratory rate more than 22 breaths per minute). A qSOFA score of 2 or more in a patient with suspected infection suggests worsened clinical outcomes and may influence triage decisions for intensive care unit (ICU)-level care.

B. SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)—Defined as a systemic response to a nonspecific infectious or noninfectious insult resulting in at least two of the following findings: (1) body temperature higher than 38°C (100.4°F) or lower than 36°C (96.8°F), (2) heart rate faster than 90 beats per minute, (3) respiratory rate more than 20 breaths per minute or hyperventilation with an arterial carbon dioxide tension (Paco₂) less than 32 mm Hg, or (4) abnormal white blood cell count (greater than 12,000/mcL or less than 4000/mcL or greater than 10% immature [band] forms). Vasodilatory shock from SIRS is often due to burns; pancreatitis; autoimmune disorders, such as vasculitis or inflammatory colitis; air or amniotic fluid embolus; ischemia; or trauma. SIRS is not included in the 2016 formal diagnostic criteria of sepsis. A 2018 meta-analysis demonstrated that SIRS criteria have higher sensitivity than qSOFA and may therefore identify patients with sepsis before other tests, suggesting that SIRS may be a better screening tool for sepsis, while qSOFA may be better used as a predictor of ICU mortality. Studies are ongoing to describe the optimal patient populations (emergency department vs hospitalized non-ICU patients) where SIRS and qSOFA scoring systems should be used.

2. Neurogenic shock—Neurogenic shock is caused by traumatic spinal cord injury or effects of an epidural or spinal anesthetic. This results in loss of sympathetic tone

with a reduction in systemic vascular resistance and hypotension without a compensatory tachycardia. Reflex vagal parasympathetic stimulation evoked by pain, gastric dilation, or fright may simulate neurogenic shock, producing hypotension, bradycardia, and syncope.

3. Endocrine shock—Endocrine shock can arise from hyperthyroidism, hypothyroidism, or adrenal insufficiency. Adrenal insufficiency most often occurs with abrupt cessation of long-term corticosteroid use, but it can also be precipitated by infection, trauma, surgery, or pituitary injury (leading to secondary adrenal insufficiency). In addition to hypotension, symptoms include weakness, nausea, abdominal pain, and confusion. Hypothyroidism can lead to myxedema coma, presenting with vasodilation and depressed cardiac output. Shock from hyperthyroidism most often produces high-output cardiac failure.

► Clinical Findings

A. Symptoms and Signs

Hypotension is traditionally defined as a systolic blood pressure of 90 mm Hg or less or a MAP of less than 60–65 mm Hg but must be evaluated relative to the patient's normal blood pressure. A drop in systolic pressure of greater than 10–20 mm Hg or an increase in pulse of more than 15 beats per minute with positional change suggests depleted intravascular volume. However, blood pressure is often not the best indicator of end-organ perfusion because compensatory mechanisms, such as increased heart rate, increased cardiac contractility, and vasoconstriction can occur to prevent hypotension. Patients with hypotension often have cool or mottled extremities and weak or thready peripheral pulses. Splanchnic vasoconstriction may lead to oliguria, bowel ischemia, and liver dysfunction, which can ultimately result in multiorgan failure. Mentation may be normal or patients may become restless, agitated, confused, lethargic, or comatose as a result of inadequate perfusion of the brain.

Hypovolemic shock is evident when signs of hypoperfusion, such as oliguria, altered mental status, and cool extremities, are present. Jugular venous pressure is low, and there is a narrow pulse pressure indicative of reduced stroke volume. Rapid replacement of fluids can restore tissue perfusion. In **cardiogenic shock**, there are also signs of global hypoperfusion with oliguria, altered mental status, and cool extremities. Jugular venous pressure is elevated and there may be evidence of pulmonary edema with respiratory compromise in the setting of left-sided heart failure. A *transthoracic echocardiogram (TTE)* or a *transesophageal echocardiogram (TEE)* is an effective diagnostic tool to differentiate hypovolemic from cardiogenic shock. In hypovolemic shock, the left ventricle will be small because of decreased filling, but contractility is often preserved. In cardiogenic shock, there is a decrease in left ventricular contractility. The left ventricle may appear dilated and full because of the inability of the left ventricle to eject a sufficient stroke volume.

In **obstructive shock**, the central venous pressure may be elevated but the TTE or TEE may show reduced left ventricular filling, a pericardial effusion in the case of

tamponade, thickened pericardium in the case of pericarditis, or right ventricular dysfunction in the case of massive pulmonary embolism. Pericardiocentesis or pericardial window for pericardial tamponade, chest tube placement for tension pneumothorax, or catheter-directed thrombolytic therapy for massive pulmonary embolism can be life-saving in cases of obstructive shock.

In **distributive shock**, signs include hyperdynamic heart sounds, warm extremities initially, and a wide pulse pressure indicative of large stroke volume. The echocardiogram may show a hyperdynamic left ventricle. **Septic shock** is diagnosed when there is clinical evidence of infection in the setting of persistent hypotension and evidence of organ hypoperfusion, such as lactic acidosis, decreased urinary output, or altered mental status despite adequate volume resuscitation. **Neurogenic shock** is diagnosed when there is evidence of central nervous system injury and persistent hypotension despite adequate volume resuscitation. A history of long-term corticosteroid use or thyroid disease can increase the likelihood of **endocrine shock**.

B. Laboratory Findings and Imaging

Blood specimens should be evaluated for complete blood count, electrolytes, glucose, arterial blood gas determinations, coagulation parameters, lactate levels, typing and cross-matching, and bacterial cultures. An electrocardiogram and chest radiograph should also be part of the initial assessment. Point-of-care ultrasonography can rapidly assess global cardiac function, presence of pericardial effusion, and intravascular volume status via inferior vena cava inspection in cases of undifferentiated hypotension. A TTE can more formally assess right- and left-sided filling pressures and cardiac output.

► Treatment

A. General Measures

Treatment depends on prompt diagnosis and an accurate appraisal of inciting conditions. Initial management consists of basic life support with an assessment of the patient's circulation, airway, and breathing. This may entail airway intubation and mechanical ventilation. Ventilatory failure should be anticipated in patients with severe metabolic acidosis due to shock. Mechanical ventilation along with sedation can decrease respiratory muscle oxygen demand and allow improved oxygen delivery to hypoperfused tissues. Intravenous access and fluid resuscitation should be instituted along with cardiac monitoring and assessment of hemodynamic parameters such as blood pressure and heart rate. Cardiac monitoring can detect myocardial ischemia or malignant arrhythmias, which can be treated by standard advanced cardiac life support (ACLS) protocols.

Unresponsive or minimally responsive patients should have their glucose checked immediately, and if their glucose levels are low, 1 ampule of 50% dextrose intravenously should be given. An arterial line should be placed for continuous blood pressure measurement, and an indwelling urinary catheter should be inserted to monitor urinary output.

B. Hemodynamic Measurements

Early consideration is given to placement of a central venous catheter (CVC) for infusion of fluids and medications and for hemodynamic pressure measurements. A CVC can provide measurements of the central venous pressure (CVP) and the central venous oxygen saturation (ScvO_2), both of which can be used to manage septic and cardiogenic shock. Pulmonary artery catheters (PACs) allow measurement of the pulmonary artery pressure, left-sided filling pressure or the pulmonary capillary wedge pressure (PCWP), the mixed venous oxygen saturation (SvO_2), and cardiac output. Multiple studies suggest that PACs do not increase overall mortality or length of hospital stay but are associated with higher use of inotropes and intravenous vasodilators in select groups of critically ill patients. The attendant risks associated with PACs (infection, arrhythmias, vein thrombosis, and pulmonary artery rupture) can be as high as 4–9%; thus, the routine use of PACs cannot be recommended. However, in complex situations, PACs may be useful in distinguishing between cardiogenic and septic shock, so the value of the information they might provide must be carefully weighed in each patient. TTE is a noninvasive alternative to the PAC. TTE can provide information about the pulmonary artery pressure and current cardiac function, including cardiac output. The ScvO_2 , which is obtained through the CVC, can be used as a surrogate for the SvO_2 , which is obtained through the PAC. Pulse pressure variation, as determined by arterial waveform analysis, or stroke volume variation is much more sensitive than CVP as dynamic measures of fluid responsiveness in volume resuscitation, but these measurements have only been validated in patients who are mechanically ventilated with tidal volumes of 8 mL/kg, not triggering the ventilator, and in normal sinus rhythm. Point-of-care ultrasound measurements of the inferior vena cava (IVC) can suggest intravascular volume status and guide fluid replacement. If the patient is mechanically ventilated and the IVC dilates ~15–20% with respirations, they are likely to respond to intravenous fluids. If the patient is spontaneously breathing, they may be fluid-responsive if their IVC is less than 2 cm in diameter and collapses by more than 50% with each breath.

A CVP less than 5 mm Hg suggests hypovolemia, and a CVP greater than 18 mm Hg suggests volume overload, cardiac failure, tamponade, or pulmonary hypertension. A cardiac index lower than 2 L/min/m² indicates a need for inotropic support. A cardiac index higher than 4 L/min/m² in a hypotensive patient is consistent with early septic shock. The systemic vascular resistance is low (less than 800 dynes · s/cm⁻⁵) in sepsis and neurogenic shock and high (greater than 1500 dynes · s/cm⁻⁵) in hypovolemic and cardiogenic shock. Treatment is directed at maintaining a CVP of 8–12 mm Hg, a MAP of 65 mm Hg or higher, a cardiac index of 2–4 L/min/m², and a ScvO_2 greater than 70%.

C. Volume Replacement

Volume replacement is critical in the initial management of shock. **Hemorrhagic shock** is treated with immediate

efforts to achieve hemostasis and rapid infusions of blood substitutes, such as type-specific or type O negative packed red blood cells (PRBCs) or whole blood, which provides extra volume and clotting factors. Each unit of PRBC or whole blood is expected to raise the hematocrit by 3%. **Hypovolemic shock** secondary to dehydration is managed with rapid boluses of isotonic crystalloid solutions, usually in 1-L increments. **Cardiogenic shock** in the absence of fluid overload requires smaller fluid challenges, usually in increments of 250 mL. **Septic shock** usually requires large volumes of fluid for resuscitation (typically 30 mL/kg) as the associated capillary leak releases fluid into the extravascular space. *Caution must be used in cases of large-volume resuscitation with unwarmed fluids because this can produce hypothermia, which can lead to hypothermia-induced coagulopathy.* Warming of fluids before administration can avoid this complication.

Crystalloid solution is the resuscitation fluid of choice in most settings. Historically, 0.9% saline was the most widely used crystalloid solution in resuscitation. Data suggest that balanced crystalloids, like lactated Ringer solution or Plasma-Lyte, are associated with less kidney injury, fewer instances of hyperchloremic metabolic acidosis, and decreased overall mortality. Comparisons of 0.9% saline and colloid (albumin) solutions in critically ill patients found no difference in outcome except in patients with traumatic brain injury, where albumin resuscitation led to higher mortality. Thus, the use of balanced crystalloid solutions for volume resuscitation in shock is favored. If the patient does not respond to fluid resuscitation, early use of vasopressors should be considered.

D. Early Goal-Directed Therapy

Compensated shock can occur in the setting of normalized hemodynamic parameters with ongoing global tissue hypoxia. Traditional endpoints of resuscitation such as blood pressure, heart rate, urinary output, mental status, and skin perfusion can therefore be misleading. Following set protocols for the treatment of septic shock by adjusting the use of fluids, vasopressors, and inotropes as well as by using blood transfusions to meet hemodynamic targets (MAP 65 mm Hg or higher, CVP 8–12 mm Hg, ScvO_2 greater than 70%) is termed **early goal-directed therapy (EGDT)**. Lactate clearance of more than 10% can be used as a substitute for ScvO_2 criteria if ScvO_2 monitoring is not available.

Two large randomized trials published in 2014 (ProCESS and ARISE) demonstrated no mortality benefit from the institution of the original algorithm for EGDT, but this may have been due to earlier administration of antibiotics, components of EGDT becoming part of the “usual care” that clinicians deliver, and the effectiveness of education about detecting and treating sepsis in a timely fashion.

The Surviving Sepsis Campaign’s recommendations for patients with sepsis or septic shock are to measure lactate level; obtain blood cultures prior to administration of broad-spectrum antibiotics, *which should occur within 1 hour of sepsis diagnosis*; and administer 30 mL/kg crystalloid for hypotension or lactate greater than 4 mmol/L within the first 3 hours of presentation. Smaller

resuscitation volumes may be appropriate for patients with heart failure, cirrhosis, or advanced kidney disease. Vasopressors should be administered for hypotension not responsive to initial fluid resuscitation to maintain MAP 65 mm Hg or higher. Remeasure lactate if initial level was high, and reassess volume status and tissue perfusion frequently. A meta-analysis of hemodynamic optimization trials suggests that early treatment before the development of organ failure results in improved survival, and patients who respond well to initial efforts demonstrate a survival advantage over nonresponders.

E. Medications

1. Vasoactive therapy—Vasopressors and inotropic agents are administered only after adequate fluid resuscitation. Choice of vasoactive therapy depends on the presumed etiology of shock as well as cardiac output. If there is continued hypotension with evidence of high cardiac output after adequate volume resuscitation, then vasopressor support is needed to improve vasomotor tone. If there is evidence of low cardiac output with high filling pressures, inotropic support is needed to improve contractility.

A. DISTRIBUTIVE (VASODILATORY) SHOCK—When increased vasoconstriction is required to maintain an adequate perfusion pressure, alpha-adrenergic catecholamine agonists (such as norepinephrine and phenylephrine) are generally used. Although norepinephrine is both an alpha-adrenergic and beta-adrenergic agonist, it preferentially increases MAP over cardiac output. The initial dose is 1–2 mcg/min as an intravenous infusion, titrated to maintain MAP at 65 mm Hg or higher. The usual maintenance dose is 2–4 mcg/min intravenously (maximum dose is 30 mcg/min). Patients with refractory shock may require dosages of 10–30 mcg/min intravenously. Epinephrine, also with both alpha-adrenergic and beta-adrenergic effects, may be used in severe shock and during acute resuscitation. It is the vasopressor of choice for anaphylactic shock. For severe shock, give 1 mcg/min as a continuous intravenous infusion initially and titrate to hemodynamic response; the usual dosage range is 1–10 mcg/min intravenously.

Dopamine has variable effects according to dosage. At low doses (2–5 mcg/kg/min intravenously), stimulation of dopaminergic and beta-adrenergic receptors produces increased glomerular filtration, heart rate, and contractility. At doses of 5–10 mcg/kg/min, beta-1-adrenergic effects predominate, resulting in an increase in heart rate and cardiac contractility. At higher doses (greater than 10 mcg/kg/min), alpha-adrenergic effects predominate, resulting in peripheral vasoconstriction. The maximum dose is typically 50 mcg/kg/min.

There is no evidence documenting a survival benefit from, or the superiority of, a particular vasopressor in septic shock. Norepinephrine is the initial vasopressor of choice in septic shock to maintain the MAP at 65 mm Hg or higher. Phenylephrine can be used for hyperdynamic septic shock if dysrhythmias or tachycardias prevent the use of agents with beta-adrenergic activity. In meta-analyses, the use of dopamine as a first-line vasopressor in septic shock resulted in an *increase* in 28-day mortality and a higher incidence of

arrhythmic events. Dopamine should only be used as an alternative to norepinephrine in select patients with septic shock, including patients with significant bradycardia or low potential for tachyarrhythmias.

Vasopressin (antiuretic hormone or ADH) is often used as an adjunctive therapy to catecholamine vasopressors in the treatment of distributive shock. Vasopressin causes peripheral vasoconstriction via V1 receptors located on smooth muscle cells. Vasopressin also potentiates the effects of catecholamines on the vasculature and stimulates cortisol production. Intravenous infusion of vasopressin at a low dose (0.01–0.04 unit/min) as a second agent to norepinephrine has been beneficial in septic patients with hypotension refractory to fluid resuscitation and conventional catecholamine vasopressors. Higher doses of vasopressin decrease cardiac output and may put patients at greater risk for splanchnic and coronary artery ischemia. Studies do not favor the use of vasopressin as first-line therapy.

Angiotensin II, a component of the renin-angiotensin-aldosterone system axis, is a potent direct vasoconstrictor that acts on the arteries and veins to increase blood pressure. Angiotensin II (marketed as Giapreza) can be considered as an *additional agent* in vasodilatory shock that is refractory to catecholamines and vasopressin. The recommended starting dose is 20 ng/kg/min via continuous intravenous infusion through a central venous line. It can be titrated every 5 minutes by increments of up to 15 ng/kg/min as needed to achieve MAP goals, but not to exceed 80 ng/kg/min during the first 3 hours of use. Maintenance doses should not exceed 40 ng/kg/min. Concurrent venous thromboembolism (VTE) prophylaxis is indicated as studies revealed a higher incidence of VTE with angiotensin II use.

B. CARDIOGENIC SHOCK—Given meta-analyses documenting decreased mortality, expert opinion suggests norepinephrine be the first-line vasopressor for cardiogenic shock. Dobutamine, a predominantly beta-adrenergic agonist, increases contractility and decreases afterload. It is used for patients with low cardiac output and high PCWP but who do not have hypotension. Dobutamine can be added to a vasopressor if there is reduced myocardial function (decreased cardiac output and elevated PCWP), or if there are signs of hypoperfusion despite adequate volume resuscitation and an adequate MAP. The initial dose is 0.1–0.5 mcg/kg/min intravenous infusion, which can be titrated every few minutes to hemodynamic effect; the usual dosage range is 2–20 mcg/kg/min intravenously. Tachyphylaxis can occur after 48 hours secondary to the down-regulation of beta-adrenergic receptors. Amrinone and milrinone are phosphodiesterase inhibitors that can be substituted for dobutamine. These drugs increase cyclic AMP levels and increase cardiac contractility, bypassing the beta-adrenergic receptor. Vasodilation is a side effect of both amrinone and milrinone.

2. Antibiotics—Definitive therapy for septic shock includes early initiation of empiric broad-spectrum antibiotics after appropriate cultures have been obtained and within 1 hour of recognition of septic shock. Imaging studies may prove useful to attempt localization of sources of infection.

Surgical management may also be necessary if necrotic tissue or loculated infections are present in attempts to control the source of infection (see Table 30–5).

3. Corticosteroids—Corticosteroids are the treatment of choice in patients with shock secondary to adrenal insufficiency, defined as a cortisol response of 9 mcg/dL or less after one injection of 250 mcg of corticotropin. Studies supporting corticosteroid use in patients with shock from sepsis or other etiologies are mixed. Trials where either high or low doses of corticosteroids were administered to patients in septic shock did not consistently show improved survival. The ADRENAL study demonstrated shorter time to shock resolution (3 days vs 4 days) but no difference in 90-day mortality. The APROCCHSS study demonstrated lower 90-day all-cause mortality, except for those receiving hydrocortisone plus fludrocortisone. Notably, some worse outcomes were observed from increased rates of secondary infections. Corticosteroids can be administered in refractory shock to decrease shock duration; the current recommended regimen is hydrocortisone 50 mg intravenously every 6 hours for 5–7 days.

F. Other Treatment Modalities

Cardiac failure may require use of transcutaneous or transvenous pacing or placement of an intra-arterial balloon pump or left ventricular assist device. Emergent revascularization by percutaneous angioplasty or coronary artery

bypass surgery appears to improve long-term outcome with increased survival compared with initial medical stabilization for patients with myocardial ischemia leading to cardiogenic shock (see Chapter 10). Urgent renal replacement therapy may be indicated for maintenance of fluid and electrolyte balance during acute kidney injury resulting in shock from multiple modalities.

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13

Blood Disorders

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ANEMIAS

► General Approach to Anemias

Anemia is present in adults if the hematocrit is below 41% (hemoglobin less than 13.6 g/dL [135 g/L]) in males or below 36% (hemoglobin less than 12 g/dL [120 g/L]) in females. Congenital anemia is suggested by the patient's personal and family history. The most common cause of anemia is iron deficiency. Poor diet may result in folic acid deficiency and contribute to iron deficiency, but bleeding is the most common cause of iron deficiency in adults. Physical examination demonstrates pallor. Attention to physical signs of primary hematologic diseases (lymphadenopathy; hepatosplenomegaly; or bone tenderness, especially in the sternum or anterior tibia) is important. Mucosal changes such as a smooth tongue suggest megaloblastic anemia.

Anemias are classified according to their pathophysiologic basis, ie, whether related to diminished production (relative or absolute reticulocytopenia) or to increased production due to accelerated loss of red blood cells (reticulocytosis) (Table 13–1), and according to red blood cell size (Table 13–2). A reticulocytosis occurs in one of three pathophysiologic states: acute blood loss, recent replacement of a missing erythropoietic nutrient, or reduced red blood cell survival (ie, hemolysis). A severely microcytic anemia (mean corpuscular volume [MCV] less than 70 fL) is due either to iron deficiency or thalassemia, while a severely macrocytic anemia (MCV greater than 120 fL) is almost always due to either megaloblastic anemia or to cold agglutinins in blood analyzed at room temperature. A bone marrow biopsy is generally needed to complete the evaluation of anemia when the blood laboratory evaluation fails to reveal an etiology, when there are additional cytopenias present, or when an underlying primary or secondary bone marrow process is suspected.

IRON DEFICIENCY ANEMIA



ESSENTIALS OF DIAGNOSIS

- Iron deficiency: serum ferritin is < 12 ng/mL (27 pmol/L) or < 30 ng/mL (67 pmol/L) if also anemic.

- Caused by bleeding unless proved otherwise.
- Responds to iron therapy.

► General Considerations

Iron deficiency is the most common cause of anemia worldwide. The causes are listed in Table 13–3. Aside from circulating red blood cells, the major location of iron in the body is the storage pool as ferritin or as hemosiderin in macrophages.

The average American diet contains 10–15 mg of iron per day. About 10% of this amount is absorbed in the stomach, duodenum, and upper jejunum under acidic conditions. Dietary iron present as heme is efficiently absorbed (10–20%) but nonheme iron less so (1–5%), largely because of interference by phosphates, tannins, and other food constituents. The major iron transporter from the diet across the intestinal lumen is ferroportin, which also facilitates the transport of iron to apotransferrin in macrophages for delivery to erythroid progenitor cells in the bone marrow prepared to synthesize hemoglobin. Hepcidin, which is increasingly produced during inflammation, negatively regulates iron transport by promoting the degradation of ferroportin. Small amounts of iron—approximately 1 mg/day—are normally lost through exfoliation of skin and gastrointestinal mucosal cells.

Menstrual blood loss plays a major role in iron metabolism. The average monthly menstrual blood loss is approximately 50 mL but may be five times greater in some individuals. Women with heavy menstrual losses must absorb 3–4 mg of iron from the diet each day to maintain adequate iron stores, which is not commonly achieved. Women with menorrhagia of this degree will almost always become iron deficient without iron supplementation.

In general, iron metabolism is balanced between absorption of 1 mg/day and loss of 1 mg/day. Pregnancy and lactation upset the iron balance, since requirements increase to 2–5 mg of iron per day. Normal dietary iron cannot supply these requirements, and medicinal iron is needed during pregnancy and lactation. Decreased iron absorption can also cause iron deficiency, such as in people affected by celiac disease (gluten enteropathy), and it also commonly occurs after gastric resection or jejunal bypass surgery.

Table 13–1. Classification of anemia by red blood cell (RBC) pathophysiology.

Decreased RBC production (relative or absolute reticulocytopenia)
Hemoglobin synthesis lesion: iron deficiency, thalassemia, anemia of chronic disease, hypothyroidism
DNA synthesis lesion: megaloblastic anemia, folic acid deficiency, DNA synthesis inhibitor medications
Hematopoietic stem cell lesion: aplastic anemia, leukemia
Bone marrow infiltration: carcinoma, lymphoma, fibrosis, sarcoidosis, Gaucher disease, others
Immune-mediated inhibition: aplastic anemia, pure red cell aplasia
Increased RBC destruction or accelerated RBC loss (reticulocytosis)
Acute blood loss
Hemolysis (intrinsic)
Membrane lesion: hereditary spherocytosis, elliptocytosis
Hemoglobin lesion: sickle cell, unstable hemoglobin
Glycolysis lesion: pyruvate kinase deficiency
Oxidation lesion: glucose-6-phosphate dehydrogenase deficiency
Hemolysis (extrinsic)
Immune: warm antibody, cold antibody
Microangiopathic: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, mechanical cardiac valve, paravalvular leak
Infection: <i>Clostridium perfringens</i> , malaria
Hypersplenism

The most important cause of iron deficiency anemia in adults is chronic blood loss, especially menstrual and gastrointestinal blood loss. Iron deficiency demands a search for a source of gastrointestinal bleeding if other sites of blood loss

Table 13–2. Classification of anemia by mean red blood cell volume (MCV).

Microcytic
Iron deficiency
Thalassemia
Anemia of chronic disease
Lead toxicity
Zinc deficiency
Macrocytic (Megaloblastic)
Vitamin B ₁₂ deficiency
Folate deficiency
DNA synthesis inhibitors
Macrocytic (Nonmegaloblastic)
Aplastic anemia
Myelodysplasia
Liver disease
Reticulocytosis
Hypothyroidism
Bone marrow failure state (eg, aplastic anemia, marrow infiltrative disorder, etc)
Copper deficiency
Normocytic
Kidney disease
Non-thyroid endocrine gland failure
Copper deficiency
Mild form of most acquired microcytic or macrocytic etiologies of anemia

Table 13–3. Causes of iron deficiency.

Deficient diet
Decreased absorption
Autoimmune gastritis
Celiac disease
<i>Helicobacter pylori</i> gastritis
Hereditary iron-refractory iron deficiency anemia
Zinc deficiency
Increased requirements
Pregnancy
Lactation
Blood loss (chronic)
Gastrointestinal
Menstrual
Blood donation
Hemoglobinuria
Iron sequestration
Pulmonary hemosiderosis
Idiopathic

(menorrhagia, other uterine bleeding, and repeated blood donations) are excluded. Prolonged aspirin or nonsteroidal anti-inflammatory drug use may cause it even without a documented structural lesion. Celiac disease, even when asymptomatic, can cause iron deficiency through poor absorption in the gastrointestinal tract. Zinc deficiency is another cause of poor iron absorption. Chronic hemoglobinuria may lead to iron deficiency, but this is uncommon. Traumatic hemolysis due to a prosthetic cardiac valve and other causes of intravascular hemolysis (eg, paroxysmal nocturnal hemoglobinuria) should also be considered. The cause of iron deficiency is not found in up to 5% of cases.

Pure iron deficiency might prove refractory to oral iron replacement. Refractoriness is defined as a hemoglobin increment of less than 1 g/dL (10 g/L) after 4–6 weeks of 100 mg/day of elemental oral iron. The differential diagnosis in these cases (Table 13–3) includes malabsorption from autoimmune gastritis, *Helicobacter pylori* gastric infection, celiac disease, and hereditary iron-refractory iron deficiency anemia. Iron-refractory iron deficiency anemia is a rare autosomal recessive disorder due to mutations in the transmembrane serine protease 6 (*TMPRSS6*) gene, which normally down-regulates hepcidin. In iron-refractory iron deficiency anemia, hepcidin levels are normal to high and ferritin levels are high despite the iron deficiency.

► Clinical Findings

A. Symptoms and Signs

The primary symptoms of iron deficiency anemia are those of the anemia itself (easy fatigability, tachycardia, palpitations, and dyspnea on exertion). Severe deficiency causes skin and mucosal changes, including a smooth tongue, brittle nails, spooning of nails (koilonychia), and cheilosis. Dysphagia due to the formation of esophageal webs (Plummer-Vinson syndrome) may occur in severe iron deficiency. Many iron-deficient patients develop pica, craving for specific foods (ice chips, etc) often not rich in iron.

B. Laboratory Findings

Iron deficiency develops in stages. The first is depletion of iron stores without anemia followed by anemia with a normal red blood cell size (normal MCV) followed by anemia with reduced red blood cell size (low MCV). The reticulocyte count is low or inappropriately normal. Ferritin is a measure of total body iron stores. A ferritin value less than 12 ng/mL (27 pmol/L) (in the absence of scurvy) is a highly reliable indicator of reduced iron stores. Note that the lower limit of normal for ferritin is often below 12 ng/mL (27 pmol/L) in women due to the fact that the normal ferritin range is generated by including healthy menstruating women who are iron deficient but not anemic. However, because serum ferritin levels may rise in response to inflammation or other stimuli, a normal or elevated ferritin level does not exclude a diagnosis of iron deficiency. A ferritin level less than 30 ng/mL (67 pmol/L) almost always indicates iron deficiency in anyone who is anemic. As iron deficiency progresses, serum iron values decline to less than 30 mcg/dL (67 pmol/L) and transferrin (the iron transport protein) levels rise to compensate, leading to transferrin saturations of less than 15%. Low transferrin saturation is also seen in anemia of inflammation, so caution in the interpretation of this test is warranted. Isolated iron deficiency anemia has a low hepcidin level, not yet a clinically available test. As the MCV falls (ie, microcytosis), the blood smear shows hypochromic microcytic cells. With further progression, anisocytosis (variations in red blood cell size) and poikilocytosis (variation in shape of red cells) develop. Severe iron deficiency will produce a bizarre peripheral blood smear, with severely hypochromic cells, target cells, and pencil-shaped or cigar-shaped cells. Bone marrow biopsy for evaluation of iron stores is rarely performed. If the biopsy is done, it shows the absence of iron in erythroid progenitor cells by Prussian blue staining. The platelet count is commonly increased, but it usually remains under 800,000/mcL ($800 \times 10^9/\text{L}$).

Differential Diagnosis

Other causes of microcytic anemia include anemia of chronic disease (specifically, anemia of inflammation), thalassemia, lead poisoning, zinc deficiency, and congenital X-linked sideroblastic anemia. Anemia of chronic disease is characterized by normal or increased iron stores in bone marrow macrophages and a normal or elevated ferritin level; the serum iron and transferrin saturation are low, often drastically so, and the total iron-binding capacity (TIBC) (the blood's capacity for iron to bind to transferrin) and transferrin are either normal or low. Thalassemia produces a greater degree of microcytosis for any given level of anemia than does iron deficiency and, unlike virtually every other cause of anemia, has a normal or elevated (rather than a low) red blood cell count as well as a reticulocytosis. In thalassemia, red blood cell morphology on the peripheral smear resembles severe iron deficiency.

Treatment

The diagnosis of iron deficiency anemia can be made either by the laboratory demonstration of an iron-deficient state or by evaluating the response to a therapeutic trial of iron

replacement. Since the anemia itself is rarely life-threatening, the most important part of management is identification of the cause—especially a source of occult blood loss.

A. Oral Iron

Ferrous sulfate, 325 mg once daily or every other day on an empty stomach, is a standard approach for replenishing iron stores. As oral iron stimulates hepcidin production, once daily or every other day dosing maximizes iron absorption compared to multiple doses per day, and with fewer side effects. Nausea and constipation limit compliance with ferrous sulfate. Extended-release ferrous sulfate with mucoprotease is a well-tolerated oral preparation. Taking ferrous sulfate with food reduces side effects but also its absorption. An appropriate response to oral iron is a return of the hematocrit level halfway toward normal within 3 weeks with full return to baseline after 2 months. Iron therapy should continue for 3–6 months after restoration of normal hematologic values to replenish iron stores. Failure of response to iron therapy is usually due to non-compliance, although occasional patients may absorb iron poorly, particularly if the stomach is achlorhydric. Such patients may benefit from concomitant administration of oral ascorbic acid. Other reasons for failure to respond include incorrect diagnosis (anemia of chronic disease, thalassemia), celiac disease, and ongoing blood loss that exceeds the rate of new erythropoiesis. Treatment of *H pylori* infection, in appropriate cases, can improve oral iron absorption.

B. Parenteral Iron

The indications are intolerance of or refractoriness to oral iron (including those with iron-refractory iron deficiency anemia), gastrointestinal disease (usually inflammatory bowel disease) precluding the use of oral iron, and continued blood loss that cannot be corrected, such as chronic hemodialysis. Historical parenteral iron preparations, such as high-molecular-weight iron dextran, were problematic due to long infusion times (hours), polyarthralgia, and hypersensitivity reactions, including anaphylaxis. Current parenteral iron preparations coat the iron in protective carbohydrate shells or contain low-molecular-weight iron dextran, are safe, and can be administered over 15 minutes to 1 hour. Most iron deficient patients need 1–1.5 g of parenteral iron; this dose corrects for the iron deficit and replenishes iron stores for the future.

Ferric pyrophosphate citrate (Triferic) is an FDA-approved additive to the dialysate designed to replace the 5–7 mg of iron that patients with chronic kidney disease tend to lose during each hemodialysis treatment. Ferric pyrophosphate citrate delivers sufficient iron to the marrow to maintain hemoglobin and not increase iron stores; it may obviate the need for intravenous iron in hemodialysis patients.

When to Refer

Patients should be referred to a hematologist if the suspected diagnosis is not confirmed or if they are not responsive to oral iron therapy.

- Camaschella C. Iron deficiency. *Blood*. 2019;133:30. [PMID: 30401704]
 Cappellini MD et al. Iron deficiency anaemia revisited. *J Intern Med*. 2020;287:153. [PMID: 31665543]
 Powers JM et al. Disorders of iron metabolism: new diagnostic and treatment approaches to iron deficiency. *Hematol Oncol Clin North Am*. 2019;33:393. [PMID: 31030809]

ANEMIA OF CHRONIC DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Mild or moderate normocytic or microcytic anemia.
- ▶ Normal or increased ferritin and normal or reduced transferrin.
- ▶ Underlying chronic disease.

General Considerations

Many chronic systemic diseases are associated with mild or moderate anemia. The anemias of chronic disease are characterized according to etiology and pathophysiology. First, the **anemia of inflammation** is associated with chronic inflammatory states (such as inflammatory bowel disease, rheumatologic disorders, chronic infections, and malignancy) and is mediated through hepcidin (a negative regulator of ferroportin) primarily via elevated IL-6, resulting in reduced iron uptake in the gut and reduced iron transfer from macrophages to erythroid progenitor cells in the bone marrow. This is referred to as iron-restricted erythropoiesis since the patient is iron replete. There is also reduced responsiveness to erythropoietin, the elaboration of hemolysins that shorten red blood cell survival, and the production of other inflammatory cytokines that dampen red cell production. The serum iron is low in the anemia of inflammation. Second, the **anemia of organ failure** can occur with kidney disease, liver failure, and endocrine gland failure. Erythropoietin is reduced and the red blood cell mass decreases in response to the diminished signal for red blood cell production; the serum iron is normal (except in chronic kidney disease where it is low due to the reduced hepcidin clearance and subsequent enhanced degradation of ferroportin). Third, the **anemia of older adults** is present in up to 20% of individuals over age 85 years in whom a thorough evaluation for an explanation of anemia is negative. The anemia is a consequence of (1) a relative resistance to red blood cell production in response to erythropoietin, (2) a decrease in erythropoietin production relative to the nephron mass, (3) a negative erythropoietic influence of higher levels of chronic inflammatory cytokines in older adults, and (4) the presence of various somatic mutations in myeloid genes typically associated with myeloid neoplasms. The latter condition is now referred to as **clonal cytopenias of undetermined significance**, which has a 1–1.5% per year rate of transformation to a myeloid neoplasm, such as a myelodysplastic syndrome (MDS). The serum iron is normal.

Clinical Findings

A. Symptoms and Signs

The clinical features are those of the causative condition. The diagnosis should be suspected in patients with known chronic diseases. In cases of significant anemia, coexistent iron deficiency or folic acid deficiency should be suspected. Decreased dietary intake of iron or folic acid is common in chronically ill patients, many of whom will also have ongoing gastrointestinal blood losses. Patients undergoing hemodialysis regularly lose both iron and folic acid during dialysis.

B. Laboratory Findings

The hematocrit rarely falls below 60% of baseline (except in kidney failure). The MCV is usually normal or slightly reduced. Red blood cell morphology is usually normal, and the reticulocyte count is mildly decreased or normal.

1. Anemia of inflammation—In the anemia of inflammation, serum iron and transferrin values are low, and the transferrin saturation may be extremely low, leading to an erroneous diagnosis of iron deficiency. In contrast to iron deficiency, serum ferritin values should be normal or increased. A serum ferritin value less than 30 ng/mL (67 pmol/L) indicates coexistent iron deficiency. Anemia of inflammation has elevated hepcidin levels; however, no clinical test is yet available. A particular challenge is the diagnosis of iron deficiency in the setting of the anemia of inflammation, in which the serum ferritin can be as high as 200 ng/mL (450 pmol/L). The diagnosis is established by a bone marrow biopsy with iron stain. Absent iron staining indicates iron deficiency, whereas iron localized in marrow macrophages indicates pure anemia of inflammation. However, bone marrow biopsies are rarely done for this purpose. Two other tests all support iron deficiency in the setting of inflammation: a reticulocyte hemoglobin concentration of less than 28 pg or a soluble serum transferrin receptor (units: mg/L) to log ferritin (units: mcg/L) ratio of 1–8 (a ratio of less than 1 is virtually diagnostic of pure anemia of chronic disease). A functional test is hemoglobin response to oral or parenteral iron in the setting of inflammation when iron deficiency is suspected. A note of caution: certain circumstances of iron-restricted erythropoiesis (such as malignancy) will partially respond to parenteral iron infusion even when the iron stores are replete due to the immediate distribution of iron to erythropoietic progenitor cells after the infusion.

2. Other anemias of chronic disease—In the anemias of organ failure and of older adults, the iron studies are generally normal. The anemia of older persons is a diagnosis of exclusion. Clonal cytopenias of undetermined significance are diagnosed by sending a blood sample for myeloid gene sequencing.

Treatment

In most cases, no treatment of the anemia of chronic disease is necessary and the primary management is to address the condition causing the anemia. When the anemia is

severe or is adversely affecting the quality of life or functional status, then treatment involves either red blood cell transfusions or parenteral recombinant erythropoietin (epoetin alfa or darbepoetin). The FDA-approved indications for recombinant erythropoietin are hemoglobin less than 10 g/dL and anemia due to rheumatoid arthritis, inflammatory bowel disease, hepatitis C, zidovudine therapy in HIV-infected patients, myelosuppressive chemotherapy of solid malignancy (treated with palliative intent only), or chronic kidney disease (estimated glomerular filtration rate of less than 60 mL/min). The dosing and schedule of recombinant erythropoietin are individualized to maintain the hemoglobin between 10 g/dL (100 g/L) and 12 g/dL (120 g/L). The use of recombinant erythropoietin is associated with an increased risk of venothromboembolism and arterial thrombotic episodes, especially if the hemoglobin rises to greater than 12 g/dL (120 g/L). There is concern that recombinant erythropoietin is associated with reduced survival in patients with malignancy. For patients with end-stage renal disease receiving recombinant erythropoietin who are on hemodialysis, the anemia of chronic kidney disease can be more effectively corrected by adding soluble ferric pyrophosphate to their dialysate than by administering intravenous iron supplementation.

► When to Refer

Referral to a hematologist is not usually necessary.

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THE THALASSEMIAS



ESSENTIALS OF DIAGNOSIS

- ▶ Microcytosis disproportionate to the degree of anemia.
- ▶ Positive family history.
- ▶ Lifelong personal history of microcytic anemia.
- ▶ Normal or elevated red blood cell count.
- ▶ Abnormal red blood cell morphology with microcytes, hypochromia, acanthocytes, and target cells.
- ▶ In beta-thalassemia, elevated levels of hemoglobin A₂ and F.

► General Considerations

The thalassemias are hereditary disorders characterized by reduction in the synthesis of globin chains (alpha or beta).

Reduced globin chain synthesis causes reduced hemoglobin synthesis and a hypochromic microcytic anemia because of defective hemoglobinization of red blood cells. Thalassemias can be considered among the hyperproliferative hemolytic anemias, the anemias related to abnormal hemoglobin, and the hypoproliferative anemias, since all of these factors play a role in pathogenesis. The hallmark laboratory features are small (low MCV) and pale (low mean corpuscular hemoglobin [MCH]) red blood cells, anemia, and a normal to elevated red blood cell count (ie, a large number of the small and pale red blood cells are being produced). Although patients often exhibit an elevated reticulocyte count, generally the degree of reticulocyte output is inadequate to meet the degree of red blood cell destruction (hemolysis) occurring in the bone marrow and the patients remain anemic.

Normal adult hemoglobin is primarily hemoglobin A, which represents approximately 98% of circulating hemoglobin. Hemoglobin A is formed from a tetramer of two alpha-globin chains and two beta-globin chains—and is designated alpha₂beta₂. Two copies of the alpha-globin gene are located on each chromosome 16, and there is no substitute for alpha-globin in the formation of adult hemoglobin. One copy of the beta-globin gene resides on each chromosome 11 adjacent to genes encoding the beta-like globins delta and gamma (the so-called beta-globin gene cluster region). The tetramer of alpha₂delta₂ forms hemoglobin A₂, which normally composes 1–3% of adult hemoglobin. The tetramer alpha₂gamma₂ forms hemoglobin F, which is the major hemoglobin of fetal life but which composes less than 1% of normal adult hemoglobin.

The thalassemias are described as **thalassemia trait** when there are laboratory features without significant clinical impact, **thalassemia intermedia** when there is an occasional red blood cell transfusion requirement or other moderate clinical impact, and **thalassemia major** when the disorder is life-threatening and the patient is transfusion-dependent. Most patients with thalassemia major die of the consequences of iron overload from red blood cell transfusions.

Alpha-thalassemia is due primarily to gene deletions causing reduced alpha-globin chain synthesis (Table 13–4).

Table 13–4. Alpha-thalassemia syndromes.

Number of Alpha-Globin Genes Transcribed	Syndrome	Hematocrit	MCV
4	Normal	Normal	Normal
3	Silent carrier	Normal	Normal
2	Thalassemia minor (or trait)	28–40%	60–75 fL
1	Hemoglobin H disease	22–32%	60–70 fL
0	Hydrops fetalis ¹	< 18%	< 60 fL

¹Die in utero.

MCV, mean corpuscular volume.

Table 13–5. Beta-thalassemia syndromes.

	Beta-Globin Genes Transcribed	Hb A	Hb A ₂	Hb F	Transfusions
Normal	Homozygous beta	97–99%	1–3%	< 1%	None
Thalassemia minor	Heterozygous beta ⁰	80–95%	4–8%	1–5%	None
	Heterozygous beta ⁺	80–95%	4–8%	1–5%	None
Thalassemia intermedia	Homozygous beta ⁺ (mild)	0–30%	4–8%	6–10%	Occasional
Thalassemia major	Homozygous beta ⁰	0%	4–10%	90–96%	Dependent
	Homozygous beta ⁺ (severe)	0–10%	4–10%	90–96%	Dependent

Hb, hemoglobin; beta⁰, no beta-globin produced; beta⁺, some beta-globin produced.

Each alpha-globin gene produces one-quarter of the total alpha-globin quantity, so there is a predictable proportionate decrease in alpha-globin output with each lost alpha-globin gene. Since all adult hemoglobins are alpha containing, alpha-thalassemia produces no change in the proportions of hemoglobins A, A₂, and F on hemoglobin electrophoresis. In severe forms of alpha-thalassemia, excess beta chains may form a beta-4 tetramer called hemoglobin H. In the presence of reduced alpha chains, the excess beta chains are unstable and precipitate, leading to damage of red blood cell membranes. This leads to both intramedullary (bone marrow) and peripheral blood hemolysis.

Beta-thalassemias are usually caused by point mutations rather than deletions (Table 13–5). These mutations result in premature chain termination or in problems with transcription of RNA and ultimately result in reduced or absent beta-globin chain synthesis. The molecular defects leading to beta-thalassemia are numerous and heterogeneous. Defects that result in absent beta-globin chain expression are termed beta⁰, whereas those causing reduced but not absent synthesis are termed beta⁺. In beta⁺ thalassemia, the degree of reduction of beta-globin synthesis is consistent within families but is quite variable between families. The reduced beta-globin chain synthesis in beta-thalassemia results in a relative increase in the proportions of hemoglobins A₂ and F compared to hemoglobin A on hemoglobin electrophoresis, as the beta-like globins (delta and gamma) substitute for the missing beta chains. In the presence of reduced beta chains, the excess alpha chains are unstable and precipitate, leading to damage of red blood cell membranes. This leads to both intramedullary (bone marrow) and peripheral blood hemolysis. The bone marrow demonstrates erythroid hyperplasia under the stimuli of anemia and ineffective erythropoiesis (intramedullary destruction of the developing erythroid cells). In cases of severe thalassemia, the marked expansion of the erythroid compartment in the bone marrow may cause severe bony deformities, osteopenia, and pathologic bone fractures.

Clinical Findings

A. Symptoms and Signs

The **alpha-thalassemia** syndromes are seen primarily in persons from southeast Asia and China and, less commonly, in Blacks and persons of Mediterranean origin

(Table 13–4). Normally, adults have four copies of the alpha-globin chain. When three alpha-globin genes are present, the patient is hematologically normal (silent carrier). When two alpha-globin genes are present, the patient is said to have **alpha-thalassemia trait**, a form of thalassemia minor. In alpha-thalassemia-1 trait, the alpha gene deletion is heterozygous (alpha⁻/alpha⁻) and affects mainly those of Asian descent. In alpha-thalassemia-2 trait, the alpha gene deletion is homozygous (alpha⁻/alpha⁻) and affects mainly Blacks. These patients are clinically normal and have a normal life expectancy and performance status, with a mild microcytic anemia. When only one alpha globin chain is present (alpha^{-/-}), the patient has **hemoglobin H disease** (alpha-thalassemia-3). This is a chronic hemolytic anemia of variable severity (thalassemia minor or intermedia). Physical examination might reveal pallor and splenomegaly. Affected individuals usually do not need transfusions; however, they may be required during transient periods of hemolytic exacerbation caused by infection or other stressors or during periods of erythropoietic shutdown caused by certain viruses (“aplastic crisis”). When all four alpha-globin genes are deleted, no normal hemoglobin is produced and the affected fetus is stillborn (**hydrops fetalis**). In hydrops fetalis, the only hemoglobin species made is gamma and is called hemoglobin Bart’s (gamma4).

Beta-thalassemia primarily affects persons of Mediterranean origin (Italian, Greek) and to a lesser extent Asians and Blacks (Table 13–5). Patients homozygous for beta-thalassemia (beta^{0/beta⁰ or some with beta^{+/beta⁺) have **beta-thalassemia major** (Cooley anemia). Affected children are normal at birth, but after 6 months, when hemoglobin synthesis switches from hemoglobin F to hemoglobin A, severe anemia develops that requires transfusion. Numerous clinical problems ensue, including stunted growth, bony deformities (abnormal facial structure, pathologic bone fractures), hepatosplenomegaly, jaundice (due to gallstones, hepatitis-related cirrhosis, or both), and thrombophilia. The clinical course is modified significantly by transfusion therapy, but transfusional iron overload (hemochromatosis) results in a clinical picture similar to hemochromatosis, with heart failure, cardiac arrhythmias, cirrhosis, endocrinopathies, and pseudoxanthoma elasticum (calcification and fragmentation of the elastic fibers of the skin, retina, and cardiovascular system), usually after more than 100 units of red blood cells have been}}

transfused. Iron overloading occurs because the human body has no active iron excretory mechanism. Before the application of allogeneic stem cell transplantation and the development of more effective forms of iron chelation, death from iron overload usually occurred between the ages of 20 and 30 years.

Patients homozygous for a milder form of beta-thalassemia (β^+/β^+ , but allowing a higher rate of beta-globin synthesis) have **beta-thalassemia intermedia**. These patients have chronic hemolytic anemia but do not require transfusions except under periods of stress or during aplastic crises. They also may develop iron overload because of periodic transfusion. They survive into adult life but with hepatosplenomegaly and bony deformities. Patients heterozygous for beta-thalassemia (β/β^0 or β/β^+) have **beta-thalassemia minor** and a clinically insignificant microcytic anemia.

Prenatal diagnosis is available, and genetic counseling should be offered and the opportunity for prenatal diagnosis discussed.

B. Laboratory Findings

1. Alpha-thalassemia trait—These patients have mild or no anemia, with hematocrits between 28% and 40%. The MCV is strikingly low (60–75 fL) despite the modest anemia, and the red blood count is normal or increased. The peripheral blood smear shows microcytes, hypochromia, occasional target cells, and acanthocytes (cells with irregularly spaced spiked projections). The reticulocyte count and iron parameters are normal. Hemoglobin electrophoresis is normal. Alpha-thalassemia trait is thus usually diagnosed by exclusion. Genetic testing to demonstrate alpha-globin gene deletion is available.

2. Hemoglobin H disease—These patients have a more marked anemia, with hematocrits between 22% and 32%. The MCV is remarkably low (60–70 fL) and the peripheral blood smear is markedly abnormal, with hypochromia, microcytosis, target cells, and poikilocytosis. The reticulocyte count is elevated and the red blood cell count is normal or elevated. Hemoglobin electrophoresis will show a fast-migrating hemoglobin (hemoglobin H), which comprises 10–40% of the hemoglobin. A peripheral blood smear can be stained with supravital dyes to demonstrate the presence of hemoglobin H.

3. Beta-thalassemia minor—These patients have a modest anemia with hematocrit between 28% and 40%. The MCV ranges from 55 fL to 75 fL, and the red blood cell count is normal or increased. The reticulocyte count is normal or slightly elevated. The peripheral blood smear is mildly abnormal, with hypochromia, microcytosis, and target cells. In contrast to alpha-thalassemia, basophilic stippling is present. Hemoglobin electrophoresis shows an elevation of hemoglobin A_2 to 4–8% and occasional elevations of hemoglobin F to 1–5%.

4. Beta-thalassemia intermedia—These patients have a moderate anemia with hematocrit between 17% and 33%. The MCV ranges from 55 fL to 75 fL, and the red blood cell count is normal or increased. The reticulocyte count is

elevated. The peripheral blood smear is abnormal with hypochromia, microcytosis, basophilic stippling, and target cells. Hemoglobin electrophoresis shows up to 30% hemoglobin A, an elevation of hemoglobin A_2 up to 10%, and elevation of hemoglobin F from 6% to 10%.

5. Beta-thalassemia major—These patients have severe anemia, and without transfusion the hematocrit may fall to less than 10%. The peripheral blood smear is bizarre, showing severe poikilocytosis, hypochromia, microcytosis, target cells, basophilic stippling, and nucleated red blood cells. Little or no hemoglobin A is present. Variable amounts of hemoglobin A_2 are seen, and the predominant hemoglobin present is hemoglobin F.

Differential Diagnosis

Mild forms of thalassemia must be differentiated from iron deficiency. Compared to iron deficiency anemia, patients with thalassemia have a lower MCV, a normal or elevated red blood cell count (rather than low), a more abnormal peripheral blood smear at modest levels of anemia, and usually a reticulocytosis. Iron studies are normal or the transferrin saturation or ferritin (or both) are elevated. Severe forms of thalassemia may be confused with other hemoglobinopathies. The diagnosis of beta-thalassemia is made by the above findings and hemoglobin electrophoresis showing elevated levels of hemoglobins A_2 and F (provided the patient is replete in iron), or beta-gene sequencing. The diagnosis of alpha-thalassemia is made by exclusion since there is no change in the proportion of the normal adult hemoglobin species or confirmed by alpha gene deletion studies. The only other microcytic anemia with a normal or elevated red blood cell count is iron deficiency in a patient with polycythemia vera.

Treatment

Patients with mild thalassemia (alpha-thalassemia trait or beta-thalassemia minor) require no treatment and should be identified so that they will not be subjected to repeated evaluations and treatment for iron deficiency. Patients with hemoglobin H disease should take folic acid supplementation (1 mg/day orally) and avoid medicinal iron and oxidative drugs such as sulfonamides. Patients with severe thalassemia are maintained on a regular transfusion schedule (in part to suppress endogenous erythropoiesis and therefore bone marrow expansion) and receive folic acid supplementation. Splenectomy is performed if hypersplenism causes a marked increase in the transfusion requirement or refractory symptoms. Patients with regular transfusion requirements should be treated with iron chelation (oral or parenteral) in order to prevent or delay life-limiting organ damage from iron overload. A new agent, luspatercept, has been FDA approved for transfusion-dependent beta-thalassemia. It is a TGF-beta ligand trap that promotes erythroid maturation and reduces transfusion needs.

Allogeneic stem cell transplantation is the treatment of choice for beta-thalassemia major and the only available cure. Children who have not yet experienced organ damage from iron overload do well, with long-term survival in more than 80% of cases. Autologous gene therapy is showing promise for thalassemia major.

► When to Refer

All patients with thalassemia intermedia or major should be referred to a hematologist. Any patient with an unexplained microcytic anemia should be referred to help establish a diagnosis. Patients with thalassemia minor or intermedia should be offered genetic counseling because offspring of thalassemic couples are at risk for inheriting thalassemia major.

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VITAMIN B₁₂ DEFICIENCY



ESSENTIALS OF DIAGNOSIS

- ▶ Macrocytic anemia.
- ▶ Megaloblastic blood smear (macro-ovalocytes and hypersegmented neutrophils).
- ▶ Low serum vitamin B₁₂ level.

► General Considerations

Vitamin B₁₂ belongs to the family of cobalamins and serves as a cofactor for two important reactions in humans. As methylcobalamin, it is a cofactor for methionine synthetase in the conversion of homocysteine to methionine, and as adenosylcobalamin for the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. Vitamin B₁₂ comes from the diet and is present in all foods of animal origin. The daily absorption of vitamin B₁₂ is 5 mcg.

The liver contains 2–5 mg of stored vitamin B₁₂. Since daily utilization is 3–5 mcg, the body usually has sufficient stores of vitamin B₁₂ so that it takes more than 3 years for vitamin B₁₂ deficiency to occur if all intake or absorption immediately ceases.

Since vitamin B₁₂ is present in foods of animal origin, dietary vitamin B₁₂ deficiency is extremely rare but is seen in vegans—strict vegetarians who avoid all dairy products, meat, and fish (Table 13–6). Pernicious anemia is an autoimmune illness whereby autoantibodies destroy gastric parietal cells (that produce intrinsic factor) and cause atrophic gastritis or bind to and neutralize intrinsic factor, or both. Abdominal surgery may lead to vitamin B₁₂ deficiency in several ways. Gastrectomy will eliminate the site of intrinsic factor production; blind loop syndrome will cause competition for vitamin B₁₂ by bacterial overgrowth in the lumen of the intestine; and surgical resection of the

Table 13–6. Causes of vitamin B₁₂ deficiency.

Dietary deficiency
Decreased production or availability of intrinsic factor
Pernicious anemia (autoimmune)
Gastrectomy
<i>Helicobacter pylori</i> infection
Competition for vitamin B ₁₂ in the gut
Blind loop syndrome
Fish tapeworm (rare)
Pancreatic insufficiency
Proton pump inhibitors
Decreased ileal absorption of vitamin B ₁₂
Surgical resection
Crohn disease
Transcobalamin II deficiency (rare)

ileum will eliminate the site of vitamin B₁₂ absorption. Rare causes of vitamin B₁₂ deficiency include fish tapeworm (*Diphyllobothrium latum*) infection, in which the parasite uses luminal vitamin B₁₂; pancreatic insufficiency (with failure to inactivate competing cobalamin-binding proteins [R-factors]); severe Crohn disease, causing sufficient destruction of the ileum to impair vitamin B₁₂ absorption; and perhaps prolonged use of proton pump inhibitors.

► Clinical Findings

A. Symptoms and Signs

Vitamin B₁₂ deficiency causes a moderate to severe anemia of slow onset; patients may have few symptoms relative to the degree of anemia. In advanced cases, the anemia may be severe, with hematocrits as low as 10–15%, and may be accompanied by leukopenia and thrombocytopenia. The deficiency also produces changes in mucosal cells, leading to glossitis, as well as other vague gastrointestinal disturbances such as anorexia and diarrhea. Vitamin B₁₂ deficiency also leads to a complex neurologic syndrome. Peripheral nerves are usually affected first, and patients complain initially of paresthesias. As the posterior columns of the spinal cord become impaired, patients complain of difficulty with balance or proprioception, or both. In more advanced cases, cerebral function may be altered as well, and on occasion dementia and other neuropsychiatric abnormalities may be present. It is critical to recognize that the nonhematologic manifestations of vitamin B₁₂ deficiency can be manifest despite a completely normal complete blood count.

Patients are usually pale and may be mildly icteric or sallow. Typically, later in the disease course, neurologic examination may reveal decreased vibration and position sense or memory disturbance (or both).

B. Laboratory Findings

The diagnosis of vitamin B₁₂ deficiency is made by finding a low serum vitamin B₁₂ (cobalamin) level. Whereas the normal vitamin B₁₂ level is greater than 300 pg/mL (221 pmol/L), most patients with overt vitamin B₁₂ deficiency

have serum levels less than 200 pg/mL (148 pmol/L), with symptomatic patients often having levels less than 100 pg/mL (74 pmol/L). The diagnosis of vitamin B₁₂ deficiency in low or low-normal values (level of 200–300 pg/mL [147.6–221.3 pmol/L]) is best confirmed by finding an elevated level of serum methylmalonic acid or homocysteine. Of note, elevated levels of serum methylmalonic acid can be due to kidney disease.

The anemia of vitamin B₁₂ deficiency is typically moderate to severe with the MCV quite elevated (110–140 fL). However, it is possible to have vitamin B₁₂ deficiency with a normal MCV from coexistent thalassemia or iron deficiency; in other cases, the reason is obscure. Patients with neurologic symptoms and signs that suggest possible vitamin B₁₂ deficiency should be evaluated for that deficiency despite a normal MCV or the absence of anemia. In typical cases, the peripheral blood smear is megaloblastic, defined as red blood cells that appear as macro-ovalocytes, (although other shape changes are usually present) and neutrophils that are hypersegmented (six [or greater]-lobed neutrophils or mean neutrophil lobe counts greater than four). The reticulocyte count is reduced. Because vitamin B₁₂ deficiency can affect all hematopoietic cell lines, the white blood cell count and the platelet count are reduced in severe cases.

Other laboratory abnormalities include elevated serum lactate dehydrogenase (LD) and a modest increase in indirect bilirubin. These two findings reflect the intramedullary destruction of developing abnormal erythroid cells.

Bone marrow morphology is characteristically abnormal. Marked erythroid hyperplasia is present as a response to defective red blood cell production (ineffective erythropoiesis). Megaloblastic changes in the erythroid series include abnormally large cell size and asynchronous maturation of the nucleus and cytoplasm—ie, cytoplasmic maturation continues while impaired DNA synthesis causes retarded nuclear development. In the myeloid series, giant bands and meta-myelocytes are characteristically seen.

Differential Diagnosis

Vitamin B₁₂ deficiency should be differentiated from folic acid deficiency, the other common cause of megaloblastic anemia, in which red blood cell folic acid is low while vitamin B₁₂ levels are normal. The bone marrow findings of vitamin B₁₂ deficiency are sometimes mistaken for a MDS or even acute erythrocytic leukemia. The distinction between vitamin B₁₂ deficiency and myelodysplasia is based on the characteristic morphology and the low vitamin B₁₂ and elevated methylmalonic acid levels.

Treatment

Initially, patients with vitamin B₁₂ deficiency are usually treated with parenteral therapy. Intramuscular or subcutaneous injections of 100–1000 mcg of vitamin B₁₂ are adequate for each dose (with the higher dose recommended initially). Replacement is usually given daily for the first week, weekly for the next month, and then monthly for life. The vitamin deficiency will recur if patients discontinue their therapy. Oral or sublingual methylcobalamin

(1 mg/day) may be used instead of parenteral therapy once initial correction of the deficiency has occurred. Oral or sublingual replacement is effective, even in pernicious anemia, since approximately 1% of the dose is absorbed in the intestine via passive diffusion in the absence of active transport. It must be continued indefinitely and serum vitamin B₁₂ levels must be monitored to ensure adequate replacement. For patients with neurologic symptoms caused by vitamin B₁₂ deficiency, long-term parenteral vitamin B₁₂ therapy is recommended, though its superiority over oral vitamin B₁₂ therapy has not been proven. Because some patients are concurrently folic acid deficient from intestinal mucosal atrophy, simultaneous folic acid replacement (1 mg daily) is advised for the first several months of vitamin B₁₂ replacement.

Patients respond to therapy with an immediate improvement in their sense of well-being. Hypokalemia may complicate the first several days of therapy, particularly if the anemia is severe. A brisk reticulocytosis occurs in 5–7 days, and the hematologic picture normalizes in 2 months. Central nervous system symptoms and signs are potentially reversible if they have been present for less than 6 months. Red blood cell transfusions are rarely needed despite the severity of anemia, but when given, diuretics are also recommended to avoid heart failure because this anemia develops slowly and the plasma volume is increased at the time of diagnosis.

When to Refer

Referral to a hematologist is not usually necessary.

Socha DS et al. Severe megaloblastic anemia: vitamin deficiency and other causes. Cleve Clin J Med. 2020;87:153. [PMID: 32127439]

Wolffenbuttel BHR et al. The many faces of cobalamin (vitamin B₁₂) deficiency. Mayo Clin Proc Innov Qual Outcomes. 2019;3:200. [PMID: 31193945]

FOLIC ACID DEFICIENCY

ESSENTIALS OF DIAGNOSIS

- ▶ Macrocytic anemia.
- ▶ Megaloblastic blood smear (macro-ovalocytes and hypersegmented neutrophils).
- ▶ Reduced folic acid levels in red blood cells or serum.
- ▶ Normal serum vitamin B₁₂ level.

General Considerations

“Folic acid” is the term commonly used for pteroylmonoglutamic acid. Folic acid is present in most fruits and vegetables (especially citrus fruits and green leafy vegetables). Daily dietary requirements are 50–100 mcg. Total body stores of folic acid are approximately 5 mg, enough to supply requirements for 2–3 months.

Table 13–7. Causes of folic acid deficiency.

Dietary deficiency
Decreased absorption
Celiac disease
Medications: phenytoin, sulfasalazine, trimethoprim-sulfamethoxazole
Concurrent vitamin B ₁₂ deficiency
Increased requirement
Chronic hemolytic anemia
Pregnancy
Exfoliative skin disease
Excess loss: hemodialysis
Inhibition of reduction to active form
Methotrexate

The most common cause of folic acid deficiency is inadequate dietary intake (Table 13–7). Alcoholic or anorectic patients, persons who do not eat fresh fruits and vegetables, and those who overcook their food are candidates for folic acid deficiency. Reduced folic acid absorption is rarely seen, since absorption occurs from the entire gastrointestinal tract. However, medications such as phenytoin, trimethoprim-sulfamethoxazole, or sulfasalazine may interfere with its absorption. Folic acid absorption is poor in some patients with vitamin B₁₂ deficiency due to gastrointestinal mucosal atrophy. Folic acid requirements are increased in pregnancy, hemolytic anemia, and exfoliative skin disease, and in these cases the increased requirements (5–10 times normal) may not be met by a normal diet.

► Clinical Findings

A. Symptoms and Signs

The clinical features are similar to those of vitamin B₁₂ deficiency. However, isolated folic acid deficiency does not result in neurologic abnormalities.

B. Laboratory Findings

Megaloblastic anemia is identical to anemia resulting from vitamin B₁₂ deficiency. A red blood cell folic acid level below 150 ng/mL (340 nmol/L) is diagnostic of folic acid deficiency. Whether to order a serum or a red blood cell folate level remains unsettled since there are few, if any, data to support one test over the other. Usually the serum vitamin B₁₂ level is normal, and it should always be measured when folic acid deficiency is suspected. In some instances, folic acid deficiency is a consequence of the gastrointestinal mucosal atrophy from vitamin B₁₂ deficiency.

► Differential Diagnosis

The megaloblastic anemia of folic acid deficiency should be differentiated from vitamin B₁₂ deficiency by the finding of a normal vitamin B₁₂ level and a reduced red blood cell (or serum) folic acid level. Alcoholic patients, who often have nutritional deficiency, may also have anemia of liver disease. Pure anemia of liver disease causes a macrocytic

anemia but does not produce megaloblastic morphologic changes in the peripheral blood; rather, target cells are present. Hypothyroidism is associated with mild macrocytosis and also with pernicious anemia.

► Treatment

Folic acid deficiency is treated with daily oral folic acid (1 mg). The response is similar to that seen in the treatment of vitamin B₁₂ deficiency, with rapid improvement and a sense of well-being, reticulocytosis in 5–7 days, and total correction of hematologic abnormalities within 2 months. Large doses of folic acid may produce hematologic responses in cases of vitamin B₁₂ deficiency, but permit neurologic damage to progress; hence, obtaining a serum vitamin B₁₂ level in suspected folic acid deficiency is paramount.

► When to Refer

Referral to a hematologist is not usually necessary.

Sobczyńska-Malefors A et al. Laboratory assessment of folate (vitamin B₉) status. *J Clin Pathol.* 2018;71:949. [PMID: 30228213]

Socha DS et al. Severe megaloblastic anemia: vitamin deficiency and other causes. *Cleve Clin J Med.* 2020;87:153. [PMID: 32127439]

HEMOLYTIC ANEMIAS

The hemolytic anemias are a group of disorders in which red blood cell survival is reduced, either episodically or continuously. The bone marrow has the ability to increase erythroid production up to eightfold in response to reduced red cell survival, so anemia will be present only when the ability of the bone marrow to compensate is outstripped. This will occur when red cell survival is extremely short or when the ability of the bone marrow to compensate is impaired.

Hemolytic disorders are generally classified according to whether the defect is intrinsic to the red cell or due to some external factor (Table 13–8). Intrinsic defects have been described in all components of the red blood cell, including the membrane, enzyme systems, and hemoglobin; most of these disorders are hereditary. Hemolytic anemias due to external factors are immune, microangiopathic hemolytic anemias, and infections of red blood cells.

Certain laboratory features are common to all hemolytic anemias. Haptoglobin, a normal plasma protein that binds and clears free hemoglobin released into plasma, is depressed in hemolytic disorders. However, the haptoglobin level is influenced by many factors and is not always a reliable indicator of hemolysis, particularly in end-stage liver disease (its site of synthesis). When intravascular hemolysis occurs, transient hemoglobinemia ensues. Hemoglobin is filtered through the renal glomerulus and is usually reabsorbed by tubular cells. Hemoglobinuria will be present only when the capacity for reabsorption of hemoglobin by renal tubular cells is exceeded. In the absence of hemoglobinuria, evidence for prior intravascular hemolysis is the presence of hemosiderin in shed renal

Table 13–8. Classification of hemolytic anemias.

Intrinsic
Membrane defects: hereditary spherocytosis, hereditary elliptocytosis, paroxysmal nocturnal hemoglobinuria
Glycolytic defects: pyruvate kinase deficiency, severe hypophosphatemia
Oxidation vulnerability: glucose-6-phosphate dehydrogenase deficiency, methemoglobinemia
Hemoglobinopathies: sickle cell syndromes, thalassemia, unstable hemoglobins, methemoglobinemia
Extrinsic
Immune: autoimmune, lymphoproliferative disease, drug-induced, idiopathic
Microangiopathic: thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, valve hemolysis, metastatic adenocarcinoma, vasculitis, copper overload
Infection: <i>Plasmodium</i> , <i>Clostridium</i> , <i>Borrelia</i>
Hypersplenism
Burns

tubular cells (positive urine hemosiderin). With severe intravascular hemolysis, hemoglobinemia and methemoglobinemia may be present. Hemolysis increases the indirect bilirubin, and the total bilirubin may rise to 4 mg/dL (68 μmol/L) or more. Bilirubin levels higher than this may indicate some degree of hepatic dysfunction. Serum LD levels are strikingly elevated in cases of microangiopathic hemolysis (thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome) and may be elevated in other hemolytic anemias.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA



ESSENTIALS OF DIAGNOSIS

- ▶ Episodic hemoglobinuria.
- ▶ Thrombosis is common.
- ▶ Suspect in confusing cases of hemolytic anemia with or without pancytopenia.
- ▶ Flow cytometry demonstrates deficiencies of CD55 and CD59.

► General Considerations

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal hematopoietic stem cell disorder that results in abnormal sensitivity of the red blood cell membrane to lysis by complement and therefore hemolysis. Free hemoglobin is released into the blood that scavenges nitric oxide and promotes esophageal spasms, male erectile dysfunction, kidney damage, and thrombosis. Patients with significant PNH live about 10–15 years following diagnosis; thrombosis is the primary cause of death.

► Clinical Findings

A. Symptoms and Signs

Classically, patients report episodic hemoglobinuria resulting in reddish-brown urine. Hemoglobinuria is most often noticed in the first morning urine due to the fall in blood pH while sleeping (hypoventilation) that facilitates this hemolysis. Besides anemia, these patients are prone to thrombosis, especially within mesenteric and hepatic veins, central nervous system veins (sagittal vein), and skin vessels (with formation of painful nodules). As this is a hematopoietic stem cell disorder, PNH may appear de novo or arise in the setting of aplastic anemia or myelodysplasia with possible progression to acute myeloid leukemia (AML). It is common that patients with idiopathic aplastic anemia have a small PNH clone (less than 2%) on blood or bone marrow analysis; this should not be considered true PNH per se, especially in the absence of a reticulocytosis or thrombosis.

B. Laboratory Findings

Anemia is of variable severity and frequency, so reticulocytosis may or may not be present at any given time. Abnormalities on the blood smear are nondiagnostic but may include macro-ovalocytes and polychromasia. Since the episodic hemolysis is mainly intravascular, urine hemosiderin is a useful test. Serum LD is characteristically quite elevated. Iron deficiency is commonly present, related to chronic iron loss from hemoglobinuria.

The white blood cell count and platelet count may be decreased and are always decreased in the setting of aplastic anemia. The best screening test is flow cytometry of blood erythrocytes, granulocytes, and monocytes to demonstrate deficiency of CD55 and CD59. The proportion of erythrocytes deficient in these proteins might be low due to the ongoing destruction of affected erythrocytes. The FLAER assay (fluorescein-labeled proaerolysin) by flow cytometry is more sensitive. Bone marrow morphology is variable and may show either generalized hypoplasia or erythroid hyperplasia or both. The bone marrow karyotype may be either normal or demonstrate a clonal abnormality.

► Treatment

Many patients with PNH have mild disease not requiring intervention. In severe cases and in those occurring in the setting of myelodysplasia or previous aplastic anemia, allogeneic hematopoietic stem cell transplantation may prove curative. In patients with severe hemolysis (usually requiring red cell transfusions) or thrombosis (or both), treatment with eculizumab is warranted. Eculizumab is a humanized monoclonal antibody against complement protein C5 given every 2 weeks. Binding of eculizumab to C5 prevents its cleavage so the membrane attack complex cannot assemble. Eculizumab improves quality of life and reduces hemolysis, transfusion requirements, fatigue, and thrombosis risk. Eculizumab increases the risk of *Neisseria meningitidis* infections; patients receiving the antibody should undergo meningococcal vaccination (including vaccines for serogroup B) and take oral penicillin (or equivalent) meningococcal prophylaxis. Ravulizumab is a longer-acting version of eculizumab; it is given

every 8 weeks and demonstrates fewer breakthrough hemolytic episodes than eculizumab. Iron replacement is indicated for treatment of iron deficiency when present, which may improve the anemia while also causing a transient increase in hemolysis. For unclear reasons, corticosteroids are effective in decreasing hemolysis.

► When to Refer

Most patients with PNH should be under the care of a hematologist.

Devos T et al. Diagnosis and management of PNH: review and recommendations from a Belgian expert panel. *Eur J Haematol*. 2018;101:737. [PMID: 30171728]

Patriquin CJ et al. How we treat paroxysmal nocturnal hemoglobinuria: a consensus statement of the Canadian PNH Network and review of the national registry. *Eur J Haematol*. 2019;102:36. [PMID: 30242915]

Tomazos I et al. Cost burden of breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria receiving ravelizumab versus eculizumab. *Hematology*. 2020;25:327. [PMID: 32765045]

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY



ESSENTIALS OF DIAGNOSIS

- ▶ X-linked recessive disorder seen commonly in American Black men.
- ▶ Episodic hemolysis in response to oxidant drugs or infection.
- ▶ Bite cells and blister cells on the peripheral blood smear.
- ▶ Reduced levels of glucose-6-phosphate dehydrogenase between hemolytic episodes.

► General Considerations

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a hereditary enzyme defect that causes episodic hemolytic anemia because of the decreased ability of red blood cells to deal with oxidative stresses. G6PD deficiency leads to excess oxidized glutathione that forces hemoglobin to denature and form precipitants called Heinz bodies. Heinz bodies cause red blood cell membrane damage, which leads to premature removal of these red blood cells by reticuloendothelial cells within the spleen (ie, extravascular hemolysis).

Numerous G6PD isoenzymes have been described. The usual isoenzyme found in American Blacks is designated G6PD-A and that found in Whites is designated G6PD-B, both of which have normal function and stability and therefore no hemolytic anemia. Ten to 15 percent of American Blacks have the variant G6PD isoenzyme designated A-, in which there is both a reduction in normal enzyme activity and a reduction in its stability. The A- isoenzyme activity declines rapidly as the red blood cell ages past 40 days, a fact that explains the clinical findings in this disorder.

More than 150 G6PD isoenzyme variants have been described, including some Mediterranean, Ashkenazi Jewish, and Asian variants with very low enzyme activity, episodic hemolysis, and exacerbations due to oxidizing substances including fava beans. Patients with G6PD deficiency seem to be protected from malaria parasitic infection, have less coronary artery disease, and possibly have fewer cancers and greater longevity.

► Clinical Findings

G6PD deficiency is an X-linked disorder affecting 10–15% of American hemizygous Black males and rare female homozygotes. Female carriers are rarely affected—only when an unusually high percentage of cells producing the normal enzyme are X-inactivated.

A. Symptoms and Signs

Patients are usually healthy, without chronic hemolytic anemia or splenomegaly. Hemolysis occurs episodically as a result of oxidative stress on the red blood cells, generated either by infection or exposure to certain medications. Medications initiating hemolysis that should be avoided include dapsone, methylene blue, phenazopyridine, primaquine, rasburicase, toluidine blue, nitrofurantoin, trimethoprim/sulfamethoxazole, sulfadiazine, pégloticase, and quinolones. Other medications, such as chloroquine, quinine, high-dose aspirin, and isoniazid, have been implicated but are less certain as offenders since they are often given during infections. Even with continuous use of the offending medication, the hemolytic episode is self-limited because older red blood cells (with low enzyme activity) are removed and replaced with a population of young red blood cells (reticulocytes) with adequate functional levels of G6PD. Severe G6PD deficiency (as in Mediterranean variants) may produce a chronic hemolytic anemia.

B. Laboratory Findings

Between hemolytic episodes, the blood is normal. During episodes of hemolysis, the hemoglobin rarely falls below 8 g/dL (80 g/L), and there is reticulocytosis and increased serum indirect bilirubin. The peripheral blood cell smear often reveals a small number of “bite” cells—cells that appear to have had a bite taken out of their periphery, or “blister” cells. This indicates pitting of precipitated membrane hemoglobin aggregates (ie, Heinz bodies) by the splenic macrophages. Heinz bodies may be demonstrated by staining a peripheral blood smear with cresyl violet; they are not visible on the usual Wright-Giemsa-stained blood smear. Specific enzyme assays for G6PD reveal a low level but may be falsely normal if they are performed during or shortly after a hemolytic episode during the period of reticulocytosis. In these cases, the enzyme assays should be repeated weeks after hemolysis has resolved. In severe cases of G6PD deficiency, enzyme levels are always low.

► Treatment

No treatment is necessary except to avoid known oxidant medications.

Belfield KD et al. Review and drug therapy implications of glucose-6-phosphate dehydrogenase deficiency. *Am J Health Syst Pharm.* 2018;75:97. [PMID: 29305344]

Georgakouli K et al. Exercise in glucose-6-phosphate dehydrogenase deficiency: harmful or harmless? A narrative review. *Oxid Med Cell Longev.* 2019;2019:8060193. [PMID: 31089417]

SICKLE CELL ANEMIA & RELATED SYNDROMES



ESSENTIALS OF DIAGNOSIS

- ▶ Recurrent pain episodes.
- ▶ Positive family history and lifelong history of hemolytic anemia.
- ▶ Irreversibly sickled cells on peripheral blood smear.
- ▶ Hemoglobin S is the major hemoglobin seen on electrophoresis.

► General Considerations

Sickle cell anemia is an autosomal recessive disorder in which an abnormal hemoglobin leads to chronic hemolytic anemia with numerous clinical consequences. A single DNA base change leads to an amino acid substitution of valine for glutamate in the sixth position on the beta-globin chain. The abnormal beta chain is designated beta^s and the tetramer of alpha-2beta^s-2 is designated hemoglobin SS. Hemoglobin S is unstable and polymerizes in the setting of various stressors, including hypoxemia and acidosis, leading to the formation of sickled red blood cells. Sickled cells result in hemolysis and the release of ATP, which is converted to adenosine. Adenosine binds to its receptor (A2B), resulting in the production of 2,3-biphosphoglycerate and the induction of more sickling, and to its receptor (A2A) on natural killer cells, resulting in pulmonary inflammation. The free hemoglobin from hemolysis scavenges nitric oxide causing endothelial dysfunction, vascular injury, and pulmonary hypertension.

The rate of sickling is influenced by the intracellular concentration of hemoglobin S and by the presence of other hemoglobins within the cell. Hemoglobin F cannot participate in polymer formation, and its presence markedly retards sickling. Factors that increase sickling are red blood cell dehydration and factors that lead to formation of deoxyhemoglobin S (eg, acidosis and hypoxemia), either systemic or local in tissues. Hemolytic crises may be related to splenic sequestration of sickled cells (primarily in childhood before the spleen has been infarcted as a result of repeated sickling) or with coexistent disorders such as G6PD deficiency.

The beta^s gene is carried in 8% of American Blacks, and 1 of 400 American Black children will be born with sickle cell anemia; prenatal diagnosis is available when sickle cell anemia is suspected. Genetic counseling should be made available to patients.

► Clinical Findings

A. Symptoms and Signs

The disorder has its onset during the first year of life, when hemoglobin F levels fall as a signal is sent to switch from production of gamma-globin to beta-globin. Chronic hemolytic anemia produces jaundice, pigment (calcium bilirubinate) gallstones, splenomegaly (early in life), and poorly healing skin ulcers over the lower tibia. Life-threatening severe anemia can occur during hemolytic or aplastic crises, the latter generally associated with viral or other infection caused by immunoincompetence from hypersplenism or by folic acid deficiency causing reduced erythropoiesis.

Acute painful episodes due to acute vaso-occlusion from clusters of sickled red cells may occur spontaneously or be provoked by infection, dehydration, or hypoxia. Common sites of acute painful episodes include the spine and long appendicular bones. These episodes last hours to days and may produce low-grade fever. Acute vaso-occlusion may cause strokes due to sagittal sinus venous thrombosis or to bland or hemorrhagic central nervous system arterial ischemia. Vaso-occlusion may also cause priapism. Vaso-occlusive episodes are not associated with increased hemolysis.

Repeated episodes of vascular occlusion especially affect the heart, lungs, and liver. The acute chest syndrome is characterized by acute chest pain, hypoxemia, and pulmonary infiltrates on a chest radiograph and must be distinguished from an infectious pneumonia. Ischemic necrosis of bones may occur, rendering the bone susceptible to osteomyelitis due to salmonellae and (somewhat less commonly) staphylococci. Infarction of the papillae of the renal medulla causes renal tubular concentrating defects and gross hematuria, more often encountered in sickle cell trait than in sickle cell anemia. Retinopathy similar to that noted in diabetes mellitus is often present and may lead to visual impairment. Pulmonary hypertension may develop and is associated with a poor prognosis. These patients are prone to delayed puberty. An increased incidence of infection is related to hypersplenism as well as to defects in the alternate complement pathway.

On examination, patients are often chronically ill and jaundiced. There is often hepatomegaly, but the spleen is not palpable in adult life. The heart may be enlarged with a hyperdynamic precordium and systolic murmurs and, in some cases, a pronounced increase in P2. Nonhealing cutaneous ulcers of the lower leg and retinopathy may be present.

B. Laboratory Findings

Chronic hemolytic anemia is present. The hematocrit is usually 20–30%. The peripheral blood smear is characteristically abnormal, with sickled cells comprising 5–50% of red cells. Other findings include reticulocytosis (10–25%), nucleated red blood cells, and hallmarks of hypersplenism such as Howell-Jolly bodies and target cells. The white blood cell count is characteristically elevated to 12,000–15,000/mcL (12–15 × 10⁹/L), and reactive thrombocytosis may occur. Indirect bilirubin levels are high.

The diagnosis of sickle cell anemia is confirmed by hemoglobin electrophoresis (Table 13–9). Hemoglobin S

Table 13–9. Hemoglobin distribution in sickle cell syndromes.

Genotype	Clinical Diagnosis	Hb A	Hb S	Hb A ₂	Hb F
AA	Normal	97–99%	0%	1–2%	< 1%
AS	Sickle trait	60%	40%	1–2%	< 1%
AS, alpha-thalassemia	Sickle trait, alpha-thalassemia	70–75%	25–30%	1–2%	< 1%
SS	Sickle cell anemia	0%	86–98%	1–3%	5–15%
SS, alpha-thalassemia (3 genes)	SS alpha-thalassemia, silent	0%	90%	3%	7–9%
SS, alpha-thalassemia (2 genes)	SS alpha-thalassemia, trait	0%	80%	3%	11–21%
S, beta ⁰ -thalassemia	Sickle beta ⁰ -thalassemia	0%	70–80%	3–5%	10–20%
S, beta ⁺ -thalassemia	Sickle beta ⁺ -thalassemia	10–20%	60–75%	3–5%	10–20%

Hb, hemoglobin; beta⁰, no beta-globin produced; beta⁺, some beta-globin produced.

will usually comprise 85–98% of hemoglobin. In homozygous S disease, no hemoglobin A will be present. Hemoglobin F levels are sometimes increased, and high hemoglobin F levels (15–20%) are associated with a more benign clinical course. Patients with S-beta⁺-thalassemia and SS alpha-thalassemia also have a more benign clinical course than straight sickle cell anemia (SS) patients.

Treatment

When allogeneic hematopoietic stem cell transplantation is performed before the onset of significant end-organ damage, it can cure more than 80% of children with sickle cell anemia who have suitable HLA-matched donors, with a reasonably good quality of life. Transplantation remains investigational in adults. Other therapies modulate disease severity: hydroxyurea increases hemoglobin F levels epigenetically. Hydroxyurea (500–750 mg orally daily) reduces the frequency of painful crises in patients whose quality of life is disrupted by frequent vaso-occlusive pain episodes (three or more per year). Long-term follow-up of patients taking hydroxyurea demonstrates it improves overall survival and quality of life with little evidence for secondary malignancy. The use of omega-3 (n-3) fatty acid supplementation may also reduce vaso-occlusive episodes and reduce transfusion needs in patients with sickle cell anemia. L-glutamine has been shown to favorably modulate sickle pain crises and acute chest syndrome. A monoclonal antibody (crizanlizumab-tmca) reduces vaso-occlusive episodes by 50%. It blocks P-selectin on activated endothelial cells and thus disrupts the adverse interactions of platelets, red blood cells, and leukocytes with the endothelial wall. Voxelotor inhibits the polymerization of deoxygenated sickle red blood cells and increases the hemoglobin in SS patients age 12 years or older.

Supportive care is the mainstay of treatment for sickle cell anemia. Patients are maintained on folic acid supplementation (1 mg orally daily) and given transfusions for aplastic or hemolytic crises. When acute painful episodes occur, precipitating factors should be identified and infections treated if present. The patient should be kept well hydrated, given generous analgesics, and supplied oxygen

if hypoxic. Pneumococcal vaccination reduces the incidence of infections with this pathogen while hydroxyurea and L-glutamine reduce hospitalizations for acute pain. Angiotensin-converting enzyme inhibitors are recommended in patients with microalbuminuria.

Exchange transfusions are indicated for the treatment of severe or intractable acute vaso-occlusive crises, acute chest syndrome, priapism, and stroke. Long-term transfusion therapy has been shown to be effective in reducing the risk of recurrent stroke in children. Phenotypically matched transfused red blood cells are recommended to reduce the risk of red blood cell alloimmunization. It has been recommended that children with SS who are aged 2–16 years have annual transcranial ultrasounds and, if the Doppler velocity is abnormal (200 cm/s or greater), the clinician should strongly consider beginning transfusions to prevent stroke. Iron chelation is needed for those on chronic transfusion therapy.

Prognosis

Sickle cell anemia becomes a chronic multisystem disease, leading to organ failure that may result in early death. With improved supportive care, average life expectancy is now between 40 and 50 years of age.

When to Refer

Patients with sickle cell anemia should have their care coordinated with a hematologist and should be referred to a Comprehensive Sickle Cell Center, if one is available.

When to Admit

Patients should be admitted for management of acute chest syndrome, for aplastic crisis, or for painful episodes that do not respond to outpatient interventions.

DeBaun MR et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv.* 2020;4:1554. [PMID: 32298430]

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SICKLE CELL TRAIT

People with the heterozygous hemoglobin genotype AS have **sickle cell trait**. These persons are hematologically normal, with no anemia and normal red blood cells on peripheral blood smear. Hemoglobin electrophoresis will reveal that approximately 40% of hemoglobin is hemoglobin S (Table 13–9). People with sickle cell trait experience more rhabdomyolysis during vigorous exercise but do not have increased mortality compared to the general population. They may be at increased risk for venous thromboembolism. Chronic sickling of red blood cells in the acidotic renal medulla results in microscopic and gross hematuria, hyposthenuria (poor urine concentrating ability), and possibly chronic kidney disease. No treatment is necessary but genetic counseling is recommended.

Liem RI. Balancing exercise risk and benefits: lessons learned from sickle cell trait and sickle cell anemia. *Hematology Am Soc Hematol Educ Program.* 2018;2018:418. [PMID: 30504341]

Pecker LH et al. The current state of sickle cell trait: implications for reproductive and genetic counseling. *Hematology Am Soc Hematol Educ Program.* 2018;2018:474. [PMID: 30504348]

SICKLE THALASSEMIA

Patients with homozygous sickle cell anemia and alpha-thalassemia have less vigorous hemolysis and run higher hemoglobins than SS patients due to reduced red blood cell sickling related to a lower hemoglobin concentration within the red blood cell and higher hemoglobin F levels (Table 13–9). The MCV is low, and the red cells are hypochromic.

Patients who are compound heterozygotes for beta^a and beta-thalassemia are clinically affected with sickle cell syndromes. Sickle beta⁰-thalassemia is clinically very similar to homozygous SS disease. Vaso-occlusive crises may be somewhat less severe, and the spleen is not always infarcted. The MCV is low, in contrast to the normal MCV of sickle cell anemia. Hemoglobin electrophoresis reveals no hemoglobin A but will show an increase in hemoglobins A₂ and F (Table 13–9).

Sickle beta⁺-thalassemia is a milder disorder than homozygous SS disease, with fewer pain episodes but more acute chest syndrome than sickle beta⁰-thalassemia. The spleen is usually palpable. The hemolytic anemia is less severe, and the hematocrit is usually 30–38%, with reticulocytes of 5–10%. Hemoglobin electrophoresis shows the presence of some hemoglobin A and elevated hemoglobins A₂ and F (Table 13–9). The MCV is low.

AUTOIMMUNE HEMOLYTIC ANEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Acquired hemolytic anemia caused by IgG autoantibody.
- ▶ Spherocytes and reticulocytosis on peripheral blood smear.
- ▶ Positive antiglobulin (Coombs) test.

General Considerations

Warm autoimmune hemolytic anemia is an acquired disorder in which an IgG autoantibody is formed that binds to a red blood cell membrane protein and does so most avidly at body temperature (ie, a “warm” autoantibody). The antibody is most commonly directed against a basic component of the Rh system present on most human red blood cells. When IgG antibodies coat the red blood cell, the Fc portion of the antibody is recognized by macrophages present in the spleen and other portions of the reticuloendothelial system. The interaction between splenic macrophages and the antibody-coated red blood cell results in removal of red blood cell membrane and the formation of a spherocyte due to the decrease in surface-to-volume ratio of the surviving red blood cell. These spherocytic cells have decreased deformability and are unable to squeeze through the 2-mcm fenestrations of splenic sinusoids and become trapped in the red pulp of the spleen. When large amounts of IgG are present on red blood cells, complement may be fixed. Direct complement lysis of cells is rare, but the presence of C3b on the surface of red blood cells allows Kupffer cells in the liver to participate in the hemolytic process via C3b receptors. The destruction of red blood cells in the spleen and liver designates this as extravascular hemolysis.

Approximately one-half of all cases of autoimmune hemolytic anemia are idiopathic. The disorder may also be seen in association with systemic lupus erythematosus, other rheumatic disorders, chronic lymphocytic leukemia (CLL), or lymphomas. It must be distinguished from drug-induced hemolytic anemia. When penicillin (or other medications, especially cefotetan, ceftriaxone, and piperacillin) coats the red blood cell membrane, the autoantibody is directed against the membrane-drug complex. Fludarabine, an anti-neoplastic, causes autoimmune hemolytic anemia through its immunosuppression; there is defective self- versus non-self-immune surveillance permitting the escape of a B-cell clone, which produces the offending autoantibody.

Clinical Findings

A. Symptoms and Signs

Autoimmune hemolytic anemia typically produces an anemia of rapid onset that may be life-threatening. Patients complain of fatigue and dyspnea and may present with angina pectoris or heart failure. On examination, jaundice and splenomegaly are usually present.

B. Laboratory Findings

The anemia is of variable degree but may be very severe, with hematocrit of less than 10%. Reticulocytosis is present, and spherocytes are seen on the peripheral blood smear. In cases of severe hemolysis, the stressed bone marrow may also release nucleated red blood cells. As with other hemolytic disorders, the serum indirect bilirubin is increased and the haptoglobin is low. Approximately 10% of patients with autoimmune hemolytic anemia have coincident immune thrombocytopenia (Evans syndrome).

The antiglobulin (Coombs) test forms the basis for diagnosis. The Coombs reagent is a rabbit IgM antibody raised against human IgG or human complement. The direct antiglobulin (Coombs) test is performed by mixing the patient's red blood cells with the Coombs reagent and looking for agglutination, which indicates the presence of antibody or complement or both on the red blood cell surface. The indirect antiglobulin (Coombs) test is performed by mixing the patient's serum with a panel of type O red blood cells. After incubation of the test serum and panel red blood cells, the Coombs reagent is added. Agglutination in this system indicates the presence of free antibody (autoantibody or alloantibody) in the patient's serum.

The direct antiglobulin test is positive (for IgG, complement, or both) in about 90% of patients with autoimmune hemolytic anemia. The indirect antiglobulin test may or may not be positive. A positive indirect antiglobulin test indicates the presence of a large amount of autoantibody that has saturated binding sites on the red blood cell and consequently appears in the serum. Because the patient's serum usually contains the autoantibody, it may be difficult to obtain a "compatible" cross-match with homologous red blood cells for transfusions since the cross-match indicates the possible presence (true or false) of a red blood cell "alloantibody."

Treatment

Initial treatment consists of prednisone, 1–2 mg/kg/day orally in divided doses. Patients with DAT-negative and DAT-positive autoimmune hemolysis respond equally well to corticosteroids. Transfused red blood cells will survive similarly to the patient's own red blood cells. Because of difficulty in performing the cross-match, possible "incompatible" blood may need to be given. Decisions regarding transfusions should be made in consultation with a hematologist and a blood bank specialist. Death from cardiovascular collapse can occur in the setting of rapid hemolysis. In patients with rapid hemolysis, therapeutic plasmapheresis should be performed early in management to remove autoantibodies. If prednisone is ineffective or if the disease recurs on tapering the dose, splenectomy should be considered, which may cure the disorder. Patients with autoimmune hemolytic anemia refractory to prednisone and splenectomy may also be treated with a variety of agents. Treatment with rituximab, a monoclonal antibody against the B cell antigen CD20, is effective in some cases. The suggested dose is 375 mg/m² intravenously weekly for 4 weeks. Rituximab is used in conjunction with corticosteroids as initial therapy in some patients with severe disease. In patients with past hepatitis B virus (HBV) infection,

rituximab should be used with anti-HBV agent prophylaxis since HBV reactivation, fulminant hepatitis, and, rarely, death can occur otherwise. Danazol, 400–800 mg/day orally, is less often effective than in immune thrombocytopenia but is well suited for long-term use because of its low toxicity profile. Immunosuppressive agents, including cyclophosphamide, vincristine, azathioprine, mycophenolate mofetil, alemtuzumab (an anti-CD52 antibody), or cyclosporine, may also be used. High-dose intravenous immune globulin (1 g/kg daily for 2 days) may be effective in controlling hemolysis. The benefit is short-lived (1–3 weeks), and immune globulin is very expensive. The long-term prognosis for patients with this disorder is good, especially if there is no other underlying autoimmune disorder or lymphoproliferative disorder. Treatment of an associated lymphoproliferative disorder will also treat the hemolytic anemia.

When to Refer

Patients with autoimmune hemolytic anemia should be referred to a hematologist for confirmation of the diagnosis and subsequent care.

When to Admit

Patients should be hospitalized for symptomatic anemia or rapidly falling hemoglobin levels.

Brodsky RA. Warm autoimmune hemolytic anemia. *N Engl J Med*. 2019;381:647. [PMID: 31412178]

Hill A et al. Autoimmune hemolytic anemia. *Hematology Am Soc Hematol Educ Program*. 2018;2018:382. [PMID: 30504336]

Hill QA et al. Defining autoimmune hemolytic anemia: a systematic review of the terminology used for diagnosis and treatment. *Blood Adv*. 2019;3:1897. [PMID: 31235526]

Jäger U et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. *Blood Rev*. 2020;41:100648. [PMID: 31839434]

COLD AGGLUTININ DISEASE



ESSENTIALS OF DIAGNOSIS

- Increased reticulocytes on peripheral blood smear.
- Antiglobulin (Coombs) test positive only for complement.
- Positive cold agglutinin titer.

General Considerations

Cold agglutinin disease is an acquired hemolytic anemia due to an IgM autoantibody (called a "cold agglutinin") usually directed against the I/i antigen on red blood cells. These IgM autoantibodies characteristically will react poorly with cells at 37°C but avidly at lower temperatures, usually at 0–4°C (ie, "cold" autoantibody). Since the blood temperature (even in the most peripheral parts of the body) rarely goes lower than 20°C, only cold autoantibodies reactive at relatively higher temperatures will produce

clinical effects. Hemolysis results indirectly from attachment of IgM, which in the cooler parts of the circulation (fingers, nose, ears) binds and fixes complement. When the red blood cell returns to a warmer temperature, the IgM antibody dissociates, leaving complement on the cell. Complement lysis of red blood cells rarely occurs. Rather, C3b, present on the red blood cells, is recognized by Kupffer cells (which have receptors for C3b), and red blood cell sequestration and destruction in the liver ensues (extravascular hemolysis). However, in some cases, the complement membrane attack complex forms, lysing the red blood cells (intravascular hemolysis).

Most cases of chronic cold agglutinin disease are idiopathic. Others occur in association with Waldenström macroglobulinemia, lymphoma, or CLL, in which a monoclonal IgM paraprotein is produced. Acute postinfectious cold agglutinin disease occurs following mycoplasma pneumonia or viral infection (infectious mononucleosis, measles, mumps, or cytomegalovirus [CMV] with autoantibody directed against antigen I rather than I).

Clinical Findings

A. Symptoms and Signs

In chronic cold agglutinin disease, symptoms related to red blood cell agglutination occur on exposure to cold, and patients may complain of mottled or numb fingers or toes, acrocyanosis, episodic low back pain, and dark-colored urine. Hemolytic anemia is occasionally severe, but episodic hemoglobinuria may occur on exposure to cold. The hemolytic anemia in acute postinfectious syndromes is rarely severe.

B. Laboratory Findings

Mild anemia is present with reticulocytosis and rarely spherocytes. The blood smear made at room temperature shows agglutinated red blood cells (there is no agglutination on a blood smear made at body temperature). The direct antiglobulin (Coombs) test will be positive for complement only. Serum cold agglutinin titer will semi-quantitate the autoantibody. A monoclonal IgM is often found on serum protein electrophoresis and confirmed by serum immunoelectrophoresis. There is indirect hyperbilirubinemia and the haptoglobin is low during periods of hemolysis.

Treatment

Treatment is largely symptomatic, based on avoiding exposure to cold. Splenectomy and prednisone are usually ineffective (except when associated with a lymphoproliferative disorder) since hemolysis takes place in the liver and blood stream. Rituximab is the treatment of choice but in patients with past HBV infection, it must be used with anti-HBV prophylaxis. The dose is 375 mg/m² intravenously weekly for 4 weeks. Relapses may be effectively re-treated. High-dose intravenous immunoglobulin (2 g/kg) may be effective temporarily, but it is rarely used because of the high cost and short duration of benefit. Patients with severe disease may be treated with cytotoxic agents, such as bendamustine (plus rituximab), cyclophosphamide, fludarabine, or bortezomib, or with immunosuppressive agents,

such as cyclosporine. As in warm IgG-mediated autoimmune hemolysis, it may be difficult to find compatible blood for transfusion. Red blood cells should be transfused through an in-line blood warmer.

Berentsen S et al. Novel insights into the treatment of complement-mediated hemolytic anemias. *Ther Adv Hematol.* 2019;10:2040620719873321. [PMID: 31523413]

Jäger U et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. *Blood Rev.* 2020;41:100648. [PMID: 31839434]

APLASTIC ANEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Pancytopenia.
- ▶ No abnormal hematopoietic cells seen in blood or bone marrow.
- ▶ Hypocellular bone marrow.

General Considerations

Aplastic anemia is a condition of bone marrow failure that arises from suppression of, or injury to, the hematopoietic stem cell. The bone marrow becomes hypoplastic, fails to produce mature blood cells, and pancytopenia develops.

There are a number of causes of aplastic anemia (Table 13–10). Direct hematopoietic stem cell injury may be caused by radiation, chemotherapy, toxins, or pharmacologic agents. Systemic lupus erythematosus may rarely cause suppression of the hematopoietic stem cell by an IgG autoantibody directed against it. However, the most common pathogenesis of aplastic anemia appears to be autoimmune suppression of hematopoiesis by a T-cell-mediated cellular mechanism, so-called idiopathic aplastic anemia. In some cases of idiopathic aplastic anemia, defects in maintenance of the hematopoietic stem cell telomere length (eg, dyskeratosis congenita) or in DNA repair pathways (eg, Fanconi anemia) have been identified and are likely linked to both the initiation of bone marrow failure

Table 13–10. Causes of aplastic anemia.

Autoimmune: idiopathic, systemic lupus erythematosus
Congenital: defects in telomere length maintenance or DNA repair (dyskeratosis congenita, Fanconi anemia, etc)
Chemotherapy, radiotherapy
Toxins: benzene, toluene, insecticides
Medications: chloramphenicol, gold salts, sulfonamides, phenytoin, carbamazepine, quinacrine, tolbutamide
Post-viral hepatitis (viral agent unknown)
Non-hepatitis viruses (EBV, parvovirus, CMV, echovirus 3, others)
Pregnancy
Paroxysmal nocturnal hemoglobinuria
Malignancy: large granular lymphocytic leukemia (T-LGL)

EBV, Epstein-Barr virus; CMV, cytomegalovirus.

and the propensity to later progress to myelodysplasia, PNH, or AML. Complex detrimental immune responses to viruses can also cause aplastic anemia.

► Clinical Findings

A. Symptoms and Signs

Patients come to medical attention because of the consequences of bone marrow failure. Anemia leads to symptoms of weakness and fatigue, neutropenia causes vulnerability to bacterial or fungal infections, and thrombocytopenia results in mucosal and skin bleeding. Physical examination may reveal signs of pallor, purpura, and petechiae. Other abnormalities such as hepatosplenomegaly, lymphadenopathy, or bone tenderness should *not* be present, and their presence should lead to questioning the diagnosis.

B. Laboratory Findings

The hallmark of aplastic anemia is pancytopenia. However, early in the evolution of aplastic anemia, only one or two cell lines may be reduced.

Anemia may be severe and is always associated with reticulocytopenia. Red blood cell morphology is unremarkable, but there may be mild macrocytosis (increased MCV). Neutrophils and platelets are reduced in number, and no immature or abnormal forms are seen on the blood smear. The bone marrow aspirate and the bone marrow biopsy appear hypocellular, with only scant amounts of morphologically normal hematopoietic progenitors. The prior dictum that the bone marrow karyotype should be normal (or germline if normal variant) has evolved and some clonal abnormalities or other genetic aberrations may be present even in the setting of idiopathic aplastic anemia.

► Differential Diagnosis

Aplastic anemia must be differentiated from other causes of pancytopenia (Table 13–11). Hypocellular forms of myelodysplasia or acute leukemia may occasionally be confused

with aplastic anemia. These are differentiated by the presence of cellular morphologic abnormalities, increased percentage of blasts, or abnormal karyotype in bone marrow cells typical of MDS or acute leukemia. Hairy cell leukemia has been misdiagnosed as aplastic anemia and should be recognized by the presence of splenomegaly and by abnormal “hairy” lymphoid cells in a hypocellular bone marrow biopsy. Pancytopenia with a normocellular bone marrow may be due to systemic lupus erythematosus, disseminated infection, hypersplenism, nutritional (eg, vitamin B₁₂ or folate) deficiency, or myelodysplasia. Isolated thrombocytopenia may occur early as aplastic anemia develops and may be confused with immune thrombocytopenia.

► Treatment

Mild cases of aplastic anemia may be treated with supportive care, including erythropoietic (epoetin or darbepoetin) or myeloid (filgrastim or sargramostim or biosimilars) growth factors, or both. Red blood cell transfusions and platelet transfusions are given as necessary, and antibiotics are used to treat infections.

Severe aplastic anemia is defined by a neutrophil count of less than 500/mcL ($0.5 \times 10^9/L$), platelets less than 20,000/mcL ($20 \times 10^9/L$), reticulocytes less than 1%, and bone marrow cellularity less than 20%. The treatment of choice for young adults (under age 40 years) who have an HLA-matched sibling is allogeneic bone marrow transplantation. Children or young adults may also benefit from allogeneic bone marrow transplantation using an unrelated donor. Because of the increased risks associated with unrelated donor allogeneic bone marrow transplantation compared to sibling donors, this treatment is usually reserved for patients who have not responded to immunosuppressive therapy.

For adults over age 40 years or those without HLA-matched hematopoietic stem cell donors, the treatment of choice for severe idiopathic aplastic anemia is immunosuppression with equine antithymocyte globulin (ATG) plus cyclosporine. Equine ATG is given in the hospital in conjunction with transfusion and antibiotic support. A proven regimen is equine ATG 40 mg/kg/day intravenously for 4 days in combination with cyclosporine, 6 mg/kg orally twice daily. Equine ATG is superior to rabbit ATG, resulting in a higher response rate and better survival. Eltrombopag, a thrombopoietin mimetic, is now being added to ATG plus cyclosporine with tri-lineage hematologic responses as high as 90%. ATG should be used in combination with corticosteroids (prednisone or methylprednisolone 1–2 mg/kg/day orally for 1 week, followed by a taper over 2 weeks) to avoid ATG infusion reactions and serum sickness. Responses usually occur in 1–3 months and are usually only partial, but the blood counts rise high enough to give patients a safe and transfusion-free life. The full benefit of immunosuppression is generally assessed at 4 months post-equine ATG. Cyclosporine and eltrombopag are maintained at full doses for 6 months and then stopped in responding patients. Androgens (such as fluoxymesterone 10–20 mg/day orally in divided doses or danazol 200 mg orally twice daily) have been widely used in the past, with a low response rate, and may be considered in mild cases.

Table 13–11. Causes of pancytopenia.

Primary bone marrow disorders
Aplastic anemia
Myelodysplasia
Acute leukemia
Chronic idiopathic myelofibrosis
Infiltrative disease: lymphoma, myeloma, carcinoma, hairy cell leukemia, etc
Non-primary bone marrow disorders
Hypersplenism (with or without portal hypertension)
Systemic lupus erythematosus
Infection: tuberculosis, HIV, leishmaniasis, brucellosis, CMV, parvovirus B19
Nutritional deficiency (megaloblastic anemia)
Medications
Cytotoxic chemotherapy
Ionizing radiation

CMV, cytomegalovirus.

► Course & Prognosis

Patients with severe aplastic anemia have a rapidly fatal illness if left untreated. Allogeneic bone marrow transplant from an HLA-matched sibling donor produces survival rates of over 80% in recipients under 20 years old and of about 65–70% in those 20 to 50 years old. Respective survival rates drop 10–15% when the donor is HLA-matched but unrelated. Equine ATG-cyclosporine immunosuppressive treatment leads to a response in approximately 70% of patients (including those with hepatitis virus-associated aplastic anemia) and in up to 90% of patients with the addition of eltrombopag. Up to one-third of patients will relapse with aplastic anemia after ATG-based therapy. Clonal hematologic disorders, such as PNH, AML, or myelodysplasia, may develop in one-quarter of patients treated with immunosuppressive therapy after 10 years of follow-up. Factors that predict response to ATG-cyclosporine therapy are patient's age, reticulocyte count, lymphocyte count, and age-adjusted telomere length of leukocytes at the time of diagnosis.

► When to Refer

All patients should be referred to a hematologist.

► When to Admit

Admission is necessary for treatment of neutropenic infection, the administration of ATG, or allogeneic bone marrow transplantation.

Georges GE et al. Severe aplastic anemia: allogeneic bone marrow transplantation as first line treatment. *Blood Adv.* 2020;2:2020. [PMID: 30108110]

Marsh JCW et al. The case for upfront HLA-matched unrelated donor hematopoietic stem cell transplantation as a curative option for adult acquired severe aplastic anemia. *Biol Blood Marrow Transplant.* 2019;25:e277. [PMID: 31129354]

Shallis RM et al. Aplastic anemia: etiology, molecular pathogenesis, and emerging concepts. *Eur J Haematol.* 2018;101:711. [PMID: 30055055]

Zhu Y et al. Allo-HSCT compared with immunosuppressive therapy for acquired aplastic anemia: a system review and meta-analysis. *BMC Immunol.* 2020;2:10. [PMID: 32138642]

NEUTROPENIA



ESSENTIALS OF DIAGNOSIS

- ▶ Neutrophils < 1800/mcL ($1.8 \times 10^9/L$).
- ▶ Severe neutropenia if neutrophils < 500/mcL ($0.5 \times 10^9/L$).

► General Considerations

Neutropenia is present when the absolute neutrophil count is less than 1800/mcL ($1.8 \times 10^9/L$), although Blacks, Asians, and other specific ethnic groups may have normal neutrophil counts as low as 1200/mcL ($1.2 \times 10^9/L$) or even less. The

neutropenic patient is increasingly vulnerable to infection by gram-positive and gram-negative bacteria and by fungi. The risk of infection is related to the severity of neutropenia. The risk of serious infection rises sharply with neutrophil counts below 500/mcL ($0.5 \times 10^9/L$), and a high risk of infection within days occurs with neutrophil counts below 100/mcL ($0.1 \times 10^9/L$) ("profound neutropenia"). The classification of neutropenic syndromes is unsatisfactory as the pathophysiology and natural history of different syndromes overlap. Patients with "chronic benign neutropenia" are free of infection despite very low stable neutrophil counts; they seem to physiologically respond adequately to infections and inflammatory stimuli with an appropriate neutrophil release from the bone marrow. In contrast, the neutrophil count of patients with cyclic neutropenia periodically oscillates (usually in 21-day cycles) between normal and low, with infections occurring during the nadirs. Congenital neutropenia is lifelong neutropenia punctuated with infection.

A variety of bone marrow disorders and non-marrows conditions may cause neutropenia (Table 13–12). All of the causes of aplastic anemia (Table 13–10) and pancytopenia (Table 13–11) may cause neutropenia. The new onset of an isolated neutropenia is most often due to an idiosyncratic reaction to a medication, and agranulocytosis (complete absence of neutrophils in the peripheral blood) is almost always due to a drug reaction. In these cases, examination of the bone marrow shows an almost complete absence of granulocyte precursors with other cell lines undisturbed. Neutropenia in the presence of a normal bone marrow may be due to immunologic peripheral destruction (autoimmune neutropenia), sepsis, or hypersplenism. The presence in the serum of antineutrophil antibodies supports the diagnosis of autoimmune neutropenia but does not prove this as the pathophysiologic reason for neutropenia.

Table 13–12. Causes of neutropenia.

Bone marrow disorders

- Congenital
- Dyskeratosis congenita
- Fanconi anemia
- Cyclic neutropenia
- Congenital neutropenia
- Hairy cell leukemia
- Large granular lymphoproliferative disorder
- Myelodysplasia

Non-bone marrow disorders

- Medications: antiretroviral medications, cephalosporins, chlorpromazine, chlorpropamide, cimetidine, methimazole, myelosuppressive cytotoxic chemotherapy, penicillin, phenytoin, procainamide, rituximab, sulfonamides
- Aplastic anemia
- Benign chronic neutropenia
- Pure white cell aplasia
- Hypersplenism
- Sepsis
- Other immune
- Autoimmune (idiopathic)
- Felty syndrome
- Systemic lupus erythematosus
- HIV infection

Felty syndrome is an immune neutropenia associated with seropositive nodular rheumatoid arthritis and splenomegaly. Severe neutropenia may be associated with clonal disorders of T lymphocytes, often with the morphology of large granular lymphocytes, referred to as CD3-positive T-cell large granular lymphoproliferative disorder. Isolated neutropenia is an uncommon presentation of hairy cell leukemia or MDS. By its nature, myelosuppressive cytotoxic chemotherapy causes neutropenia in a predictable manner.

► Clinical Findings

Neutropenia results in stomatitis and in infections due to gram-positive or gram-negative aerobic bacteria or to fungi such as *Candida* or *Aspergillus*. The most common infectious syndromes are septicemia, cellulitis, pneumonia, and neutropenic fever of unknown origin. Fever in neutropenic patients should always be initially assumed to be of infectious origin until proven otherwise (Chapter 30).

► Treatment

Treatment of neutropenia depends on its cause. Potential causative medications should be discontinued. Myeloid growth factors (filgrastim or sargramostim or biosimilar myeloid growth factors) help facilitate neutrophil recovery after offending medications are stopped. Chronic myeloid growth factor administration (daily or every other day) is effective at dampening the neutropenia seen in cyclic or congenital neutropenia. When Felty syndrome leads to repeated bacterial infections, splenectomy has been the treatment of choice, but sustained use of myeloid growth factors is effective and provides a nonsurgical alternative. Patients with autoimmune neutropenia often respond briefly to immunosuppression with corticosteroids and are best managed with intermittent doses of myeloid growth factors. The neutropenia associated with large granular lymphoproliferative disorder may respond to therapy with oral methotrexate, cyclophosphamide, or cyclosporine.

Fevers during neutropenia should be considered as infectious until proven otherwise. Febrile neutropenia is a life-threatening circumstance. Enteric gram-negative bacteria are of primary concern and often empirically treated with fluoroquinolones or third- or fourth-generation cephalosporins (see Infections in the Immunocompromised Patient, Chapter 30). For protracted neutropenia, fungal infections are problematic and empiric coverage with azoles (fluconazole for yeast and voriconazole, itraconazole, posaconazole, or isavuconazole for molds) or echinocandins is recommended. The neutropenia following myelosuppressive chemotherapy is predictable and is partially ameliorated by the use of myeloid growth factors. For patients with acute leukemia undergoing intense chemotherapy or patients with solid cancer undergoing high-dose chemotherapy, the prophylactic use of antimicrobial agents and myeloid growth factors is recommended.

► When to Refer

Refer to a hematologist if neutrophils are persistently and unexplainably less than 1000/mcL ($1.0 \times 10^9/L$).

► When to Admit

Neutropenia by itself is not an indication for hospitalization. However, many patients with severe neutropenia may have a serious underlying disease that may require inpatient treatment. Most patients with febrile neutropenia require hospitalization to treat infection.

Abdel-Azim H et al. Strategies to generate functionally normal neutrophils to reduce infection and infection-related mortality in cancer chemotherapy. *Pharmacol Ther*. 2019;204:107403. [PMID: 31470030]

Atallah-Yunes SA et al. Benign ethnic neutropenia. *Blood Rev*. 2019;37:100586. [PMID: 31255364]

Singh N et al. Isolated chronic and transient neutropenia. *Cureus*. 2019;11:e5616. [PMID: 31720132]

LEUKEMIAS & OTHER MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative disorders are due to acquired clonal abnormalities of the hematopoietic stem cell. Since the stem cell gives rise to myeloid, erythroid, and platelet cells, qualitative and quantitative changes are seen in all of these cell lines. Classically, the myeloproliferative disorders produce characteristic syndromes with well-defined clinical and laboratory features (Tables 13–13 and 13–14). However, these disorders are grouped together because they may evolve from one into another and because hybrid disorders are commonly seen. All of the myeloproliferative disorders may progress to AML.

The Philadelphia chromosome seen in chronic myeloid leukemia (CML) was the first recurrent cytogenetic abnormality to be described in a human malignancy. Since that time, there has been tremendous progress in elucidating

Table 13–13. World Health Organization classification of myeloproliferative disorders (modified).

Myeloproliferative neoplasms
Chronic myeloid leukemia, <i>BCR-ABL1</i> -positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis (PMF)
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified (NOS)
Myeloproliferative neoplasm, unclassifiable
Mastocytosis
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Myelodysplastic syndromes
Acute myeloid leukemia and related neoplasms
Acute myeloid leukemia with recurrent genetic abnormalities
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, NOS
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Acute leukemias of ambiguous lineage
B lymphoblastic leukemia/lymphoma
T lymphoblastic leukemia/lymphoma

Table 13–14. Laboratory features of myeloproliferative neoplasms.

	White Count	Hematocrit	Platelet Count	Red Cell Morphology
Polycythemia vera	N or ↑	↑↑	N or ↑	N
Essential thrombocythemia	N or ↑	N	↑↑	N
Primary myelofibrosis	N or ↓ or ↑	↓	↓ or N or ↑	Abn
Chronic myeloid leukemia	↑↑	N or ↓	N or ↑ or ↓	N

Abn, abnormal; N, normal.

the genetic nature of these disorders, with identification of mutations in *JAK2*, *MPL*, *CALR*, *CSF3R*, and other genes.

Masarova L et al. The rationale for immunotherapy in myeloproliferative neoplasms. *Curr Hematol Malig Rep*. 2019;14:310. [PMID: 31228096]

Rumi E et al. Myeloproliferative and lymphoproliferative disorders: state of the art. *Hematol Oncol*. 2020;38:121. [PMID: 31833567]

POLYCYTHEMIA VERA



ESSENTIALS OF DIAGNOSIS

- ▶ *JAK2 (V617F)* mutation.
- ▶ Splenomegaly.
- ▶ Normal arterial oxygen saturation.
- ▶ Usually elevated white blood count and platelet count.

► General Considerations

Polycythemia vera is an acquired myeloproliferative disorder that causes overproduction of all three hematopoietic cell lines, most prominently the red blood cells. Erythroid production is independent of erythropoietin, and the serum erythropoietin level is low. True erythrocytosis, with an elevated red blood cell mass, should be distinguished from spurious erythrocytosis caused by a constricted plasma volume.

A mutation in exon 14 of *JAK2 (V617F)*, a signaling molecule, has been demonstrated in 95% of cases. Additional *JAK2* mutations have been identified (exon 12) and suggest that *JAK2* is involved in the pathogenesis of this disease and is a potential therapeutic target.

► Clinical Findings

A. Symptoms and Signs

Headache, dizziness, tinnitus, blurred vision, and fatigue are common complaints related to expanded blood volume and increased blood viscosity. Generalized pruritus, especially following a warm shower or bath, is related to histamine release from the basophilia. Epistaxis is probably related to engorgement of mucosal blood vessels in combination with abnormal hemostasis. Sixty percent of patients

are men, and the median age at presentation is 60 years. Polycythemia rarely occurs in persons under age 40 years.

Physical examination reveals plethora and engorged retinal veins. The spleen is palpable in 75% of cases but is nearly always enlarged when imaged. Thrombosis is the most common complication of polycythemia vera and the major cause of morbidity and death in this disorder. Thrombosis appears to be related both to increased blood viscosity and abnormal platelet function. Uncontrolled polycythemia leads to a very high incidence of thrombotic complications of surgery, and elective surgery should be deferred until the condition has been treated. Paradoxically, in addition to thrombosis, increased bleeding can occur. There is also a high incidence of peptic ulcer disease.

B. Laboratory Findings

According to the WHO 2016 criteria, the hallmark of polycythemia vera is a hematocrit (at sea level) that exceeds 49% in males or 48% in females. Red blood cell morphology is normal (Table 13–14). The white blood count is usually elevated to 10,000–20,000/mcL ($10\text{--}20 \times 10^9/\text{L}$), and the platelet count is variably increased, sometimes to counts exceeding 1,000,000/mcL ($1000 \times 10^9/\text{L}$). Platelet morphology is usually normal. White blood cells are usually normal, but basophilia and eosinophilia are frequently present. Erythropoietin is suppressed and serum levels, usually low. The diagnosis should be confirmed with *JAK2* mutation screening. The absence of a mutation in either exon 14 (most common) or 12 should lead the clinician to question the diagnosis.

The bone marrow is hypercellular, with panhyperplasia of all hematopoietic elements, but bone marrow examination is not necessary to establish the diagnosis. Iron stores are usually absent from the bone marrow, having been transferred to the increased circulating red blood cell mass. Iron deficiency may also result from chronic gastrointestinal blood loss. Bleeding may lower the hematocrit to the normal range (or lower), creating diagnostic confusion, and may lead to a situation with significant microcytosis yet a normal hematocrit.

Vitamin B₁₂ levels are strikingly elevated because of increased levels of transcobalamin III (secreted by white blood cells). Overproduction of uric acid may lead to hyperuricemia.

Although red blood cell morphology is usually normal at presentation, microcytosis, hypochromia, and poikilocytosis may result from iron deficiency following treatment

Table 13–15. Causes of polycythemia.

Spurious polycythemia
Secondary polycythemia
Hypoxia: cardiac disease, pulmonary disease, high altitude
Carboxyhemoglobin: smoking
Erythropoietin-secreting tumors, eg, kidney lesions (rare)
Abnormal hemoglobins (rare)
Polycythemia vera

by phlebotomy. Progressive hypersplenism may also lead to elliptocytosis (eg, with red cells the size and shape of those in hereditary elliptocytosis).

► Differential Diagnosis

Spurious polycythemia, in which an elevated hematocrit is due to contracted plasma volume rather than increased red cell mass, may be related to diuretic use or may occur without obvious cause.

A secondary cause of polycythemia should be suspected if splenomegaly is absent and the high hematocrit is not accompanied by increases in other cell lines. Secondary causes of polycythemia include hypoxia and smoking; carboxyhemoglobin levels may be elevated in smokers (Table 13–15). A renal CT scan or sonogram may be considered to look for an erythropoietin-secreting cyst or tumor. A positive family history should lead to investigation for a congenital high-oxygen-affinity hemoglobin. An absence of a mutation in *JAK2* suggests a different diagnosis. However, *JAK2* mutations are also commonly found in other myeloproliferative disorders, essential thrombocythosis, and myelofibrosis.

Polycythemia vera should be differentiated from other myeloproliferative disorders (Table 13–14). Marked elevation of the white blood count (above 30,000/mcL [$30 \times 10^9/L$]) suggests CML. Abnormal red blood cell morphology and nucleated red blood cells in the peripheral blood are seen in myelofibrosis. Essential thrombocythosis is suggested when the platelet count is strikingly elevated.

► Treatment

The treatment of choice is phlebotomy. One unit of blood (approximately 500 mL) is removed weekly until the hematocrit is less than 45%; the hematocrit is maintained at less than 45% by repeated phlebotomy as necessary. Patients for whom phlebotomy is problematic (because of poor venous access or logistical reasons) may be managed primarily with hydroxyurea. Because repeated phlebotomy intentionally produces iron deficiency, the requirement for phlebotomy should gradually decrease. It is important to avoid medicinal iron supplementation, as this can thwart the goals of a phlebotomy program. A diet low in iron is not necessary but will increase the intervals between phlebotomies. Maintaining the hematocrit at normal levels has been shown to decrease the incidence of thrombotic complications.

Occasionally, myelosuppressive therapy is indicated. Indications include a high phlebotomy requirement, thrombocytosis, and intractable pruritus. There is evidence that reduction of the platelet count to less than 600,000/mcL

($600 \times 10^9/L$) will reduce the risk of thrombotic complications. Hydroxyurea is widely used when myelosuppressive therapy is indicated. The usual dose is 500–1500 mg/day orally, adjusted to keep platelets less than 500,000/mcL ($500 \times 10^9/L$) without reducing the neutrophil count to less than 2000/mcL ($2.0 \times 10^9/L$). The *JAK2* inhibitor ruxolitinib is FDA-approved for patients resistant or intolerant to hydroxyurea. In a randomized study comparing best available therapy to ruxolitinib, treatment with ruxolitinib was associated with greater benefit for both hematocrit control without phlebotomy (60%) and splenic volume reduction (38%). Symptom burden improved by greater than 50% in 49% of patients.

A randomized phase 3 trial comparing ropeginterferon alfa-2b, a novel interferon, to hydroxyurea demonstrated improved disease control rates in patients presenting without splenomegaly with 53% vs 38% of patients achieving a complete hematologic response and with improved disease burden at 3 years' follow up. Toxicity included abnormal liver biochemical tests in the ropeginterferon alfa-2b group, and leukopenia and thrombocytopenia in the standard therapy group, with serious adverse events occurring in 2% in the former and 4% in the latter group. As a result, ropeginterferon alfa-2b was approved by the European Medicines Agency as first-line therapy for patients without symptomatic splenomegaly. *Alkylating agents, such as busulfan and pipobroman, have been shown to increase the risk of conversion of this disease to acute leukemia and should be avoided.* Lastly, a new and promising therapeutic strategy is induction of apoptosis via the p53 pathway through pharmacologic inhibition of human double minute 2 (mdm2).

Low-dose aspirin (75–81 mg/day orally) has been shown to reduce the risk of thrombosis without excessive bleeding and should be part of therapy for all patients without contraindications to aspirin. Allopurinol 300 mg orally daily may be indicated for hyperuricemia. Antihistamine therapy with diphenhydramine or other H₁-blockers and, rarely, selective serotonin reuptake inhibitors are used to manage pruritus.

► Prognosis

Polycythemia is an indolent disease with median survival of over 15 years. The major cause of morbidity and mortality is arterial thrombosis. Over time, polycythemia vera may convert to myelofibrosis or to CML. In approximately 5% of cases, the disorder progresses to AML, which is usually refractory to therapy.

► When to Refer

Patients with polycythemia vera should be referred to a hematologist.

► When to Admit

Inpatient care is rarely required.

Gerds AT. Beyond JAK-STAT: novel therapeutic targets in Ph-negative MPN. Hematology Am Soc Hematol Educ Program. 2019;2019:407. [PMID: 31808852]

Gisslinger H et al; PROUD-PV Study Group. Ropivinterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020;7:e196. [PMID: 32014125]

Tefferi A et al. Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management. Am J Hematol. 2019;94:133. [PMID: 30281843]

gene (Philadelphia chromosome) since it can differentiate CML, where it is present, from essential thrombocytosis, where it is absent.

Differential Diagnosis

Essential thrombocytosis must be distinguished from secondary causes of an elevated platelet count. In reactive thrombocytosis, the platelet count seldom exceeds 1,000,000/mcL ($1000 \times 10^9/L$). Inflammatory disorders such as rheumatoid arthritis and ulcerative colitis cause significant elevations of the platelet count, as may chronic infection. The thrombocytosis of iron deficiency is observed only when anemia is significant. The platelet count is temporarily elevated after a splenectomy. *JAK2* mutations are found in over 50% of cases. *MPL* and *CALR* mutations frequently occur in patients with *JAK2*-negative essential thrombocytosis.

Regarding other myeloproliferative disorders, the lack of erythrocytosis distinguishes it from polycythemia vera. Unlike myelofibrosis, red blood cell morphology is normal, nucleated red blood cells are absent, and giant degranulated platelets are not seen. In CML, the Philadelphia chromosome (or *bcrabl* by molecular testing) establishes the diagnosis.

Treatment

Patients are considered at high risk for thrombosis if they are older than 60 years, have a leukocyte count of 11,000/mcL ($11 \times 10^9/L$) or higher, or have a previous history of thrombosis. They also have a higher risk for bleeding. The risk of thrombosis can be reduced by control of the platelet count, which should be kept under 500,000/mcL ($500 \times 10^9/L$). The treatment of choice is oral hydroxyurea in a dose of 500–1000 mg/day. In rare cases in which hydroxyurea is not well tolerated because of anemia, low doses of anagrelide, 1–2 mg/day orally, may be added. Higher doses of anagrelide can be complicated by headache, peripheral edema, and heart failure. Pegylated interferon alfa-2 can induce significant hematologic responses and can potentially target the malignant clone in *CALR*-mutant cases. Strict control of coexistent cardiovascular risk factors is mandatory for all patients.

Vasomotor symptoms such as erythromelalgia and paresthesia respond rapidly to aspirin. Historically, low-dose aspirin (81 mg/day orally) has been used to reduce the risk of thrombotic complications in low-risk patients, but a recent study found that once daily dosing is not as effective as an every 12-hour regimen. In the unusual event of severe bleeding, the platelet count can be lowered rapidly with plateletpheresis. In cases of marked thrombocytosis (greater than or equal to 1,000,000/mcL [$1000 \times 10^9/L$]) or of any evidence of bleeding, acquired von Willebrand syndrome must be excluded before starting low-dose aspirin.

Course & Prognosis

Essential thrombocytosis is an indolent disorder that allows long-term survival. Average survival is longer than 15 years from diagnosis, and the survival of patients younger than age 50 years does not appear different from matched controls. The major source of morbidity—thrombosis—can be reduced by appropriate platelet

ESSENTIAL THROMBOCYTOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Elevated platelet count in absence of other causes.
- ▶ Normal red blood cell mass.
- ▶ Absence of *bcrabl* gene (Philadelphia chromosome).

General Considerations

Essential thrombocytosis is an uncommon myeloproliferative disorder of unknown cause in which marked proliferation of the megakaryocytes in the bone marrow leads to elevation of the platelet count. As with polycythemia vera, the finding of a high frequency of mutations of *JAK2* and others in these patients has advanced the understanding of this disorder.

Clinical Findings

A. Symptoms and Signs

The median age at presentation is 50–60 years, and there is a slightly increased incidence in women. The disorder is often suspected when an elevated platelet count is found. Less frequently, the first sign is thrombosis, which is the most common clinical problem. The risk of thrombosis rises with age. Venous thromboses may occur in unusual sites such as the mesenteric, hepatic, or portal vein. Some patients experience erythromelalgia, painful burning of the hands accompanied by erythema; this symptom is reliably relieved by aspirin. Bleeding, typically mucosal, is less common and is related to a concomitant qualitative platelet defect. Splenomegaly is present in at least 25% of patients.

B. Laboratory Findings

An elevated platelet count is the hallmark of this disorder, and may be over 2,000,000/mcL ($2000 \times 10^9/L$) (Table 13–14). The white blood cell count is often mildly elevated, usually not above 30,000/mcL ($30 \times 10^9/L$), but with some immature myeloid forms. The hematocrit is normal. The peripheral blood smear reveals large platelets, but giant degranulated forms seen in myelofibrosis are not observed. Red blood cell morphology is normal.

The bone marrow shows increased numbers of megakaryocytes but no other morphologic abnormalities. The peripheral blood should be tested for the *bcrabl* fusion

control. Late in the disease course, the bone marrow may become fibrotic, and massive splenomegaly may occur, sometimes with splenic infarction. There is a 10–15% risk of progression to myelofibrosis after 15 years, and a 1–5% risk of transformation to acute leukemia over 20 years.

► When to Refer

Patients with essential thrombocythemia should be referred to a hematologist.

- Bose P et al. Updates in the management of polycythemia vera and essential thrombocythemia. *Ther Adv Hematol*. 2019;10:2040620719870052. [PMID: 31516686]
- Rocca B et al. A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia. *Blood*. 2020;136:171. [PMID: 32266380]
- Sankar K et al. Thrombosis in the Philadelphia chromosome-negative myeloproliferative neoplasms. *Cancer Treat Res*. 2019;179:159. [PMID: 31317487]

PRIMARY MYELOFIBROSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Striking splenomegaly.
- ▶ Teardrop poikilocytosis on peripheral smear.
- ▶ Leukoerythroblastic blood picture; giant abnormal platelets.
- ▶ Initially hypercellular, then hypocellular bone marrow with reticulin or collagen fibrosis.

► General Considerations

Primary myelofibrosis is a myeloproliferative disorder characterized by clonal hematopoiesis that is often but not always accompanied by *JAK2*, *CALR*, or *MPL* mutations; bone marrow fibrosis; anemia; splenomegaly; and a leukoerythroblastic peripheral blood picture with teardrop poikilocytosis. Myelofibrosis can also occur as a secondary process following the other myeloproliferative disorders (eg, polycythemia vera, essential thrombocythemia). It is believed that fibrosis occurs in response to increased secretion of platelet-derived growth factor (PDGF) and possibly other cytokines. In response to bone marrow fibrosis, extramedullary hematopoiesis takes place in the liver, spleen, and lymph nodes. In these sites, mesenchymal cells responsible for fetal hematopoiesis can be reactivated. According to the 2016 WHO classification, “prefibrotic” primary myelofibrosis is distinguished from “overtly fibrotic” primary myelofibrosis; the former might mimic essential thrombocythemia in its presentation and it is prognostically relevant to distinguish the two.

► Clinical Findings

A. Symptoms and Signs

Primary myelofibrosis develops in adults over age 50 years and is usually insidious in onset. Patients most commonly

present with fatigue due to anemia or abdominal fullness related to splenomegaly. Uncommon presentations include bleeding and bone pain. On examination, splenomegaly is almost invariably present and is commonly massive. The liver is enlarged in more than 50% of cases.

Later in the course of the disease, progressive bone marrow failure takes place as it becomes increasingly more fibrotic. Progressive thrombocytopenia leads to bleeding. The spleen continues to enlarge, which leads to early satiety. Painful episodes of splenic infarction may occur. The patient becomes cachectic and may experience severe bone pain, especially in the upper legs. Hematopoiesis in the liver leads to portal hypertension with ascites, esophageal varices, and occasionally transverse myelitis caused by myelopoiesis in the epidural space.

B. Laboratory Findings

Patients are almost invariably anemic at presentation. The white blood count is variable—either low, normal, or elevated—and may be increased to 50,000/mcL ($50 \times 10^9/L$). The platelet count is variable. The peripheral blood smear is dramatic, with significant poikilocytosis and numerous teardrop forms in the red cell line. Nucleated red blood cells are present and the myeloid series is shifted, with immature forms including a small percentage of promyelocytes or myeloblasts. Platelet morphology may be bizarre, and giant degranulated platelet forms (megakaryocyte fragments) may be seen. The triad of teardrop poikilocytosis, leukoerythroblastic blood, and giant abnormal platelets is highly suggestive of myelofibrosis.

The bone marrow usually cannot be aspirated (dry tap), though early in the course of the disease, biopsy shows it to be hypercellular, with a marked increase in megakaryocytes. Fibrosis at this stage is detected by a silver stain demonstrating increased reticulin fibers. Later, biopsy reveals more severe fibrosis, with eventual replacement of hematopoietic precursors by collagen. There is no characteristic chromosomal abnormality. *JAK2* is mutated in ~65% of cases, and *MPL* and *CALR* are mutated in the majority of the remaining cases; 10% of cases are “triple-negative.”

► Differential Diagnosis

A leukoerythroblastic blood picture from other causes may be seen in response to severe infection, inflammation, or infiltrative bone marrow processes. However, teardrop poikilocytosis and giant abnormal platelet forms will not be present. Bone marrow fibrosis may be seen in metastatic carcinoma, Hodgkin lymphoma, and hairy cell leukemia. These disorders are diagnosed by characteristic morphology of involved tissues.

Of the other myeloproliferative disorders, CML is diagnosed when there is marked leukocytosis, normal red blood cell morphology, and the presence of the *bcr/abl* fusion gene. Polycythemia vera is characterized by an elevated hematocrit. Essential thrombocythemia shows predominant platelet count elevations.

► Treatment

Observation with supportive care is a reasonable treatment strategy for asymptomatic patients with low risk or an

intermediate risk—an intermediate-1 score on the Dynamic International Prognostic Scoring system (DIPSS-plus), especially in the absence of high-risk mutations. Anemic patients are supported with transfusion. Anemia can also be controlled with androgens, prednisone, thalidomide, or lenalidomide. First-line therapy for myelofibrosis-associated splenomegaly is hydroxyurea 500–1000 mg/day orally, which is effective in reducing spleen size by half in approximately 40% of patients. Both thalidomide and lenalidomide may improve splenomegaly and thrombocytopenia in some patients. Splenectomy is not routinely performed but is indicated for medication-refractory splenic enlargement causing recurrent painful episodes, severe thrombocytopenia, or an unacceptable transfusion requirement. Perioperative complications can occur in 28% of patients and include infections, abdominal vein thrombosis, and bleeding. Radiation therapy has a role for painful sites of extramedullary hematopoiesis, pulmonary hypertension, or severe bone pain. Transjugular intrahepatic portosystemic shunt might also be considered to alleviate symptoms of portal hypertension.

Patients with high-risk or intermediate-2-risk disease on the DIPSS-plus, or those patients harboring high-risk mutations such as *ASXL1* or *SRSF2*, should be considered for allogeneic stem cell transplant, which is currently the only potentially curative treatment modality in this disease. Nontransplant candidates may be treated with JAK2 inhibitors or immunomodulatory agents for symptom control. Ruxolitinib, the first JAK2 inhibitor to be FDA approved, results in reduction of spleen size and improvement of constitutional symptoms but does not induce complete clinical or cytogenetic remissions or significantly affect the *JAK2/CALR/MPL* mutant allele burden. Moreover, ruxolitinib can exacerbate cytopenias. The newer selective JAK2 inhibitor fedratinib, FDA approved in 2019, can lead to sustained reduction in spleen size and improvement in disease-associated symptoms for patients with advanced-stage myelofibrosis. However, it carries a significant risk of serious and fatal encephalopathy, including Wernicke encephalopathy, and providers should regularly assess thiamine levels in all patients. The immunomodulatory medications lenalidomide and pomalidomide result in control of anemia in 25% and thrombocytopenia in ~58% of cases, without significant reduction in splenic size.

► Course & Prognosis

The median survival from time of diagnosis is approximately 5 years. Therapies with biologic agents and the application of reduced-intensity allogeneic stem cell transplantation appear to offer the possibility of improving the outcome for many patients. End-stage myelofibrosis is characterized by generalized asthenia, liver failure, and bleeding from thrombocytopenia, with some cases terminating in AML. The DIPSS-plus incorporates clinical and genetic risk variables and is associated with overall survival. Most recently, DIPSS-plus-independent adverse prognostic relevance has been demonstrated for certain mutations including *ASXL1* and *SRSF2*. By contrast, patients with type 1/like *CALR* mutations, compared to their counterparts with other driver mutations, displayed significantly better survival.

► When to Refer

Patients in whom myelofibrosis is suspected should be referred to a hematologist.

► When to Admit

Admission is not usually necessary.

Finazzi G et al. Prefibrotic myelofibrosis: treatment algorithm 2018. *Blood Cancer J*. 2018;8:104. [PMID: 30405096]
Schieber M et al. Myelofibrosis in 2019: moving beyond JAK2 inhibition. *Blood Cancer J*. 2019;9:74. [PMID: 31511492]

CHRONIC MYELOID LEUKEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Elevated white blood cell count.
- ▶ Markedly left-shifted myeloid series but with a low percentage of promyelocytes and blasts.
- ▶ Presence of *bcr/abl* gene (Philadelphia chromosome).

► General Considerations

CML is a myeloproliferative disorder characterized by overproduction of myeloid cells. These myeloid cells continue to differentiate and circulate in increased numbers in the peripheral blood.

CML is characterized by a specific chromosomal abnormality and a specific molecular abnormality. The **Philadelphia chromosome** is a reciprocal translocation between the long arms of chromosomes 9 and 22. The portion of 9q that is translocated contains *abl*, a protooncogene that is received at a specific site on 22q, the break point cluster (*bcr*). The fusion gene *bcr/abl* produces a novel protein that possesses tyrosine kinase activity. This disorder is the first recognized example of tyrosine kinase “addiction” by cancer cells.

Early CML (“chronic phase”) does not behave like a malignant disease. Normal bone marrow function is retained, white blood cells differentiate, and despite some qualitative abnormalities, the neutrophils combat infection normally. However, untreated CML is inherently unstable, and without treatment, the disease progresses to an “accelerated” phase and then an “acute blast” phase, which is morphologically indistinguishable from acute leukemia.

► Clinical Findings

A. Symptoms and Signs

CML is a disorder of middle age (median age at presentation is 55 years). Patients usually complain of fatigue, night sweats, and low-grade fevers related to the hypermetabolic state caused by overproduction of white blood cells. Patients may also complain of abdominal fullness related to splenomegaly. In some cases, an elevated white blood count is discovered incidentally. Rarely, the patient will present with

a clinical syndrome related to leukostasis with blurred vision, respiratory distress, or priapism. The white blood count in these cases is usually greater than 100,000/mcL ($100 \times 10^9/\text{L}$) but less than 500,000/mcL ($500 \times 10^9/\text{L}$). On examination, the spleen is enlarged (often markedly so), and sternal tenderness may be present as a sign of marrow overexpansion. In cases discovered during routine laboratory monitoring, these findings are often absent. Acceleration of the disease is often associated with fever (in the absence of infection), bone pain, and splenomegaly.

B. Laboratory Findings

CML is characterized by an elevated white blood cell count; the median white blood count at diagnosis is 150,000/mcL ($150 \times 10^9/\text{L}$), although in some cases the white blood cell count is only modestly increased (Table 13–14). The peripheral blood is characteristic. The myeloid series is left shifted, with mature forms dominating and with cells usually present in proportion to their degree of maturation. Blasts are usually less than 5%. Basophilia and eosinophilia may be present. At presentation, the patient is usually not anemic. Red blood cell morphology is normal, and nucleated red blood cells are rarely seen. The platelet count may be normal or elevated (sometimes to strikingly high levels). A bone marrow biopsy is essential to ensure sufficient material for a complete karyotype and for morphologic evaluation to confirm the phase of disease. The bone marrow is hypercellular, with left-shifted myelopoiesis. Myeloblasts compose less than 5% of marrow cells. The hallmark of the disease is the *bcr/abl* gene that is detected by the polymerase chain reaction (PCR) test in the peripheral blood and bone marrow.

With progression to the accelerated and blast phases, progressive anemia and thrombocytopenia occur, and the percentage of blasts in the blood and bone marrow increases. Blast-phase CML is diagnosed when blasts comprise more than 20% of bone marrow cells.

► Differential Diagnosis

Early CML must be differentiated from the reactive leukocytosis associated with infection. In such cases, the white blood count is usually less than 50,000/mcL ($50 \times 10^9/\text{L}$), splenomegaly is absent, and the *bcr/abl* gene is not present.

CML must be distinguished from other myeloproliferative disease (Table 13–14). The hematocrit should not be elevated, the red blood cell morphology is normal, and nucleated red blood cells are rare or absent. Definitive diagnosis is made by finding the *bcr/abl* gene.

► Treatment

Treatment is usually not emergent even with white blood counts over 200,000/mcL ($200 \times 10^9/\text{L}$), since the majority of circulating cells are mature myeloid cells that are smaller and more deformable than primitive leukemic blasts. In the rare instances in which symptoms result from extreme hyperleukocytosis (priapism, respiratory distress, visual blurring, altered mental status), emergent leukapheresis is performed in conjunction with myelosuppressive therapy.

In chronic-phase CML, the goal of therapy is normalization of the hematologic abnormalities and suppression of the

malignant *bcr/abl*-expressing clone. The treatment of choice consists of a tyrosine kinase inhibitor (eg, imatinib, nilotinib, dasatinib) targeting the aberrantly active *abl* kinase. It is expected that a hematologic complete remission, with normalization of blood counts and splenomegaly will occur within 3 months of treatment initiation. Second, a reduction of *bcr/abl* transcripts to less than 10% on the international scale should be achieved, ideally within 3 months but certainly within 6 months. Finally, a major molecular response (less than or equal to 0.1% transcripts) is desired within 12 months. Patients who achieve this level of molecular response have an excellent prognosis, with overall survival approaching 100% since disease progression is uncommon. On the other hand, patients have a worse prognosis if these targets are not achieved, molecular response is subsequently lost, or new mutations or cytogenetic abnormalities develop.

Imatinib mesylate was the first tyrosine kinase inhibitor to be approved and it results in nearly universal (98%) hematologic control of chronic-phase disease at a dose of 400 mg/day. The rate of a major molecular response with imatinib in chronic-phase disease is ~30% at 1 year. The second-generation tyrosine kinase inhibitors, nilotinib and dasatinib, are also used as front-line therapy and can significantly increase the rate of a major molecular response compared to imatinib (71% for nilotinib at 300–400 mg twice daily by 2 years, 64% for dasatinib at 100 mg/day by 2 years) and result in a lower rate of progression to advanced-stage disease. However, these agents are associated with additional toxicity. Since they can still salvage 90% of patients who do not respond to treatment with imatinib, they may be reserved for use in that situation. A dual *bcr/abl* tyrosine kinase inhibitor, bosutinib, is used for patients who are resistant or intolerant to the other tyrosine kinase inhibitors. The complete cytogenetic response rate to bosutinib is 25%, but it is not active against the *T315I* mutation.

Patients taking tyrosine kinase inhibitors should be monitored with a quantitative PCR assay. Those with a consistent increase in *bcr/abl* transcript or those with a suboptimal molecular response as defined above should undergo *abl* mutation testing and then be switched to an alternative tyrosine kinase inhibitor. The *T315I* mutation in *abl* is specifically resistant to therapy with imatinib, dasatinib, nilotinib, and bosutinib but appears to be sensitive to the third-generation agent ponatinib. However, ponatinib is associated with a high rate of vascular thrombotic complications. For patients with the *T315I* mutation as well as patients who have not responded to multiple tyrosine kinase inhibitors, including ponatinib, the novel allosteric inhibitor asciminib can be tried. It has shown a 54% complete hematologic response rate and a 48% sustained major molecular response in heavily pretreated patients. Dose-limiting toxic effects include asymptomatic elevations in the lipase level and clinical pancreatitis. Lastly, omacetaxine—a non-tyrosine kinase inhibitor therapy approved for patients with CML who are resistant to at least two tyrosine kinase inhibitors—can produce major cytogenetic responses in 18% of patients. Patients in whom a good molecular response to any of these agents cannot be achieved or in whom disease progresses despite therapy should be considered for allogeneic stem cell transplantation.

Patients with advanced-stage disease (accelerated phase or myeloid/lymphoid blast crisis) should be treated with a tyrosine kinase inhibitor alone or in combination with myelosuppressive chemotherapy. The doses of tyrosine kinase inhibitors in that setting are usually higher than those appropriate for chronic-phase disease. Since the duration of response to tyrosine kinase inhibitors in this setting is limited, patients who have accelerated or blast-phase disease should ultimately be considered for allogeneic stem cell transplantation.

► Course & Prognosis

Patients with good molecular responses to tyrosine kinase inhibitor therapy have an excellent prognosis, with essentially 100% survival at last follow up. Studies suggest that tyrosine kinase inhibitor therapy may be safely discontinued after 2 years in patients who achieve a sustained major molecular response, with ~50% of patients remaining in molecular remission at least 1 year posttreatment. Of importance, more than 80% of recurrences occur within the first 6–8 months after stopping therapy, and loss of major molecular response is uncommon after 1 year. About 90–95% of patients who experience molecular recurrence regain their initial molecular level after restarting tyrosine kinase inhibitor therapy.

► When to Refer

All patients with CML should be referred to a hematologist.

► When to Admit

Hospitalization is rarely necessary and should be reserved for symptoms of leukostasis at diagnosis or for transformation to acute leukemia.

Craddock CF. We do still transplant CML, don't we? Hematology Am Soc Hematol Educ Program. 2018;2018:177. [PMID: 30504307]

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Molica M et al. Insights into the optimal use of ponatinib in patients with chronic phase chronic myeloid leukaemia. Ther Adv Hematol. 2019;10:2040620719826444. [PMID: 30854182]

MYELODYSPLASTIC SYNDROMES



ESSENTIALS OF DIAGNOSIS

- Cytopenias with a hypercellular bone marrow.
- Morphologic abnormalities in one or more hematopoietic cell lines.

► General Considerations

The MDS are a group of acquired clonal disorders of the hematopoietic stem cell. They are characterized by the constellation of cytopenias, a usually hypercellular marrow,

morphologic dysplasia, and genetic abnormalities. The disorders are usually idiopathic but may be caused by prior exposure to cytotoxic chemotherapy, radiation or both. In addition to cytogenetics, sequencing can detect genetic mutations in 80–90% of MDS patients. Importantly, acquired clonal mutations identical to those seen in MDS can occur in the hematopoietic cells of ~10% of apparently healthy older individuals, defining the disorder of **clonal hematopoiesis of indeterminate potential (CHIP)**.

Myelodysplasia encompasses several heterogeneous syndromes. A key distinction is whether there is an increase in bone marrow blasts (greater than 5% of marrow elements). The category of MDS with excess blasts represents a more aggressive form of the disease, often leading to AML. Those without excess blasts are characterized by the degree of dysplasia, eg, MDS with single lineage dysplasia and MDS with multilineage dysplasia. The morphologic finding of **ringed sideroblasts** is used to define a subcategory of the lower-risk MDS syndromes. Patients with **isolated 5q loss**, which is characterized by the cytogenetic finding of loss of part of the long arm of chromosome 5, comprise an important subgroup of patients with a different natural history. Lastly, a proliferative syndrome including sustained peripheral blood monocytosis more than 1000/mcL ($1.0 \times 10^9/L$) is termed **chronic myelomonocytic leukemia (CMML)**, a disorder that shares features of myelodysplastic and myeloproliferative disorders. An International Prognostic Scoring System (IPSS) classifies patients by risk status based on the percentage of bone marrow blasts, cytogenetics, and severity of cytopenias. The IPSS is associated with the rate of progression to AML and with overall survival, which can range from a median of 6 years for the low-risk group to 5 months for the high-risk patients.

► Clinical Findings

A. Symptoms and Signs

Patients are usually over age 60 years. Many patients are asymptomatic when the diagnosis is made because of the finding of abnormal blood counts. Fatigue, infection, or bleeding related to bone marrow failure are usually the presenting symptoms and signs. The course may be indolent, and the disease may present as a wasting illness with fever, weight loss, and general debility. On examination, splenomegaly may be present in combination with pallor, bleeding, and various signs of infection. MDS can also be accompanied by a variety of paraneoplastic syndromes prior to or following this diagnosis.

B. Laboratory Findings

Anemia may be marked with the MCV normal or increased, and transfusion support may be required. On the peripheral blood smear, macro-ovalocytes may be seen. The white blood cell count is usually normal or reduced, and neutropenia is common. The neutrophils may exhibit morphologic abnormalities, including deficient numbers of granules or deficient segmentation of the nucleus, even a bilobed nucleus (the so-called Pelger-Huët abnormality). The myeloid series may be left shifted, and small numbers of promyelocytes or blasts may

be seen. The platelet count is normal or reduced, and hypogranular platelets may be present.

The bone marrow is characteristically hypercellular but occasionally may be hypocellular. Erythroid hyperplasia is common, and signs of abnormal erythropoiesis include megaloblastic features, nuclear budding, or multinucleated erythroid precursors. The Prussian blue stain may demonstrate ringed sideroblasts. In the marrow, too, the myeloid series is often left shifted, with variable increases in blasts. Deficient or abnormal granules may be seen. A characteristic abnormality is the presence of dwarf megakaryocytes with a unilobed nucleus. Genetic abnormalities define MDS; there are frequent cytogenetic abnormalities involving chromosomes 5 and 7. Some patients with an indolent form have an isolated partial deletion of chromosome 5 (MDS with isolated del[5q]). Aside from cytogenetic abnormalities, the most commonly mutated genes are *SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, *RUNX1*, *U2AF1*, *TP53*, and *EZH2*.

► Differential Diagnosis

MDS should be distinguished from megaloblastic anemia, aplastic anemia, myelofibrosis, HIV-associated cytopenias, and acute or chronic drug effect. In subtle cases, cytogenetic evaluation of the bone marrow may help distinguish this clonal disorder from other causes of cytopenias. As the number of blasts increases in the bone marrow, myelodysplasia is arbitrarily separated from AML by the presence of less than 20% blasts.

► Treatment

Myelodysplasia is a heterogeneous disease, and the appropriate treatment depends on a number of factors. For patients with anemia who have a low serum erythropoietin level (500 units/L or less), erythropoiesis-stimulating agents may raise the hematocrit and reduce the red cell transfusion requirement in 40%. Addition of intermittent granulocyte colony-stimulating factor (G-CSF) therapy may augment the erythroid response to epoetin. Unfortunately, the patients with the highest transfusion requirements and those with erythropoietin levels above 200 units/L are the least likely to respond. Patients who remain dependent on red blood cell transfusion and who can tolerate it should receive iron chelation in order to prevent serious iron overload; the dose of oral agent deferasirox is 20 mg/kg/day in divided dosing. Patients affected primarily with severe neutropenia may benefit from the use of myeloid growth factors such as filgrastim. Oral thrombopoietin analogs, such as romiplostim and eltrombopag, have shown effectiveness in raising the platelet count in myelodysplasia. Finally, occasional patients can benefit from immunosuppressive therapy including ATG. Predictors of response to ATG include age younger than 60 years, absence of 5q-, and presence of HLA DR15.

For patients who do not respond to these interventions, there are several therapeutic options available. Lenalidomide is the treatment of choice in patients with MDS with isolated del(5q) with significant responses in 70% of patients, and responses typically lasting longer than 2 years. In addition, nearly half of these patients enter a cytogenetic remission

with clearing of the abnormal 5q- clone. The recommended initial dose is 10 mg/day orally. The most common side effects are neutropenia and thrombocytopenia, but venous thrombosis occurs and warrants prophylaxis with aspirin, 325 mg/day orally. A novel agent, luspatercept, has been developed to target signaling via the SMAD2-SMAD3 pathway, which is constitutively increased in the bone marrow cells of patients with MDS and ineffective erythropoiesis. In a randomized study, luspatercept induced transfusion independence in 38% of lower-risk MDS patients who had not responded to growth factor therapy compared to 13% in the placebo arm. The most common adverse events included fatigue, diarrhea, asthenia, nausea, and dizziness.

For patients with high-risk MDS, hypomethylating agents are the treatment of choice. Azacitidine can improve both symptoms and blood counts and prolong overall survival and time to conversion to acute leukemia. It is used at a dose of 75 mg/m² daily for 5–7 days every 28 days and up to six cycles of therapy may be required to achieve a response. Decitabine, a related hypomethylating agent, given at 20 mg/m² daily for 5 days every 28 days can produce similar hematologic responses but has not demonstrated a benefit in overall survival compared to supportive care alone. Unfortunately, the progress that has been made over the past decade in understanding the complex molecular mechanisms underlying MDS has not yet translated into new therapeutic options.

Allogeneic stem cell transplantation is the only curative therapy for myelodysplasia, but its role is limited by the advanced age of many patients and the variably indolent course of the disease.

► Course & Prognosis

Myelodysplasia is an ultimately fatal disease, and allogeneic transplantation is the only curative therapy, with cure rates of 30–60% depending primarily on the risk status of the disease. Patients most commonly die of infections or bleeding. Patients with MDS with isolated del(5q) have a favorable prognosis, with 5-year survival over 90%. Other patients with low-risk disease (with absence of both excess blasts and adverse cytogenetics) may also do well, with similar survival. Those with excess blasts or CMML have a higher (30–50%) risk of developing acute leukemia, and short survival (less than 2 years) without allogeneic transplantation.

► When to Refer

All patients with myelodysplasia should be referred to a hematologist.

► When to Admit

Hospitalization is needed only for specific complications, such as severe infection.

Angelucci E et al. Iron chelation in transfusion-dependent patients with low- to intermediate-1-risk myelodysplastic syndromes: a randomized trial. Ann Intern Med. 2020;172:513. [PMID: 32203980]

Fenaux P et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med.* 2020;382:140. [PMID: 31914241]

Park S et al. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-risk myelodysplastic syndrome: a systematic literature review. *Br J Haematol.* 2019;184:134. [PMID: 30549002]

Santini V. How I treat MDS after hypomethylating agent failure. *Blood.* 2019;133:521. [PMID: 30545832]

ACUTE LEUKEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Short duration of symptoms, including fatigue, fever, and bleeding.
- ▶ Cytopenias or pancytopenia.
- ▶ Blasts in peripheral blood in 90% of patients.
- ▶ More than 20% blasts in the bone marrow.

► General Considerations

Acute leukemia is a malignancy of the hematopoietic progenitor cell. Malignant immature cells proliferate in an uncontrolled fashion and replace normal bone marrow elements. Most cases arise with no clear cause. However, radiation and some toxins (benzene) are leukemogenic. In addition, a number of chemotherapeutic agents (especially cyclophosphamide, melphalan, other alkylating agents, and etoposide) may cause leukemia. The leukemias seen after toxin or chemotherapy exposure often develop from a myelodysplastic prodrome and are often associated with abnormalities in chromosomes 5 and 7. Those related to etoposide or anthracyclines may have abnormalities in chromosome 11q23 (MLL locus).

Most of the clinical findings in acute leukemia are due to replacement of normal bone marrow elements by the malignant cells. Less common manifestations result from organ infiltration (skin, gastrointestinal tract, meninges). Acute leukemia is potentially curable with combination chemotherapy.

The myeloblastic subtype, AML, is primarily an adult disease with a median age at presentation of 60 years and an increasing incidence with advanced age. Acute promyelocytic leukemia (APL) is characterized by the chromosomal translocation t(15;17), which produces the fusion gene *PML-RAR-alpha*, leading to a block in differentiation that can be overcome with pharmacologic doses of retinoic acid. The lymphoblastic subtype of acute leukemia, ALL, comprises 80% of the acute leukemias of childhood. The peak incidence is between 3 and 7 years of age. It is also seen in adults, causing approximately 20% of adult acute leukemias.

► Classification of the Leukemias

A. Acute Myeloid Leukemia (AML)

AML is primarily categorized based on recurrent structural chromosomal and molecular abnormalities. The cytogenetic abnormalities can be identified on traditional karyotyping

or metaphase fluorescence in situ hybridization (FISH) and the molecular abnormalities are identified by either targeted or genome-wide sequencing of tumor DNA. Favorable cytogenetics such as t(8;21) producing a chimeric RUNX1/RUNX1T1 protein and inv(16)(p13;q22) are seen in 15% of cases and are termed the “core-binding factor” leukemias. These patients have a higher chance of achieving both short- and long-term disease control. Unfavorable cytogenetics confer a very poor prognosis. These consist of chromosomal translocations [t(6;9), t(3;3) or inv (3), t(v;11q23)], isolated monosomy 5 or 7, the presence of two or more other monosomies, or three or more separate cytogenetic abnormalities and account for 25% of the cases. The majority of cases of AML are of intermediate risk by traditional cytogenetics and have either a normal karyotype or chromosomal abnormalities that do not confer strong prognostic significance. However, there are several recurrent gene mutations with prognostic significance in this subgroup. On the one hand, internal tandem duplication in the gene *FLT3* occurs in ~30% of AML and is conditionally associated with a very poor prognosis in the setting of wild type *NPM1*. Other mutations conferring a poor prognosis occur in *RUNX1*, *ASXL1*, and *TP53*. On the other hand, a relatively favorable group of patients has been identified that lacks *FLT3-ITD* mutations and includes mutations of nucleophosmin 1 (*NPM1*) or carries *CEBPA* biallelic mutations.

B. Acute Promyelocytic Leukemia (APL)

In considering the various types of AML, APL is discussed separately because of its unique biologic features and response to non-chemotherapy treatments. APL is characterized by the cytogenetic finding of t(15;17) and the fusion gene *PML-RAR-alpha*. It is a highly curable form of leukemia (over 90%) with integration of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) in induction, consolidation, and maintenance regimens.

C. Acute Lymphoblastic Leukemia (ALL)

ALL is most usefully classified by immunologic phenotype as follows: common, early B lineage, and T cell. Hyperdiploidy (with more than 50 chromosomes), especially of chromosomes 4, 10, and 17, and translocation t(12;21) (TEL-AML1), is associated with a better prognosis. Unfavorable cytogenetics are hypodiploidy (less than 44 chromosomes), the Philadelphia chromosome t(9;22), the t(4;11) translocation (which has fusion genes involving the *MLL* gene at 11q23), and a complex karyotype with more than five chromosomal abnormalities.

D. Mixed Phenotype Acute Leukemias

These leukemias consist of blasts that lack differentiation along the lymphoid or myeloid lineage or blasts that express both myeloid and lymphoid lineage-specific antigens. This group is considered very high risk and has a poor prognosis. The limited available data suggest that an “acute lymphoblastic leukemia-like” regimen followed by allogeneic stem cell transplant may be advisable; addition of a tyrosine kinase inhibitor in patients with t(9;22) translocation is recommended.

► Clinical Findings

A. Symptoms and Signs

Most patients have been ill only for days or weeks. Bleeding (usually due to thrombocytopenia) occurs in the skin and mucosal surfaces, with gingival bleeding, epistaxis, or menorrhagia. Less commonly, widespread bleeding is seen in patients with disseminated intravascular coagulation (DIC) (in APL and monocytic leukemia). Infection is due to neutropenia, with the risk of infection rising as the neutrophil count falls below 500/mcL ($0.5 \times 10^9/L$). Common presentations include cellulitis, pneumonia, and perirectal infections; death within a few hours may occur if treatment with appropriate antibiotics is delayed. Fungal infections are also commonly seen.

Patients may also seek medical attention because of gum hypertrophy and bone and joint pain. The most dramatic presentation is hyperleukocytosis, in which a markedly elevated circulating blast count (total white blood count greater than 100,000/mcL [$100 \times 10^9/L$]) leads to impaired circulation, presenting as headache, confusion, and dyspnea. Such patients require emergent chemotherapy with adjunctive leukapheresis since mortality approaches 40% in the first 48 hours.

On examination, patients appear pale and have purpura and petechiae; signs of infection may not be present. Stomatitis and gum hypertrophy may be seen in patients with monocytic leukemia, as may rectal fissures. There is variable enlargement of the liver, spleen, and lymph nodes. Bone tenderness may be present, particularly in the sternum, tibia, and femur.

B. Laboratory Findings

The hallmark of acute leukemia is the combination of pancytopenia with circulating blasts. However, blasts may be absent from the peripheral smear in as many as 10% of cases ("aleukemic leukemia"). The bone marrow is usually hypercellular and dominated by blasts (greater than 20%).

Hyperuricemia may be seen. If DIC is present, the fibrinogen level will be reduced, the prothrombin time prolonged, and fibrin degradation products or fibrin D-dimers present. Patients with ALL (especially T cell) may have a mediastinal mass visible on chest radiograph. Meningeal leukemia will have blasts present in the spinal fluid, seen in approximately 5% of cases at diagnosis; it is more common in monocytic types of AML and can be seen with ALL.

The **Auer rod**, an eosinophilic needle-like inclusion in the cytoplasm, is a characteristic of AML (though sometimes seen in APL, high-grade MDS, and myeloproliferative disorders). The phenotype of leukemia cells is usually demonstrated by flow cytometry or immunohistochemistry. AML cells usually express myeloid antigens such as CD13 or CD33 and myeloperoxidase. ALL cells of B lineage will express CD19, and most cases will express CD10, formerly known as the "common ALL antigen." ALL cells of T lineage will usually not express mature T-cell markers, such as CD3, CD4, or CD8, but will express some combination of CD2, CD5, and CD7 and will not express surface immunoglobulin. Almost all cells express terminal deoxynucleotidyl transferase (TdT).

► Differential Diagnosis

AML must be distinguished from other myeloproliferative disorders, CML, and MDS. Acute leukemia may also resemble a left-shifted bone marrow recovering from a previous toxic insult. If the diagnosis is in doubt, a bone marrow study should be repeated in several days to see if maturation has taken place. ALL must be separated from other lymphoproliferative disease such as CLL, lymphomas, and hairy cell leukemia. It may also be confused with the atypical lymphocytosis of mononucleosis and pertussis.

► Treatment

Acute leukemia is considered a curable disease, especially among younger patients without significant comorbidities. The first step in treatment is to obtain complete remission, defined as normal peripheral blood with resolution of cytopenias, normal bone marrow with no excess blasts, and normal clinical status. The type of initial chemotherapy depends on the subtype of leukemia.

1. AML—Most patients with AML who are treated with a curative intent receive a combination of an anthracycline (daunorubicin or idarubicin) plus cytarabine, either alone or in combination with other agents (eg, gemtuzumab ozogamicin). This therapy will produce complete remissions in 80–90% of patients under age 60 years and in 50–60% of older patients (see Table 39–2). Patients with secondary AML (evolved from prior myelodysplastic or myeloproliferative disorders) or treatment-associated AML should receive the drug Vyxeos (a liposomal formulation of daunorubicin and cytarabine). Patients with a *FLT3* mutation benefit from the addition of the *FLT3* kinase inhibitor midostaurin to their regimen. Post-remission therapy options include additional chemotherapy and allogeneic stem cell transplantation. Patients with a favorable genetic profile can be treated with chemotherapy alone or with autologous transplant with cure rates of 60–80%. For intermediate-risk patients with AML, cure rates are 35–40% with chemotherapy and 40–60% with allogeneic transplantation. Patients who do not enter remission (primary induction failure) or those with high-risk genetics have cure rates of less than 10% with chemotherapy alone and are referred for allogeneic stem cell transplantation.

Patients who are not treated with initial curative intent (those older than 75 years or with significant comorbidities) can derive benefit from newer targeted agents, including the *bcl2* inhibitor venetoclax added to a hypomethylating agent or low-dose cytarabine, enasidenib (targeting *IDH2* mutations), ivosidenib (targeting *IDH2* mutations), or glesdegib. Some of these patients can still benefit from a reduced-intensity allogeneic transplant if they achieve good disease control.

Once leukemia has recurred after initial chemotherapy, the prognosis is poor. For patients in second remission, allogeneic transplantation offers a 20–30% chance of cure. Targeted therapies described above are useful for selected patients and can offer long-term disease control.

2. ALL—Adults with ALL are treated with combination chemotherapy, including daunorubicin, vincristine,

prednisone, and asparaginase. This treatment produces complete remissions in 90% of patients. Those patients with Philadelphia chromosome-positive ALL (or *bcr-abl*-positive ALL) should receive a tyrosine kinase inhibitor, such as dasatinib or ponatinib, added to their initial chemotherapy. Remission induction therapy for ALL is less myelosuppressive than treatment for AML and does not necessarily produce prolonged marrow aplasia. Patients should also receive central nervous system prophylaxis so that meningeal sequestration of leukemic cells does not develop.

After achieving complete remission, patients may be treated with either additional cycles of chemotherapy or high-dose chemotherapy and stem cell transplantation. Treatment decisions are made based on patient age and disease risk factors. Adults younger than 39 years have uniformly better outcomes when treated under pediatric protocols. For older patients, minimal residual disease testing early on can identify high-risk patients who will not be cured with chemotherapy alone and who will do better with allogeneic transplantation. For patients with relapsed disease, the bispecific antibody blinatumomab targeting CD19 and the antibody-drug conjugate inotuzumab ozogamicin targeting CD22 have shown remarkable activity and are considered superior to traditional chemotherapy options. Tisagenlecleucel is a therapy utilizing autologous T cells engineered to express an anti-CD-19 antigen receptor (CART-19) and is FDA-approved for the treatment of children and young adults with relapsed/refractory B-ALL.

► Prognosis

Approximately 70–80% of adults with AML under age 60 years achieve complete remission and ~50% are cured using risk-adapted post-remission therapy. Older adults with AML achieve complete remission in up to 50% of instances. The cure rates for older patients with AML have been very low (approximately 10–20%) even if they achieve remission and are able to receive post-remission chemotherapy.

Patients younger than 39 years with ALL have excellent outcomes after undergoing chemotherapy followed by risk-adapted intensification and transplantation (cure rates of 60–80%). Patients with adverse cytogenetics, poor response to chemotherapy, or older age have a much lower chance of cure (cure rates of 20–40%).

► When to Refer

All patients should be referred to a hematologist.

► When to Admit

Most patients with acute leukemia will be admitted for treatment.

Sekeres MA et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. *Blood Adv.* 2020;4:3528. [PMID: 32761235]
Smith CC. The growing landscape of FLT3 inhibition in AML. *Hematology Am Soc Hematol Educ Program.* 2019;2019:539. [PMID: 31808872]

CHRONIC LYMPHOCYTIC LEUKEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ B-cell lymphocytosis with CD19 expression > 5000/mcL (> 5.0 × 10⁹/L).
- ▶ Coexpression of CD19, CD5 on lymphocytes.

► General Considerations

CLL is a clonal malignancy of B lymphocytes. The disease is usually indolent, with slowly progressive accumulation of long-lived small lymphocytes. These cells are immune-incompetent and respond poorly to antigenic stimulation.

CLL is manifested clinically by immunosuppression, bone marrow failure, and organ infiltration with lymphocytes. Immunodeficiency is also related to inadequate antibody production by the abnormal B cells. With advanced disease, CLL may cause damage by direct tissue infiltration.

CLL usually pursues an indolent course, but some subtypes behave more aggressively; a variant, prolymphocytic leukemia, is more aggressive. The morphology of the latter is different, characterized by larger and more immature cells. In 5–10% of cases, CLL may be complicated by autoimmune hemolytic anemia or autoimmune thrombocytopenia. In approximately 5% of cases, while the systemic disease remains stable, an isolated lymph node transforms into an aggressive large-cell lymphoma (**Richter syndrome**).

► Clinical Findings

A. Symptoms and Signs

CLL is a disease of older patients, with 90% of cases occurring after age 50 years and a median age at presentation of 70 years. Many patients will be incidentally discovered to have lymphocytosis. Others present with fatigue or lymphadenopathy. On examination, 80% of patients will have diffuse lymphadenopathy and 50% will have enlargement of the liver or spleen.

The long-standing Rai classification system remains prognostically useful: stage 0, lymphocytosis only; stage I, lymphocytosis plus lymphadenopathy; stage II, organomegaly (spleen, liver); stage III, anemia; stage IV, thrombocytopenia. These stages can be collapsed into low risk (stages 0–I), intermediate risk (stage II), and high risk (stages III–IV).

B. Laboratory Findings

The hallmark of CLL is isolated lymphocytosis. The white blood cell count is usually greater than 20,000/mcL

DiNardo CD et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med.* 2020;383:617. [PMID: 32786187]

DiNardo CD et al. How I treat acute myeloid leukemia in the era of new drugs. *Blood.* 2020;135:85. [PMID: 31765470]

($20 \times 10^9/\text{L}$) and may be markedly elevated to several hundred thousand. Usually 75–98% of the circulating cells are lymphocytes. Lymphocytes appear small and mature, with condensed nuclear chromatin, and are morphologically indistinguishable from normal small lymphocytes, but smaller numbers of larger and activated lymphocytes may be seen. The hematocrit and platelet count are usually normal at presentation. The bone marrow is variably infiltrated with small lymphocytes. The immunophenotype of CLL demonstrates coexpression of the B lymphocyte lineage marker CD19 with the T lymphocyte marker CD5; this finding is commonly observed only in CLL and mantle cell lymphoma. CLL is distinguished from mantle cell lymphoma by the expression of CD23, CD200, and LEF-1, low expression of surface immunoglobulin and CD20, and the absence of a translocation or overexpression of cyclin D1. Patients whose CLL cells have mutated forms of the immunoglobulin gene (IgVH somatic mutation) have a more indolent form of disease; these cells typically express low levels of the surface antigen CD38 and do not express the zeta-associated protein (ZAP-70). Conversely, patients whose cells have unmutated IgVH genes and high levels of ZAP-70 expression do less well and require treatment sooner. The assessment of genomic changes by FISH provides important prognostic information. The finding of deletion of chromosome 17p (TP53) confers the worst prognosis, while deletion of 11q (ATM) confers an inferior prognosis to the average genotype, and isolated deletion of 13q has a more favorable outcome.

Hypogammaglobulinemia is present in 50% of patients and becomes more common with advanced disease. In some, a small amount of IgM paraprotein is present in the serum.

Differential Diagnosis

Few syndromes can be confused with CLL. Viral infections producing lymphocytosis should be obvious from the presence of fever and other clinical findings; however, fever may occur in CLL from concomitant bacterial infection. Pertussis may cause a particularly high total lymphocyte count. Other lymphoproliferative diseases such as Waldenström macroglobulinemia, hairy cell leukemia, or lymphoma (especially mantle cell) in the leukemic phase are distinguished on the basis of the morphology and immunophenotype of circulating lymphocytes and bone marrow. Monoclonal B-cell lymphocytosis is a disorder characterized by fewer than 5000/mcL ($5.0 \times 10^9/\text{L}$) B cells and is considered a precursor to B-CLL.

Treatment

The treatment of CLL is evolving as several active targeted agents have emerged. Most cases of early indolent CLL require no specific therapy, and the standard of care for early-stage disease has been observation. Indications for treatment include progressive fatigue, symptomatic lymphadenopathy, anemia, or thrombocytopenia. These patients have either symptomatic and progressive Rai stage II disease or stage III/IV disease. Initial treatment for patients with CLL consists of targeted biologic therapy in most

cases. Options include ibrutinib (a Bruton tyrosine kinase inhibitor targeting B-cell receptor signaling) or venetoclax (a bcl2 inhibitor resulting in apoptosis) in combination with anti-CD20 antibody therapy. Choice between these agents is based on toxicity as well as preference. Ibrutinib is a well-tolerated, oral agent given at 420 mg daily; it can be associated with hypertension, cardiac arrhythmias, rash, and increased infections. Caution should be exercised when this agent is used in conjunction with CYP3A inhibitors or inducers. In addition, there is a potential for serious bleeding when it is used in patients taking warfarin. Venetoclax (slowly titrated up to 400 mg daily) is usually given for a shorter course of therapy and is associated with tumor lysis syndrome and neutropenia; some patients may require hospitalization for initial therapy. Venetoclax has to be combined with a monoclonal CD20 antibody, usually obinutuzumab, which can result in infusion reactions. Traditional combination chemotherapy is used only in selected cases (see Table 39–3). For older patients, chlorambucil, 0.6–1 mg/kg orally every 4 weeks, in combination with obinutuzumab is another therapy option.

For patients with relapsed or refractory disease, both venetoclax and ibrutinib or another BTK inhibitor, acalabrutinib, demonstrate significant activity, even for patients with high-risk genetics. Other options include idelalisib and duvelisib (inhibitors of PI3 kinase delta), which are associated with higher toxicity. The dosage for idelalisib is 150 mg orally twice a day, and the dosage for duvelisib is 25 mg orally twice a day. There are risks for colitis, liver injury, and fatal infectious complications in patients treated with PI3k inhibitors. Patients should be given antimicrobial prophylaxis and monitored closely while taking these agents.

Of note, BTK and PI3k inhibitors can be initially associated with marked lymphocytosis due to release of tumor cells from the lymph nodes into the peripheral blood. This results in a significant early reduction in lymphadenopathy but a potentially misleading, more delayed clearance of lymphocytes from peripheral blood and bone marrow.

Associated autoimmune hemolytic anemia or immune thrombocytopenia may require treatment with rituximab, prednisone, or splenectomy. Fludarabine should be avoided in patients with autoimmune hemolytic anemia since it may exacerbate it. Rituximab should be used with anti-HBV agent prophylaxis in patients with past HBV infection. Patients with recurrent bacterial infections and hypogammaglobulinemia benefit from prophylactic infusions of gamma globulin (0.4 g/kg/month), but this treatment is cumbersome and expensive, justified only when these infections are severe. Patients undergoing therapy with a nucleoside analog (fludarabine, pentostatin) should receive anti-infective prophylaxis for *Pneumocystis jirovecii* pneumonia, herpes viruses, and invasive fungal infections until there is evidence of T-cell recovery.

Allogeneic transplantation offers potentially curative treatment for patients with CLL, but it should be used only in patients whose disease cannot be controlled by the available therapies. Nonmyeloablative allogeneic transplant can

result in over 40% long-term disease control in CLL but with risk of moderate toxicity.

► Prognosis

Therapies have changed the prognosis of CLL. Patients with stage 0 or stage I disease have a median survival of 10–15 years, and these patients may be reassured that they can live a normal life. Patients with stage III or stage IV disease had a median survival of less than 2 years in the past, but with current therapies, 5-year survival is more than 70% and the long-term outlook appears to be substantially changed. For patients with high-risk and resistant forms of CLL, there is evidence that allogeneic transplantation can overcome risk factors and lead to long-term disease control.

► When to Refer

All patients with CLL should be referred to a hematologist.

► When to Admit

Hospitalization is rarely needed.

Aitken MJL et al. Emerging treatment options for patients with p53-pathway-deficient CLL. *Ther Adv Hematol*. 2019;10: 2040620719891356. [PMID: 31839919]

Burger JA. Treatment of chronic lymphocytic leukemia. *N Engl J Med*. 2020;383:460. [PMID: 32726532]

Wierda WG et al. How I manage CLL with venetoclax-based treatments. *Blood*. 2020;135:142. [PMID: 32076705]

Woyach JA. Treatment-naïve CLL: lessons from phase 2 and phase 3 clinical trials. *Blood*. 2019;134:1796. [PMID: 31751484]

HAIRY CELL LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- ▶ Pancytopenia.
- ▶ Splenomegaly, often massive.
- ▶ Hairy cells present on blood smear and especially in bone marrow biopsy.

► General Considerations

Hairy cell leukemia is a rare malignancy of hematopoietic stem cells differentiated as mature B lymphocytes with hairy cytoplasmic projections. The V600E mutation in the *BRAF* gene is recognized as the causal genetic event of hairy cell leukemia, since it is detectable in almost all cases at diagnosis and is present at relapse.

► Clinical Findings

A. Symptoms and Signs

The disease characteristically presents in middle-aged men. The median age at presentation is 55 years, and there

is a striking 5:1 male predominance. Most patients present with gradual onset of fatigue, others complain of symptoms related to markedly enlarged spleen, and some come to attention because of infection.

Splenomegaly is almost invariably present and may be massive. The liver is enlarged in 50% of cases; lymphadenopathy is uncommon.

Hairy cell leukemia is usually an indolent disorder whose course is dominated by pancytopenia and recurrent infections, including mycobacterial infections.

B. Laboratory Findings

The hallmark of hairy cell leukemia is pancytopenia. Anemia is nearly universal, and 75% of patients have thrombocytopenia and neutropenia. The “hairy cells” are usually present in small numbers on the peripheral blood smear and have a characteristic appearance with numerous cytoplasmic projections. The bone marrow is usually inaspirable (dry tap), and the diagnosis is made by characteristic morphology on bone marrow biopsy. The hairy cells have a characteristic histochemical staining pattern with tartrate-resistant acid phosphatase (TRAP). On immunophenotyping, the cells coexpress the antigens CD11c, CD20, CD22, CD25, CD103, and CD123. Pathologic examination of the spleen shows marked infiltration of the red pulp with hairy cells. This is in contrast to the usual predilection of lymphomas to involve the white pulp of the spleen.

► Differential Diagnosis

Hairy cell leukemia should be distinguished from other lymphoproliferative diseases such as Waldenström macroglobulinemia and non-Hodgkin lymphomas. It also may be confused with other causes of pancytopenia, including hypersplenism due to any cause, aplastic anemia, and paroxysmal nocturnal hemoglobinuria.

► Treatment

Treatment is indicated for symptomatic disease, ie, splenic discomfort, recurrent infections, or significant cytopenias. The treatment of choice is a nucleoside analog, specifically pentostatin or cladribine for a single course, producing a complete remission in 70–95% of patients. Treatment is associated with infectious complications, and patients should be closely monitored. The median duration of response is over 8 years and patients who relapse a year or more after initial therapy can be treated again with one of these agents. Rituximab can be used in the relapsed setting either as a single agent or in combination with a nucleoside analog. The BRAF inhibitor vemurafenib exhibits ~100% overall response rate in patients with refractory/relapsed hairy cell leukemia, with 35–40% complete remissions. The median relapse-free survival is ~19 months in patients who achieved complete remission and 6 months in those who obtained a partial response. Moxetumomab pasudotox is a recombinant CD22-targeting immunotoxin approved for patients with refractory disease. It has shown a durable complete response rate of 31% in the pivotal trial. However,

it can be associated with capillary leak and hemolytic-uremic syndrome attributable to the diphtheria toxin moiety.

► Course & Prognosis

More than 95% of patients with hairy cell leukemia live longer than 10 years.

- Grever MR et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. *Blood*. 2017;129:553. [PMID: 27903528]
- Liebers N et al. BRAF inhibitor treatment in classic hairy cell leukemia: a long-term follow-up study of patients treated outside clinical trials. *Leukemia*. 2020;34:1454. [PMID: 31740808]
- Maitre E et al. Hairy cell leukemia: 2020 update on diagnosis, risk stratification, and treatment. *Am J Hematol*. 2019;94:1413. [PMID: 31591741]

▼ LYMPHOMAS

NON-HODGKIN LYMPHOMAS



ESSENTIALS OF DIAGNOSIS

- ▶ Often present with painless lymphadenopathy.
- ▶ Diagnosis is made by tissue biopsy.

► General Considerations

The non-Hodgkin lymphomas are a heterogeneous group of cancers of lymphocytes usually presenting as enlarged lymph nodes. The disorders vary in clinical presentation and course from indolent to rapidly progressive.

Molecular biology has provided clues to the pathogenesis of these disorders, often a matter of balanced chromosomal translocations whereby an oncogene becomes juxtaposed next to either an immunoglobulin gene (B-cell lymphoma) or the T-cell receptor gene or related gene (T-cell lymphoma). The net result is oncogene overexpression and development of lymphoma. The best-studied example is Burkitt lymphoma, in which a characteristic cytogenetic abnormality of translocation between the long arms of chromosomes 8 and 14 has been identified. The protooncogene *c-myc* is translocated from its normal position on chromosome 8 to the immunoglobulin heavy chain locus on chromosome 14. Overexpression of *c-myc* is related to malignant transformation through excess B-cell proliferation. In follicular lymphoma, the t(14;18) translocation is characteristic and *bcl-2* is overexpressed, resulting in protection against apoptosis, the usual mechanism of B-cell death.

Classification of the lymphomas is a dynamic area still undergoing evolution. The 2017 grouping (Table 13–16) separates diseases based on both clinical and pathologic features. Eighty-five percent of non-Hodgkin lymphomas are B-cell and 15% are T-cell or NK-cell in origin. Even though non-Hodgkin lymphomas represent a diverse group of diseases, they are historically divided in two

Table 13–16. World Health Organization classification of lymphomas.

Precursor B-cell lymphoblastic lymphoma
Mature B-cell lymphomas
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
Hairy cell leukemia
Plasma cell myeloma
Diffuse large B-cell lymphoma
Primary diffuse large B-cell lymphoma of the CNS
High-grade B-cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements
Mediastinal large B-cell lymphoma
Follicular lymphoma
Small lymphocytic lymphoma
Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)
Mantle cell lymphoma
Burkitt lymphoma
Marginal zone lymphoma
MALT type
Nodal type
Splenic type
Mature T (and NK cell) lymphomas
Anaplastic large-cell lymphoma
Angioimmunoblastic T-cell lymphoma
Peripheral T-cell lymphoma, NOS
Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)
Extranodal NK/T-cell lymphoma, nasal type
Adult T-cell leukemia/lymphoma
T-cell large granular lymphocytic leukemia
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classic Hodgkin lymphoma
Posttransplant lymphoproliferative disorders
Histiocytic and dendritic cell neoplasms

CNS, central nervous system; MALT, mucosa-associated lymphoid tissue; NOS, not otherwise specified.

categories based on clinical behavior and pathology: the indolent (low-grade) and the aggressive (intermediate- or high-grade).

► Clinical Findings

A. Symptoms and Signs

Patients with non-Hodgkin lymphomas usually present with lymphadenopathy. Involved lymph nodes may be present peripherally or centrally (in the retroperitoneum, mesentery, and pelvis). The indolent lymphomas are usually disseminated at the time of diagnosis, and bone marrow involvement is frequent. Many patients with lymphoma have constitutional symptoms such as fever, drenching night sweats, and weight loss of greater than 10% of prior body weight (referred to as “B symptoms”).

On examination, lymphadenopathy may be isolated or diffuse, and extranodal sites of disease (such as the skin, gastrointestinal tract, liver, and bone marrow) may be found. Patients with Burkitt lymphoma are noted to have

abdominal pain or abdominal fullness because of the predilection of the disease for the abdomen.

Once a pathologic diagnosis is established, staging is done using a whole-body positron emission tomography (PET)/CT scan, a bone marrow biopsy, and, in patients with high-grade lymphoma or intermediate-grade lymphoma with high-risk features, a lumbar puncture.

B. Laboratory Findings

The peripheral blood is usually normal even with extensive bone marrow involvement by lymphoma. Circulating lymphoma cells in the blood are not commonly seen.

Bone marrow involvement is manifested as paratrabecular monoclonal lymphoid aggregates. In some high-grade lymphomas, the meninges are involved and malignant cells are found with cerebrospinal fluid cytology. The serum LD, a useful prognostic marker, is incorporated in risk stratification of treatment.

The diagnosis of lymphoma is made by tissue biopsy. Needle aspiration may yield evidence for non-Hodgkin lymphoma, but a lymph node biopsy (or biopsy of involved extranodal tissue) is required for accurate diagnosis and classification.

► Treatment

A. Indolent Lymphomas

The most common lymphomas in this group are follicular lymphoma, marginal zone lymphomas, and small lymphocytic lymphoma (SLL). The treatment of **indolent lymphomas** depends on the stage of disease and the clinical status of the patient. A small number of patients have limited disease with only one or two contiguous abnormal lymph node groups and may be treated with localized irradiation with curative intent. However, most patients (85%) with indolent lymphoma have disseminated disease at the time of diagnosis and are not considered curable. Historically, treatment of these patients has not affected overall survival; therefore, treatment is offered only when symptoms develop or for high tumor bulk. Following each treatment response, patients will experience a relapse at traditionally shorter intervals. Some patients will have temporary spontaneous remissions (8%). There are an increasing number of reasonable treatment options for indolent lymphomas, but no consensus exists on the best strategy. Treatment with rituximab (375 mg/m² intravenously weekly for 4 weeks) is commonly used either alone or in combination with chemotherapy and may be the only agent to affect overall survival in these disorders. Patients should be screened for hepatitis B because rare cases of fatal fulminant hepatitis have been described with the use of anti-CD20 monoclonal therapies without anti-HBV agent prophylaxis. Rituximab is added to chemotherapy regimens including bendamustine; cyclophosphamide, vincristine, and prednisone (R-CVP); and cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (see Table 39–3). The immunomodulatory agent lenalidomide in combination with anti-CD20 therapy is an alternative option with similar outcomes to chemotherapy. Some

patients with clinically aggressive low-grade lymphomas may be appropriate candidates for allogeneic stem cell transplantation with curative intent. The role of autologous hematopoietic stem cell transplantation remains uncertain, but some patients with recurrent disease appear to have prolonged remissions.

Patients with mucosa-associated lymphoid tissue tumors of the stomach may be appropriately treated with combination antibiotics directed against *H pylori* and with acid blockade but require frequent endoscopic monitoring. Alternatively, mucosa-associated lymphoid tissue tumors confined to the stomach can also be cured with whole-stomach radiotherapy. Mucosa-associated lymphoid tumors of the spleen are usually associated with hepatitis C and may remit following hepatitis C eradication therapy.

B. Aggressive Lymphomas

Patients with **diffuse large B-cell lymphoma** are treated with curative intent. Most patients are treated with six cycles of immunochemotherapy such as R-CHOP (see Table 39–3). Involved nodal radiotherapy (INRT) may be added for patients with bulky or extranodal disease. About 25% of patients with diffuse large B-cell lymphoma have been identified as “double-protein expressors” with overexpression of MYC and BCL2 proteins by immunohistochemistry. While the outcomes with R-CHOP are inferior, no definitive alternative treatment recommendations can be made at this time. **High-grade lymphoma** with chromosomal translocations affecting MYC, such as t(8;14), and translocations affecting BCL2, such as t(14;18), also called “double-hit lymphoma,” has a very aggressive course. Patients with this disease may do better with dose-adjusted R-EPOCH as front-line therapy.

Patients with diffuse large B-cell lymphoma or high-grade lymphoma who relapse after initial chemotherapy can still be cured by autologous hematopoietic stem cell transplantation if their disease remains responsive to chemotherapy. For patients who do not respond to second-line chemotherapy, the treatment of choice is chimeric antigen receptor T-cell therapy targeting CD19 with either axicabtagene ciloleucel or tisagenlecleucel, which produces durable complete response rates of ~40%.

Mantle cell lymphoma is not effectively treated with standard immunochemotherapy regimens. Intensive initial immunochemotherapy including autologous hematopoietic stem cell transplantation has been shown to improve outcomes. The BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib are active in relapsed or refractory patients with mantle cell lymphoma. Reduced-intensity allogeneic stem cell transplantation offers curative potential for selected patients. Chimeric antigen receptor T-cell therapy with brexucabtagene autoleucel shows promising activity in patients whose disease progresses after treatment with BTK inhibitors. For **primary central nervous system lymphoma**, repetitive cycles of high-dose intravenous methotrexate with rituximab early in the treatment course produce better results than whole-brain radiotherapy and with less cognitive impairment.

Patients with **highly aggressive lymphomas** (Burkitt or lymphoblastic) require urgent, intense, cyclic chemotherapy in the hospital similar to that given for ALL, and they

also require intrathecal chemotherapy as central nervous system prophylaxis.

Patients with **peripheral T-cell lymphomas** usually have advanced stage nodal and extranodal disease and typically have inferior response rates to therapy compared to patients with aggressive B-cell lymphomas. Autologous stem cell transplantation is often incorporated in first-line therapy. The antibody-drug conjugate brentuximab vedotin has significant activity in patients with CD30 positive peripheral T-cell lymphomas, such as anaplastic large-cell lymphoma.

► Prognosis

The median survival of patients with indolent lymphomas is 10–15 years. These diseases ultimately become refractory to chemotherapy. This often occurs at the time of histologic progression of the disease to a more aggressive form of lymphoma.

The International Prognostic Index is widely used to categorize patients with aggressive lymphoma into risk groups. Factors that confer adverse prognosis are age over 60 years, elevated serum LD, stage III or stage IV disease, more than one extranodal site of disease, and poor performance status. Cure rates range from more than 80% for low-risk patients (zero risk factors) to less than 50% for high-risk patients (four or more risk factors).

For patients who relapse after initial chemotherapy, autologous hematopoietic stem cell transplantation and chimeric antigen receptor T-cell therapy offer a 40–50% chance of long-term lymphoma-free survival.

The treatment of older patients with lymphoma has been difficult because of poorer tolerance of aggressive chemotherapy. The use of reduced-intensity regimens (eg, R-miniCHOP) with myeloid growth factors and prophylactic antibiotics is preferred.

► When to Refer

All patients with lymphoma should be referred to a hematologist or an oncologist.

► When to Admit

Admission is necessary only for specific complications of lymphoma or its treatment and for the treatment of all high-grade lymphomas.

- Chiappella A et al. Diffuse large B-cell lymphoma in the elderly: standard treatment and new perspectives. *Expert Rev Hematol.* 2017;10:289. [PMID: 28290728]
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- Munshi PN et al. The acceleration of CAR-T therapy in non-Hodgkin lymphoma. *Hematol Oncol.* 2019;37:233. [PMID: 30427551]
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HODGKIN LYMPHOMA



ESSENTIALS OF DIAGNOSIS

- ▶ Often painless lymphadenopathy.
- ▶ Constitutional symptoms may or may not be present.
- ▶ Pathologic diagnosis by lymph node biopsy.

► General Considerations

Hodgkin lymphoma is characterized by lymph node biopsy showing Reed-Sternberg cells in an appropriate reactive cellular background. The malignant cell is derived from B lymphocytes of germinal center origin.

► Clinical Findings

There is a bimodal age distribution, with one peak in the 20s and a second over age 50 years. Most patients seek medical attention because of a painless mass, commonly in the neck. Others may seek medical attention because of constitutional symptoms such as fever, weight loss, or drenching night sweats, or because of generalized pruritus. An unusual symptom of Hodgkin lymphoma is pain in an involved lymph node following alcohol ingestion.

An important feature of Hodgkin lymphoma is its tendency to arise within single lymph node areas and spread in an orderly fashion to contiguous areas of lymph nodes. Late in the course of the disease, vascular invasion leads to widespread hematogenous dissemination.

Hodgkin lymphoma is divided into two subtypes: classic Hodgkin (nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted) and non-classic Hodgkin (nodular lymphocyte predominant). Hodgkin lymphoma should be distinguished pathologically from other malignant lymphomas and may occasionally be confused with reactive lymph nodes seen in infectious mononucleosis, cat-scratch disease, or drug reactions (eg, phenytoin).

Patients undergo a staging evaluation to determine the extent of disease, including serum chemistries, whole-body PET/CT scan, and bone marrow biopsy.

► Treatment

Chemotherapy is the mainstay of treatment for Hodgkin lymphoma, and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) remains the standard first-line regimen. The substitution of the antibody-drug conjugate brentuximab vedotin for bleomycin (AAVD) has demonstrated superior progression-free survival to ABV but no change in overall survival. The more intense regimen, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), is associated with increased toxicity and is reserved for patients with activity on an interim PET/CT scan after starting ABVD or AAVD. Low-risk patients are those with

stage I or II disease without bulky lymphadenopathy or evidence of systemic inflammation. They traditionally receive a combination of short-course chemotherapy with INRT, but INRT can be eliminated for those with an early negative PET/CT scan without a significant change in outcomes (see Table 39–3). High-risk patients are those with stage III or IV disease or with stage II disease and a large mediastinal or other bulky mass or systemic inflammation. These patients are treated with a full course of chemotherapy for six cycles. Pulmonary toxicity can unfortunately occur following either chemotherapy (bleomycin) or radiation and should be treated aggressively in these patients, since it can lead to permanent fibrosis and death. A negative interim PET/CT scan after two cycles of chemotherapy can be used to identify patients with an excellent progression-free survival who can have bleomycin eliminated from their treatment. Conversely, an abnormal interim PET/CT scan is associated with a worse prognosis and should prompt early intensification of treatment to achieve a complete response (CR).

Classic Hodgkin lymphoma relapsing after initial treatment is treatable with high-dose chemotherapy and autologous hematopoietic stem cell transplantation. This offers a 35–50% chance of cure when disease is still chemotherapy responsive. Brentuximab vedotin has shown impressive activity in patients relapsing after autologous stem cell transplantation (overall response rate [ORR] of 75%; CR of 34%) and is FDA-approved for this indication. Last, immune checkpoint inhibition by PD1 blockade with nivolumab or pembrolizumab has shown remarkable activity (ORR of 65%) and is another option for patients with relapsed or refractory disease.

► Prognosis

All patients should be treated with curative intent. Prognosis in advanced stage Hodgkin lymphoma is influenced by seven features: stage, age, gender, hemoglobin, albumin, white blood cell count, and lymphocyte count. The cure rate is 75% if zero to two risk features are present and 55% when three or more risk features are present. The prognosis of patients with stage IA or IIA disease is excellent, with 10-year survival rates in excess of 90%. Patients with advanced disease (stage III or IV) have 10-year survival rates of 50–60%. Inferior results are seen in patients who are older, those who have bulky disease, and those with lymphocyte depletion or mixed cellularity on histologic examination. Non-classic Hodgkin lymphoma (nodular lymphocyte predominant) is highly curable with radiotherapy alone for early-stage disease; however, for high-stage disease, it is characterized by long survival with repetitive relapses after chemotherapy or monoclonal anti-CD20 antibody therapy.

► When to Refer

- All patients should be sent to an oncologist or hematologist.
- Secondary referral to a radiation oncologist might be appropriate.

► When to Admit

Patients should be admitted for complications of the disease or its treatment.

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PLASMA CELL MYELOMA

ESSENTIALS OF DIAGNOSIS

- ▶ Bone pain, often in the spine, ribs, or proximal long bones.
- ▶ Monoclonal immunoglobulin (ie, paraprotein) in the serum or urine.
- ▶ Clonal plasma cells in the bone marrow or in a tissue biopsy, or both.
- ▶ Organ damage due to plasma cells (eg, bones, kidneys, hypercalcemia, anemia) or other defined criteria.

► General Considerations

Plasma cell myeloma (previously called multiple myeloma) is a malignancy of hematopoietic stem cells terminally differentiated as plasma cells. It is characterized by infiltration of the bone marrow, bone destruction, and paraprotein formation. The diagnosis is established when monoclonal plasma cells (either kappa or lambda light chain restricted) in the bone marrow (any percentage) or as a tumor (plasmacytoma), or both, are associated with end-organ damage (such as bone disease [lytic lesions seen on bone radiographs, magnetic resonance imaging {MRI}, or PET/CT scan], anemia [hemoglobin less than 10 g/dL {100 g/L}], hypercalcemia [calcium greater than 11 mg/dL {2.75 mmol/L}], or kidney injury [creatinine greater than 2 mg/dL {176.8 μmol/L} or creatinine clearance less than 40 mL/min]) with or without paraprotein elaboration. Sixty percent or more clonal plasma cells in the bone marrow, or a serum free kappa to lambda ratio of greater than 100 or less than 0.01 (both criteria regardless of end-organ damage), are also diagnostic of plasma cell myeloma. Smoldering myeloma is defined as 10–59% clonal plasma cells in the bone marrow, a serum paraprotein level of 3 g/dL (30 g/L) or higher, or both, without plasma cell-related end-organ damage.

Malignant plasma cells can form tumors (plasmacytomas) that may cause spinal cord compression or other

soft-tissue-related problems. Bone disease is common and due to excessive osteoclast activation mediated largely by the interaction of the receptor activator of NF-kappa-B (RANK) with its ligand (RANKL). In plasma cell myeloma, osteoprotegerin (a decoy receptor for RANKL) is under-produced, thus promoting the binding of RANK with RANKL with consequent excessive bone resorption.

The paraproteins (monoclonal immunoglobulins) secreted by the malignant plasma cells may cause problems in their own right. Very high paraprotein levels (either IgG or IgA) may cause hyperviscosity, although this is more common with the IgM paraprotein in Waldenström macroglobulinemia. The light chain component of the immunoglobulin, when produced in excess, often leads to kidney injury (frequently aggravated by hypercalcemia or hyperuricemia, or both). Light chain components may be deposited in tissues as amyloid, resulting in kidney failure with albuminuria and a vast array of other systemic syndromes (restrictive cardiomyopathy, autonomic and peripheral neuropathy, enlarged tongue, etc.).

Myeloma patients are prone to recurrent infections for a number of reasons, including neutropenia, the underproduction of normal immunoglobulins (so-called immunoparesis), and the immunosuppressive effects of chemotherapy. Myeloma patients are especially prone to infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

► Clinical Findings

A. Symptoms and Signs

Myeloma is a disease of older adults (median age 65 years). The most common presenting complaints are those related to anemia, bone pain, kidney disease, and infection. Bone pain is most common in the back, hips, or ribs or may present as a pathologic fracture, especially of the femoral neck or vertebrae. Patients may also come to medical attention because of spinal cord compression from a plasmacytoma or the hyperviscosity syndrome (mucosal bleeding, vertigo, nausea, visual disturbances, alterations in mental status, hypoxia). Many patients are diagnosed because of laboratory findings of elevated total protein, hypercalcemia, proteinuria, elevated sedimentation rate, or abnormalities on serum protein electrophoresis obtained for symptoms or in routine screening studies. A few patients come to medical attention because of organ dysfunction due to amyloidosis.

Examination may reveal pallor, bone tenderness, or soft tissue masses. Patients may have neurologic signs related to neuropathy or spinal cord compression. Fever occurs mainly with infection. Acute oliguric or nonoliguric kidney injury may be present due to hypercalcemia, hyperuricemia, light chain cast injury, or primary amyloidosis.

B. Laboratory Findings

Anemia is nearly universal. Red blood cell morphology is normal, but rouleaux formation is common and may be marked. The absence of rouleaux formation, however, excludes neither plasma cell myeloma nor the presence of a serum paraprotein. The neutrophil and platelet counts are usually normal at presentation. Only rarely will plasma

cells be visible on peripheral blood smear (plasma cell leukemia if greater than 20%).

The hallmark of myeloma is the finding of a paraprotein on serum or urine protein electrophoresis (PEP) or immunofixation electrophoresis (IFE). The majority of patients will have a monoclonal spike visible in the gamma- or beta-globulin region of the PEP. The semi-quantification of the paraprotein on the PEP is referred to as the M-protein, and IFE will reveal this to be a monoclonal immunoglobulin. Approximately 15% of patients will have no demonstrable paraprotein in the serum on PEP because their myeloma cells produce only light chains and not intact immunoglobulin (but often seen on serum IFE), and the light chains pass rapidly through the glomerulus into the urine. Urine PEP and IFE usually demonstrate the light chain paraprotein in this setting. The free light chain assay will sometimes demonstrate excess monoclonal light chains in serum and urine, and in a small proportion of patients, will be the only means to identify and quantify the paraprotein being produced. Overall, the paraprotein is IgG (60%), IgA (20%), or light chain only (15%) in plasma cell myeloma, with the remainder being rare cases of IgD, IgM, or biclonal gammopathy. In sporadic cases, no paraprotein is present ("nonsecretory myeloma"); these patients have particularly aggressive disease.

The bone marrow will be infiltrated by variable numbers of monoclonal plasma cells. The plasma cells may be morphologically abnormal often demonstrating multinucleation and vacuolization. The plasma cells will display marked skewing of the normal kappa-to-lambda light chain ratio, which will indicate their clonality. Many benign inflammatory processes can result in bone marrow plasmacytosis, but with the absence of clonality and morphologic atypia.

C. Imaging

Bone radiographs are important in establishing the diagnosis of myeloma. Lytic lesions are most commonly seen in the axial skeleton: skull, spine, proximal long bones, and ribs. At other times, only generalized osteoporosis is seen. The radionuclide bone scan is not useful in detecting bone lesions in myeloma, since there is little osteoblastic component. In the evaluation of patients with known or suspected plasma cell myeloma, MRI and PET/CT scans are more sensitive to detect bone disease than plain radiographs and are preferred.

► Differential Diagnosis

When a patient is discovered to have a paraprotein, the distinction between plasma cell myeloma or another lymphoproliferative malignancy with a paraprotein (CLL/SLL, Waldenström macroglobulinemia, non-Hodgkin lymphoma, primary amyloid, cryoglobulinemia) or monoclonal gammopathy of undetermined significance (MGUS) must be made. Plasma cell myeloma, smoldering plasma cell myeloma, and MGUS must be distinguished from reactive (benign) polyclonal hypergammaglobulinemia (which is commonly seen in cirrhosis or chronic inflammation).

► Treatment

Patients with low-risk smoldering myeloma are observed. Those with high-risk smoldering disease may be treated with lenalidomide (an immunomodulatory agent) and dexamethasone since this therapy prolongs the time to symptomatic myeloma and may prolong survival compared to no treatment though at the expense of treatment-related side effects.

Most patients with plasma cell myeloma require treatment at diagnosis because of bone pain or other symptoms and complications related to the disease. The initial treatment generally involves triple therapy: an immunomodulatory agent, such as lenalidomide; a proteasome inhibitor, such as bortezomib or carfilzomib; and moderate- or high-dose dexamethasone. An immunomodulatory agent is sometimes replaced with an alkylating agent, cyclophosphamide, in the setting of kidney injury. The major side effects of lenalidomide are neutropenia and thrombocytopenia, skin rash, venous thromboembolism, peripheral neuropathy, and possibly birth defects. Bortezomib and carfilzomib have the advantages of producing rapid responses and of being effective in poor-prognosis myeloma. The major side effect of bortezomib is neuropathy (both peripheral and autonomic), which is largely ameliorated when given subcutaneously rather than intravenously. Carfilzomib rarely causes neuropathy but sometimes causes acute pulmonary hypertension or cardiac systolic dysfunction that is usually reversible. A subcutaneous dose combination of daratumumab (an anti-CD38 monoclonal antibody) plus hyaluronidase-fihj has received FDA approval for treatment of patients with plasma cell myeloma, including newly diagnosed, autologous stem cell transplant-ineligible patients as well as relapsed or refractory patients.

An oral proteasome inhibitor, ixazomib, is available for relapsed disease. Pomalidomide, an immunomodulatory agent, is effective as salvage therapy after relapse. Other salvage agents include daratumumab, elotuzumab (an anti-SLAMF7 monoclonal antibody), panobinostat (a histone deacetylase inhibitor), selinexor (causes cell cycle arrest and apoptosis), and belantamab mafodotin (an anti-BCMA antibody conjugated to a cytotoxic agent).

After initial therapy, many patients under age 80 years are consolidated with autologous hematopoietic stem cell transplantation following high-dose melphalan (an alkylating chemotherapeutic agent). Autologous stem cell transplantation prolongs both duration of remission and overall survival. Lenalidomide or thalidomide prolong remission and survival when given as posttransplant maintenance therapy but at the expense of an elevated rate of second malignancies. Proteasome inhibitors prolong remissions in high-risk patients after autologous stem cell transplantation.

Localized radiotherapy may be useful for palliation of bone pain or for eradicating tumor at the site of pathologic fracture. Vertebral collapse with its attendant pain and mechanical disturbance can be treated with vertebroplasty or kyphoplasty. Hypercalcemia and hyperuricemia should be treated aggressively with immobilization and dehydration avoided. The bisphosphonates (pamidronate or zoledronic acid) or the RANKL-inhibitor (denosumab) given

intravenously monthly reduces pathologic fractures in patients with bone disease. These medications are important adjuncts in this subset of patients. The bisphosphonates are also used to treat myeloma-related hypercalcemia. However, long-term bisphosphonates have been associated with a risk of osteonecrosis of the jaw and other bony areas, so the use of bisphosphonates is limited to 1–2 years after definitive initial therapy in most patients. Myeloma patients with oliguric or anuric kidney disease at diagnosis due to high free light chain levels should be treated aggressively with chemotherapy and considered for therapeutic plasma exchange (to reduce the paraprotein burden) because return of kidney function can sometimes occur.

► Prognosis

The outlook for patients with myeloma has been steadily improving for the past decade. The median survival of patients is more than 7 years. Patients with low-stage disease who lack high-risk genomic changes respond very well to treatment and derive significant benefit from autologous hematopoietic stem cell transplantation and have survivals approaching a decade. The International Staging System for myeloma relies on two factors: beta-2-microglobulin and albumin. Stage 1 patients have both beta-2-microglobulin less than 3.5 mg/L and albumin greater than 3.5 g/dL (survival more than 5 years). Stage 3 is established when beta-2-microglobulin is greater than 5.5 mg/L (survival less than 2 years). Stage 2 is established with values in between stage 1 and 3. Other adverse prognostic findings are an elevated serum LD or bone marrow genetic abnormalities established by FISH involving the immunoglobulin heavy chain locus at chromosome 14q32, multiple copies of the 1q21-23 locus, or 17p chromosome abnormalities (causing the loss or mutation of TP53).

► When to Refer

All patients with plasma cell myeloma should be referred to a hematologist or an oncologist.

► When to Admit

Hospitalization is indicated for treatment of acute kidney injury, hypercalcemia, or suspicion of spinal cord compression, for certain chemotherapy regimens, or for autologous hematopoietic stem cell transplantation.

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MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE



ESSENTIALS OF DIAGNOSIS

- ▶ Monoclonal immunoglobulin (ie, paraprotein) in the serum (< 3 g/dL [< 30 g/L]) or urine.
- ▶ Clonal plasma cells in the bone marrow < 10% (if performed).
- ▶ No symptoms and no organ damage from the paraprotein.

Treatment

Patients with MGUS are observed without treatment.

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General Considerations

MGUS is present in 1% of all adults (3% of those over age 50 years and more than 5% of those over age 70 years). Among all patients with paraproteins, MGUS is far more common than plasma cell myeloma. MGUS is defined as bone marrow clonal plasma cells less than 10% in the setting of a paraprotein in the serum or urine (serum M-protein less than 3 g/dL [30 g/L]) and the absence of plasma cell-related end-organ damage. If an excess of serum free light chains (kappa or lambda) is established, the kappa to lambda ratio is 100 or less or 0.01 or greater (otherwise, this is diagnostic of plasma cell myeloma). In approximately one-quarter of cases, MGUS progresses to overt malignant disease in a median of one decade. The transformation of MGUS to plasma cell myeloma is approximately 1% per year. Two adverse risk factors for progression of MGUS to a plasma cell or lymphoid malignancy are an abnormal serum kappa to lambda free light chain ratio and a serum monoclonal protein (M-protein) level 1.5 g/dL or greater. Patients with MGUS have shortened survival (median 8.1 years vs 12.4 years for age- and sex-matched controls). In addition, 12% of patients with MGUS will convert to primary amyloidosis in a median of 9 years. Plasma cell myeloma, smoldering plasma cell myeloma, and MGUS must be distinguished from reactive (benign) polyclonal hypergammaglobulinemia (common in cirrhosis or chronic inflammation).

Laboratory Findings

To establish the diagnosis, serum and urine should be sent for PEP and IFE to search for a monoclonal protein; serum should be sent for free light chain analysis and quantitative immunoglobulins. Additional tests include a hemoglobin and serum albumin, calcium, and creatinine. If these additional tests are normal (or if abnormal but otherwise explained), then a bone marrow biopsy is usually deferred provided the serum M-protein is less than 3 g/dL (less than 30 g/L). In asymptomatic individuals, a skeletal survey (radiographs) is performed, but if there are some bone complaints or a question regarding bone disease, MRI or PET/CT imaging is preferred. MGUS is diagnosed if patients do not meet the criteria for smoldering plasma cell myeloma or plasma cell myeloma.

WALDENSTRÖM MACROGLOBULINEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Monoclonal IgM paraprotein.
- ▶ Infiltration of bone marrow by plasmacytic lymphocytes.
- ▶ Absence of lytic bone disease.

General Considerations

Waldenström macroglobulinemia is a syndrome of IgM hypergammaglobulinemia that occurs in the setting of a low-grade non-Hodgkin lymphoma characterized by B cells that are morphologically a hybrid of lymphocytes and plasma cells. These cells characteristically secrete the IgM paraprotein, and many clinical manifestations of the disease are related to this macroglobulin.

Clinical Findings

A. Symptoms and Signs

This disease characteristically develops insidiously in patients in their 60s or 70s. Patients usually present with fatigue related to anemia. Hyperviscosity of serum may be manifested in a number of ways. Mucosal and gastrointestinal bleeding is related to engorged blood vessels and platelet dysfunction. Other complaints include nausea, vertigo, and visual disturbances. Alterations in consciousness vary from mild lethargy to stupor and coma. The IgM paraprotein may also cause symptoms of cold agglutinin disease (hemolysis) or chronic demyelinating peripheral neuropathy.

On examination, there may be hepatosplenomegaly or lymphadenopathy. The retinal veins are engorged. Purpura may be present. There should be no bone tenderness.

B. Laboratory Findings

Anemia is nearly universal, and rouleaux formation is common, although the red blood cells are agglutinated when the blood smear is prepared at room temperature. The anemia is related in part to expansion of the plasma volume by 50–100% due to the presence of the paraprotein. Other blood counts are usually normal. The abnormal plasmacytic lymphocytes may appear in small numbers on

the peripheral blood smear. The bone marrow is characteristically infiltrated by the plasmacytic lymphocytes.

The hallmark of macroglobulinemia is the presence of a monoclonal IgM spike seen on serum PEP in the beta-globulin region. The serum viscosity is usually increased above the normal of 1.4–1.8 times that of water. Symptoms of hyperviscosity usually develop when the serum viscosity is over four times that of water, and marked symptoms usually arise when the viscosity is over six times that of water. Because paraproteins vary in their physicochemical properties, there is no strict correlation between the concentration of paraprotein and serum viscosity.

The IgM paraprotein may cause a positive antiglobulin (Coombs) test for complement and have cold agglutinin or cryoglobulin properties. If macroglobulinemia is suspected but the serum PEP shows only hypogammaglobulinemia, the test should be repeated while taking special measures to maintain the blood at 37°C, since the paraprotein may precipitate out at room temperature. Bone radiographs are normal, and there is no evidence of kidney injury.

Differential Diagnosis

Waldenström macroglobulinemia is differentiated from MGUS by the finding of bone marrow infiltration with monoclonal malignant cells. It is distinguished from CLL by bone marrow morphology, the absence of CD5 expression, and the absence of lymphocytosis, and it is distinguished from plasma cell myeloma by bone marrow morphology, the finding of the characteristic IgM paraprotein, and the absence of lytic bone disease.

Treatment

Patients with marked hyperviscosity syndrome (stupor, coma, pulmonary edema) should be treated on an emergency basis with plasmapheresis. On a chronic basis, some patients can be managed with periodic plasmapheresis alone. As with other indolent malignant lymphoid diseases, rituximab (375 mg/m² intravenously weekly for 4–8 weeks) has significant activity. However, a word of caution: the IgM often rises first after rituximab therapy before it falls. Combination therapy is recommended for advanced disease (see Table 39–3). *MYD88* is commonly mutated in Waldenström macroglobulinemia, and in these patients, the BTK inhibitor ibrutinib (420 mg daily) has shown significant activity with a 90% response rate and a 73% major response rate that can result in durable remissions. Bortezomib, lenalidomide, and bendamustine have also been shown to have activity in this disease. Autologous hematopoietic stem cell transplantation is reserved for relapsed or refractory patients.

Prognosis

Waldenström macroglobulinemia is an indolent disease with a median survival rate of 5 years, and 10% of patients are alive at 15 years.

When to Refer

All patients should be referred to a hematologist or an oncologist.

When to Admit

Patients should be admitted for treatment of hyperviscosity syndrome.

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AMYLOIDOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Congo red positive amyloid protein on tissue biopsy.
- ▶ Primary amyloid protein is kappa or lambda immunoglobulin light chain.
- ▶ Serum or urine (or both) light chain paraprotein.

General Considerations

Amyloidosis is a rare condition whereby a protein abnormally deposits in tissue resulting in organ dysfunction. The propensity of a protein to be amyloidogenic is a consequence of disturbed translational or posttranslational protein folding and lack of consequential water solubility. The input of amyloid protein into tissues far exceeds its output, so amyloid build up inexorably proceeds to organ dysfunction and ultimately organ failure and premature death.

Amyloidosis is classified according to the type of amyloid protein deposited. The six main categories are **primary** (immunoglobulin light chain [AL]), **secondary** (serum protein A, produced in inflammatory conditions [AA]), **hereditary** (mutated transthyretin [TTR]; many others), **senile** (wild-type TTR; atrial natriuretic peptide; others), **dialysis-related** (beta-2-microglobulin, not filtered out by dialysis membranes [Abeta-2M]), and **LECT2** (associated with Latino ethnicity). Amyloidosis is further classified as **localized** (amyloid deposits only in a single tissue type or organ) or, most common, **systemic** (widespread amyloid deposition).

Clinical Findings

A. Symptoms and Signs

Patients with **localized amyloidosis** have symptoms and signs related to the affected single organ, such as hoarseness (vocal cords) or proptosis and visual disturbance (orbita). Patients with **systemic amyloidosis** have symptoms and signs of unexplained medical syndromes, including heart failure (infiltrative/restrictive cardiomyopathy), nephrotic syndrome, malabsorption and weight loss, hepatic dysfunction, autonomic insufficiency, carpal tunnel syndrome (often bilateral), and sensorimotor peripheral neuropathy.

Other symptoms and signs include an enlarged tongue; waxy, rough plaques on skin; contusions (including the periorbital areas); cough or dyspnea; and disturbed deglutition. These symptoms and signs arise insidiously, and the diagnosis of amyloidosis is generally made late in the disease process.

B. Laboratory Findings

The diagnosis of amyloid protein requires a tissue biopsy that demonstrates deposition of a pink interstitial substance in the tissue with the hematoxylin and eosin stain. This protein stains red with Congo red and becomes an apple-green color when the light is polarized. Amyloid is a triple-stranded fibril composed of the amyloid protein, amyloid protein P, and glycosaminoglycan. The amyloid fibrils form beta-pleated sheets as demonstrated by electron microscopy. In primary amyloidosis, the amyloid protein is either the kappa or lambda immunoglobulin light chain.

When systemic amyloidosis is suspected, a blind aspiration of the abdominal fat pad will reveal amyloid two-thirds of the time. If the fat pad aspiration is unrevealing, then the affected organ needs biopsy. In 90% of patients with primary amyloidosis, analysis of the serum and urine will reveal a kappa or lambda light chain paraprotein by PEP, IFE, or free light chain assay; in the remainder, mass spectroscopy demonstrates light chain in the tissue biopsy. Lambda amyloid is more common than kappa amyloid, a relative proportion opposite from normal B-cell stoichiometry. Most patients with primary amyloidosis have a small excess of kappa- or lambda-restricted plasma cells in the bone marrow (but less than 10%). The bone marrow may or may not demonstrate interstitial amyloid deposition or amyloid in the blood vessels.

Patients with primary cardiac amyloidosis have an infiltrative cardiomyopathy with thick ventricular walls on echocardiogram that sometimes shows a specific speckling pattern. Paradoxically, QRS voltages are low on ECG. Cardiac MRI has a distinctive delayed enhancement of gadolinium that is virtually diagnostic. With renal amyloid, albuminuria is present, which can be in the nephrotic range. Late in renal involvement, kidney function decreases.

Differential Diagnosis

Amyloidosis must be distinguished from MGUS and plasma cell myeloma or other malignant lymphoproliferative disorders with an associated paraprotein. Of note, 12% of patients with MGUS will convert to primary amyloidosis in a median of 9 years. One-fifth of patients who have primary amyloidosis will meet the diagnostic criteria for plasma cell myeloma; conversely, 5% of patients with plasma cell myeloma will have amyloid deposition of their paraprotein at diagnosis.

Treatment

The treatment approach to primary amyloidosis closely resembles that of plasma cell myeloma. Prospective, randomized trials of plasma cell myeloma chemotherapy

versus colchicine have demonstrated a survival benefit to chemotherapy. The goal is reduction of light chain production and deposition as a means to arrest progressive end-organ dysfunction. Active agents in primary amyloidosis include melphalan, cyclophosphamide, dexamethasone, lenalidomide, and bortezomib (see Table 39–3). The anti-CD38 monoclonal antibody daratumumab has a role in relapsed or refractory disease. As in plasma cell myeloma, autologous hematopoietic stem cell transplantation after high-dose melphalan is used in patients with reasonable organ function and a good performance status. The treatment-related mortality, however, is higher in patients with primary amyloidosis than in plasma cell myeloma (6% vs 1%). Some patients will demonstrate end-organ improvement after therapy. Agents are being developed that facilitate amyloid dissolution or correct protein folding abnormalities in the amyloid protein. Treatment of AA amyloid is treatment of the underlying cause of inflammation. Treatment of familial TTR is liver transplantation and of acquired TTR is tafamidis or inotersen.

Prognosis

Untreated primary amyloidosis is associated with progressive end-organ failure and premature death. There is no known cure for primary amyloidosis. Although virtually every tissue examined at autopsy will contain amyloid, patients with primary amyloidosis usually have one or two primary failing organs that clinically drive the presentation and prognosis. The cardiac biomarkers B-type natriuretic peptide (BNP), N-terminal pro-BNP, and troponins T and I are prognostic in this disease regardless of overt clinical cardiac involvement. Historically, patients with predominantly cardiac or autonomic nerve presentations had survivals of 3–9 months, those with carpal tunnel syndrome or nephrosis had survivals of 1.5–3 years, and those with peripheral neuropathy had survivals of 5 years. These survivals are roughly doubled with plasma cell myeloma-like treatment. In those patients able to undergo autologous hematopoietic stem cell transplantation, the median survival approaches 5 years (and approaches 10 years for those achieving a complete hematologic remission).

When to Refer

- All patients who have primary amyloidosis or in whom it is suspected should be referred to a hematologist or oncologist.
- All patients with hereditary amyloidosis should be referred to a hepatologist for consideration of liver transplantation.

When to Admit

- Patients with systemic amyloidosis require hospitalization to treat exacerbations of end-organ failure, including heart, liver, or kidney.
- Patients with primary amyloidosis require hospitalization to undergo autologous hematopoietic stem cell transplantation.

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BLOOD TRANSFUSIONS

Most blood products are leukoreduced in-line during acquisition and are thus prospectively leukocyte-poor. Leukoreduced blood products reduce the incidence of leukoagglutination reactions, platelet alloimmunization, transfusion-related acute lung injury, and CMV exposure.

RED BLOOD CELL TRANSFUSIONS

Red blood cell transfusions are given to raise the hemoglobin levels in patients with anemia or to replace losses after acute bleeding episodes.

► Preparations of Red Cells for Transfusion

Several types of preparations containing red blood cells are available (whole blood, packed red blood cells, frozen red blood cells, or autologous non-frozen red blood cells).

A. Fresh Whole Blood

The advantage of whole blood for transfusion is the simultaneous presence of red blood cells, plasma, and fresh platelets. Fresh whole blood is not absolutely necessary, since all the above components are available separately. The major indications for use of whole blood are cardiac surgery or massive hemorrhage when more than 10 units of blood is required in a 24-hour period.

B. Packed Red Blood Cells

Packed red cells are the component most commonly used to raise the hemoglobin. Each unit has a volume of about 300 mL, of which approximately 200 mL consists of red blood cells. One unit of packed red cells will usually raise the hemoglobin by approximately 1 g/dL. Current guidelines recommend a transfusion “trigger” hemoglobin threshold of 7–8 g/dL (70–80 g/L) for hospitalized critically ill patients, those undergoing cardiothoracic surgery or repair of a hip fracture, those with upper gastrointestinal bleeding, and those with hematologic malignancy undergoing chemotherapy or hematopoietic cell transplant.

C. Autologous Packed Red Blood Cells

Patients scheduled for elective surgery may donate blood for autologous transfusion. These units may be stored for up to 35 days before freezing is necessary.

► Compatibility Testing

Before transfusion, the recipient's and the donor's blood are typed and cross-matched to avoid hemolytic transfusion reactions. Although many antigen systems are present on red blood cells, only the ABO and Rh systems are

specifically tested prior to all transfusions. The A and B antigens are the most important, because everyone who lacks one or both red cell antigens has IgM isoantibodies (called isoagglutinins) in his or her plasma against the missing antigen(s). The isoagglutinins activate complement and can cause rapid intravascular lysis of the incompatible red blood cells. In emergencies, type O/Rh-negative blood can be given to any recipient, but usually packed cells are given to minimize transfusion of donor plasma containing anti-A and anti-B antibodies with the use of whole blood.

The other important antigen routinely tested for is the D antigen of the Rh system. Approximately 15% of the population lacks this antigen. In patients lacking the antigen, anti-D antibodies are not naturally present, but the antigen is highly immunogenic. A recipient whose red cells lack D and who receives D-positive blood often develop anti-D antibodies that can cause severe lysis of subsequent transfusions of D-positive red cells or reject a D-positive fetus.

Blood typing includes a cross-match assay of recipient serum for alloantibodies directed against donor red blood cells by mixing recipient serum with panels of red blood cells representing commonly occurring minor red cell antigens. The screening is particularly important if the recipient has had previous transfusions or pregnancy.

► Hemolytic Transfusion Reactions

The most severe hemolytic transfusion reactions are acute (temporally related to the transfusion), involving incompatible mismatches in the ABO system that are isoagglutinin-mediated. Most of these cases are due to clerical errors and mislabeled specimens. With current compatibility testing and double-check clerical systems, the risk of an acute hemolytic reaction is 1 in 76,000 transfused units of red blood cells. Death from acute hemolytic reaction occurs in 1 in 1.8 million transfused units. When hemolysis occurs, it is rapid and intravascular, releasing free hemoglobin into the plasma. The severity of these reactions depends on the dose of red blood cells given. The most severe reactions are those seen in surgical patients under anesthesia.

Delayed hemolytic transfusion reactions are caused by minor red blood cell antigen discrepancies and are typically less severe. The hemolysis usually takes place at a slower rate and is mediated by IgG alloantibodies causing extravascular red blood cell destruction. These transfusion reactions may be delayed for 5–10 days after transfusion. In such cases, the recipient has received red blood cells containing an immunogenic antigen, and in the time since transfusion, a new alloantibody has formed. The most common antigens involved in such reactions are Duffy, Kidd, Kell, and C and E loci of the Rh system. The current risk of a delayed hemolytic transfusion reaction is 1 in 6000 transfused units of red blood cells.

A. Symptoms and Signs

Major acute hemolytic transfusion reactions cause fever and chills, with backache and headache. In severe cases, there may be apprehension, dyspnea, hypotension, and

cardiovascular collapse. Patients under general anesthesia will not manifest such symptoms, and the first indication may be tachycardia, generalized bleeding, or oliguria. *The transfusion must be stopped immediately.* In severe cases, acute DIC, acute kidney injury from tubular necrosis, or both can occur. Death occurs in 4% of acute hemolytic reactions due to ABO incompatibility. Delayed hemolytic transfusion reactions are usually without any or only mild symptoms or signs.

B. Laboratory Findings

When an acute hemolytic transfusion episode is suspected, the identification of the recipient and of the transfusion product bag label should be rechecked. The transfusion product bag with its pilot tube must be returned to the blood bank, and a fresh sample of the recipient's blood must accompany the bag for retyping and re-cross-matching of donor and recipient blood samples. The hemoglobin will fail to rise by the expected amount. Coagulation studies may reveal evidence of acute kidney injury or acute DIC. The plasma-free hemoglobin in the recipient will be elevated resulting in hemoglobinuria.

In cases of delayed hemolytic reactions, there will be an unexpected drop in hemoglobin and an increase in the total and indirect bilirubins. The new offending alloantibody is easily detected in the patient's serum.

C. Treatment

If an acute hemolytic transfusion reaction is suspected, the transfusion should be stopped at once. The patient should be vigorously hydrated to prevent acute tubular necrosis. Forced diuresis with mannitol may help prevent or minimize acute kidney injury.

► Leukoagglutinin Reactions

Most transfusion reactions are not hemolytic but represent reactions to antigens present on transfused passenger leukocytes in patients who have been sensitized to leukocyte antigens through previous transfusions or pregnancy. Transfusion products relatively rich in leukocyte-rich plasma, especially platelets, are most likely to cause this. Moderate to severe leukoagglutinin reactions occur in 1% of red blood cell transfusions and 2% of platelet transfusions. The risk of a leukoagglutination reaction is minimal if the transfused blood product is leukoreduced in-line upon collection. Most commonly, fever and chills develop in patients within 12 hours after transfusion. In severe cases, cough and dyspnea may occur and the chest radiograph may show transient pulmonary infiltrates. Because no hemolysis is involved, the hemoglobin rises by the expected amount despite the reaction.

Leukoagglutinin reactions may respond to acetaminophen (500–650 mg orally) and diphenhydramine (25 mg orally or intravenously); corticosteroids, such as hydrocortisone (1 mg/kg intravenously), are also of value. Overall, leukoagglutination reactions are diminishing through the routine use of in-line leukotrappling during blood donation (ie, leukoreduced blood). Patients experiencing severe leukoagglutination episodes despite receiving leukoreduced

blood transfusions should receive leukopenic or washed blood products.

► Hypersensitivity Reactions

Urticaria or bronchospasm may develop during or soon after a transfusion. These reactions are almost always due to exposure to allogeneic plasma proteins rather than to leukocytes. The risk is low enough that the routine use of antihistamine premedications has been eliminated before packed red blood cell transfusions. However, a hypersensitivity reaction, including anaphylactic shock, may develop in patients who are IgA deficient because of antibodies to IgA in the patient's plasma directed against the IgA in the transfused blood product. Patients with such reactions may require transfusion of washed or even frozen red blood cells to avoid future severe reactions.

► Contaminated Blood

Blood products can be contaminated with bacteria. Platelets are especially prone to bacterial contamination because they cannot be refrigerated. Bacterial contamination occurs in 1 of every 30,000 red blood cell donations and 1 of every 5000 platelet donations. Receipt of a blood product contaminated with gram-positive bacteria will cause fever and bacteremia, but rarely causes a sepsis syndrome. Receipt of a blood product contaminated with gram-negative bacteria often causes septic shock, acute DIC, and acute kidney injury due to the transfused endotoxin and is usually fatal. Strategies to reduce bacterial contamination include enhanced venipuncture site skin cleansing, diverting of the first few milliliters of donated blood, use of single-donor blood products (as opposed to pooled-donor products), and point-of-care rapid bacterial screening in order to discard questionable units. Blood products infused with psoralen and then exposed to UVA light will have no living organisms in them, but add cost to acquisition of the blood product. The current risk of a septic transfusion reaction from a culture-negative unit of single-donor platelets (not psoralen treated) is 1 in 60,000. In any patient who may have received contaminated blood, the recipient and the donor blood bag should both be cultured, and antibiotics should be given immediately to the recipient.

► Infectious Diseases Transmitted Through Transfusion

Despite the use of only volunteer blood donors and the routine screening of blood, transfusion-associated viral diseases remain a problem. All blood products (red blood cells, platelets, plasma, cryoprecipitate) can transmit viral diseases. All blood donors are screened with questionnaires designed to detect (and therefore reject) donors at high risk for transmitting infectious diseases. For example, the American Red Cross does not accept blood donation from persons with a diagnosis of COVID-19 or from contacts of persons who have or are suspected to have the causal SARS-CoV-2 virus. All blood is screened for hepatitis B surface antigen, antibody to hepatitis B core antigen and syphilis, antibodies to HIV-1 and HIV-2 and NAT (nucleic

acid amplification) for HIV, antibody to hepatitis C virus (HCV) and NAT for hepatitis C, antibody to human T-cell lymphotropic/leukemia virus (HTLV), and NAT for West Nile virus. Zika virus contamination is screened for by donor questionnaire but the routine use of an FDA-approved detection test has not been uniformly adopted to screen donated blood. It is recommended that blood donors get screened once for antibodies against *Trypanosoma cruzi*, the infectious agent that causes Chagas disease (and if negative, no further screening for additional blood donations).

With improved screening, the risk of posttransfusion hepatitis has steadily decreased after the receipt of screened “negative” blood products. The risk of acquiring hepatitis B is about 1 in 200,000 transfused units in the United States. The risk of hepatitis C acquisition is 1 in 1.5 to 2 million transfused units in the United States. The risk of HIV acquisition is 1 in 2 million transfused units. Unscreened *but* leukoreduced blood products appear to be equivalent to CMV screened-negative blood products in terms of the risk of CMV transmission to a CMV-seronegative recipient.

► Transfusion Graft-Versus-Host Disease

Allogeneic passenger lymphocytes in transfused blood products will engraft in some recipients and mount an alloimmune attack against tissues expressing discrepant HLA antigens causing graft-versus-host disease (GVHD). The symptoms and signs of transfusion-associated GVHD include fever, rash, diarrhea, hepatitis, lymphadenopathy, and severe pancytopenia. The outcome is usually fatal. Transfusion-associated GVHD occurs most often in recipients with immune defects, malignant lymphoproliferative disorders, solid tumors being treated with chemotherapy or immunotherapy, treatment with immunosuppressive medications (especially purine analogs such as fludarabine), or older patients undergoing cardiac surgery. HIV infection alone does not increase the risk. The use of leukoreduced blood products is inadequate to prevent transfusion-associated GVHD. This complication can be avoided by irradiating blood products (25 Gy or more) to prevent lymphocyte proliferation in blood products given to recipients at high risk for transfusion-associated GVHD.

► Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) occurs in 1 in every 5000 transfused units of blood products. TRALI is clinically defined as noncardiogenic pulmonary edema after a blood product transfusion without other explanation. Transfused surgical and critically ill patients seem most susceptible. It has been associated with allogeneic antibodies in the donor plasma component that bind to recipient leukocyte antigens, including HLA antigens and other granulocyte- and monocyte-specific antigens (such as human neutrophil antigen [HNA]-1a, -1b, -2a, and -3a). In 20% of cases, no antileukocyte antibodies are identified raising the concern that bioactive lipids or other substances that accumulate while the blood product is in storage can also mediate TRALI in susceptible recipients. Ten to 20% of female blood donors and 1–5% of male blood donors

have antileukocyte antibodies in their serum. The risk of TRALI is reduced through the use of male-only plasma donors, when possible. There is no specific treatment for TRALI, only supportive care.

PLATELET TRANSFUSIONS

Platelet transfusions are indicated in cases of thrombocytopenia due to decreased platelet production. They are of some use in immune thrombocytopenia when active bleeding is evident, but the clearance of transfused platelets is rapid as they are exposed to the same pathophysiologic forces as the recipient's endogenous platelets. The risk of bleeding rises when the platelet count falls to less than 80,000/mcL ($80 \times 10^9/L$), and the risk of life-threatening spontaneous bleeding increases when the platelet count is less than 5000/mcL ($5 \times 10^9/L$). Because of this, prophylactic platelet transfusions are often given at these very low levels, usually when less than 10,000/mcL ($10 \times 10^9/L$). Platelet transfusions are also given prior to invasive procedures or surgery in thrombocytopenic patients, and the goal is often to raise the platelet count to 50,000/mcL ($50 \times 10^9/L$) or more.

Platelets for transfusion are most commonly derived from single-donor apheresis collections (roughly the equivalent to the platelets recovered from six donations of whole blood). A single donor unit of platelets should raise the platelet count by 50,000 to 60,000 platelets per mcL ($50\text{--}60 \times 10^9/L$) in a transfusion-naïve recipient without hypersplenism or ongoing platelet consumptive disorder. Transfused platelets typically last for 2 or 3 days. Platelet transfusion responses may be suboptimal with poor platelet increments and short platelet survival times. This may be due to one of several causes, including fever, sepsis, hypersplenism, DIC, large body habitus, low platelet dose in the transfusion, or platelet alloimmunization (from prior transfusions, prior pregnancy or prior organ transplantation). Many, but not all, alloantibodies causing platelet destruction are directed at HLA antigens. Patients requiring long periods of platelet transfusion support should be monitored to document adequate responses to transfusions so that the most appropriate product can be used. If random platelet transfusions prove inadequate, then the patient should be cross-matched with potential donors who might prove better able to provide adequate platelet-transfusion increments and platelet survival. Patients requiring ongoing platelet transfusions who become alloimmunized may benefit from HLA-matched platelets derived from either volunteer donors or family members.

TRANSFUSION OF PLASMA COMPONENTS

Fresh frozen plasma (FFP) is available in units of approximately 200 mL. FFP contains normal levels of all coagulation factors (about 1 unit/mL of each factor). FFP is used to correct coagulation factor deficiencies and to treat thrombotic thrombocytopenia purpura or other thrombotic microangiopathies. FFP is also used to correct or prevent coagulopathy in trauma patients receiving massive transfusion of packed red blood cell (PRBC). An FFP:PRBC ratio of 1:2 or more is associated with improved survival in

trauma patients receiving massive transfusions, regardless of the presence of a coagulopathy.

Cryoprecipitate is made from fresh plasma by cooling the plasma to 4°C and collecting the precipitate. One unit of cryoprecipitate has a volume of approximately 15–20 mL and contains approximately 250 mg of fibrinogen and between 80 and 100 units of factor VIII and von Willebrand factor. Cryoprecipitate is most commonly used to supplement fibrinogen in cases of acquired hypofibrinogenemia (eg, acute DIC) or in rare instances of congenital hypofibrinogenemia. One unit of cryoprecipitate will raise the fibrinogen level by about 8 mg/dL (0.24 mcmol/L). Cryoprecipitate is sometimes used to temporarily correct

the acquired qualitative platelet dysfunction associated with kidney disease.

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14

Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy

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To evaluate patients for defects of hemostasis, the clinical context must be considered carefully (Table 14–1). Heritable defects are suggested by bleeding that begins in infancy or childhood, is recurrent, and occurs at multiple anatomic sites, although other patterns of presentation are possible. Acquired disorders of hemostasis typically are associated with bleeding that begins later in life and may relate to introduction of medications (eg, agents that affect platelet activity) or to onset of underlying medical conditions (such as kidney disease, liver disease, myelodysplasia, aortic stenosis, prosthetic aortic valve, myeloproliferative neoplasms), or may be idiopathic (acquired hemophilia A, acquired von Willebrand disease). Importantly, however, a sufficient hemostatic challenge (such as major trauma) may produce excessive bleeding even in individuals with normal hemostasis. A personal history of hemostatic challenges (eg, circumcision, trauma, injury during youth sports, tooth extractions, motor vehicle accidents, prior surgery, and pregnancy and delivery) and a family history of bleeding are critical when evaluating someone for a possible bleeding disorder.

PLATELET DISORDERS

THROMBOCYTOPENIA

Selected causes of thrombocytopenia are shown in Table 14–2. The age of the patient and presence of comorbid conditions can help direct the diagnostic workup.

The risk of clinically relevant spontaneous bleeding (including petechial hemorrhage and bruising) does not typically increase appreciably until the platelet count falls below $10,000\text{--}20,000/\text{mCL}$ ($10\text{--}20 \times 10^9/\text{L}$), although patients with dysfunctional platelets or local vascular defects can bleed with higher platelet counts. Suggested platelet counts to prevent spontaneous bleeding or to provide adequate hemostasis around the time of invasive procedures are found in Table 14–3. However, most medical centers develop their own local guidelines to have a consistent approach to such complex situations.

DECREASED PLATELET PRODUCTION

1. Bone Marrow Failure



ESSENTIALS OF DIAGNOSIS

- Determine if bone marrow failure is congenital or acquired.
- Most congenital marrow failure disorders present in childhood.

► General Considerations

Congenital conditions that cause thrombocytopenia include amegakaryocytic thrombocytopenia, the thrombocytopenia-absent radius syndrome, and Wiskott-Aldrich syndrome; these disorders usually feature isolated thrombocytopenia, whereas patients with Fanconi anemia and dyskeratosis congenita typically include cytopenias in other blood cell lineages. Mutations in genes (*FLI1*, *MYH9*, *GATA1*, *ETV6*, among others) that cause thrombocytopenia are being identified.

Acquired causes of bone marrow failure (see Chapter 13) leading to thrombocytopenia include, but are not limited to, acquired aplastic anemia, myelodysplastic syndrome (MDS), acquired amegakaryocytic thrombocytopenia (albeit a rare disorder), alcohol, and drugs. Unlike aplastic anemia, MDS is more common among older patients.

► Clinical Findings

See Chapter 13 for symptoms and signs of aplastic anemia. Acquired aplastic anemia typically presents with reductions in multiple blood cell lineages, and the CBC reveals pancytopenia (anemia, thrombocytopenia, and neutropenia). A bone marrow biopsy is required for diagnosis and reveals marked hypocellularity. MDS also presents as cytopenias and can have pancytopenia, but the marrow typically demonstrates hypercellularity and dysplastic features. The presence of macrocytosis, ringed sideroblasts on iron staining of

Table 14–1. Evaluation of the bleeding patient.

Necessary Component of Evaluation	Diagnostic Correlate
Location	
Mucocutaneous (bruises, petechiae, gingivae, nosebleeds, GI, GU)	Suggests qualitative/quantitative platelet defects; vWD
Joints, soft tissue	Suggests disorders of coagulation factors
Onset	
Infancy/childhood	Suggests heritable condition
Adulthood	Suggests milder heritable condition or acquired defect of hemostasis (eg, ITP, medication, acquired factor VIII deficiency; acquired vWD)
Clinical Context	
Postsurgical	Anatomic/surgical defect must be ruled out
Pregnancy	vWD, HELLP syndrome, ITP, acquired factor VIII inhibitor
Sepsis	May indicate DIC
Exposure to anticoagulants	Rule out excessive anticoagulation
Personal History¹	
Absent	Suggests acquired rather than congenital defect, or anatomic/surgical defect (if applicable)
Present	Suggests established acquired defect or congenital disorder
Family History	
Absent	Suggests acquired defect or no defect of hemostasis
Present	May signify hemophilia A or B, vWD, other heritable bleeding disorders

¹Includes evaluation of prior spontaneous bleeding, as well as excessive bleeding with circumcision, menses, dental extractions, trauma, minor procedures (eg, endoscopy, biopsies), and major procedures (surgery).

DIC, disseminated intravascular coagulation; GI, gastrointestinal; GU, genitourinary; HELLP, hemolysis, elevated liver enzymes, low platelets; ITP, immune thrombocytopenia; vWD, von Willebrand disease.

the bone marrow aspirate, dysplasia of hematopoietic elements, or cytogenetic abnormalities (especially monosomy 5 or 7 and trisomy 8) is more suggestive of MDS.

► Differential Diagnosis

Adult patients with acquired amegakaryocytic thrombocytopenia (rare) have isolated thrombocytopenia and reduced or absent megakaryocytes in the bone marrow, which along with failure to respond to immunomodulatory regimens typically administered in immune thrombocytopenia (ITP), distinguishes them from patients with ITP.

Table 14–2. Selected causes of thrombocytopenia.

Decreased production of platelets
Congenital bone marrow failure
Amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, Fanconi anemia
Acquired bone marrow failure
Aplastic anemia, myelodysplastic syndrome, leukemia
Exposure to chemotherapy, irradiation, medications (https://ouhsc.edu/platelets/ditp.html)
Marrow infiltration (neoplastic, infectious)
Nutritional (deficiency of vitamin B ₁₂ , folate)
Other: HIV infection, alcohol
Increased destruction of platelets
Immune thrombocytopenia (primary)
Immune thrombocytopenia (secondary), including drug-induced or related to lymphoproliferative disorders (eg, CLL, hepatitis C virus, Epstein-Barr virus, or HIV)
Heparin-induced thrombocytopenia
Thrombotic microangiopathy
Disseminated intravascular coagulation
Posttransfusion purpura
Mechanical (aortic valvular dysfunction; extracorporeal bypass)
von Willebrand disease, type 2B
Hemophagocytosis
Increased sequestration of platelets
Hypersplenism (eg, cirrhosis, myeloproliferative disorders, lymphoma)
Other conditions causing thrombocytopenia
Gestational thrombocytopenia
Bernard-Soulier syndrome, gray platelet syndrome, May-Hegglin anomaly
Pseudothrombocytopenia

CLL, chronic lymphocytic leukemia.

► Treatment

A. Congenital Conditions

Treatment is varied but may include blood product support, blood cell growth factors, androgens and, in some cases, allogeneic hematopoietic stem cell transplantation.

Table 14–3. Desired platelet count ranges.

Clinical Scenario	Platelet Count /mCL ($\times 10^9/L$)
Prevention of spontaneous mucocutaneous bleeding	> 10,000–20,000 (> 10–20)
Insertion of central venous catheters	> 20,000–50,000 ¹ (> 20–50)
Administration of therapeutic anticoagulation	> 30,000–50,000 (> 30–50)
Minor surgery and selected invasive procedures ²	> 50,000–80,000 (> 50–80)
Major surgery	> 80,000–100,000 (> 80–100)

¹A platelet target within the higher reference range is required for tunneled catheters.

²Such as endoscopy with biopsy.

B. Acquired Conditions

Patients with severe aplastic anemia are treated with immunosuppressive therapy or allogeneic hematopoietic stem cell transplantation (see Chapter 13).

Treatment of thrombocytopenia due to MDS, if clinically significant bleeding is present or if the risk of bleeding is high, is limited to chronic transfusion of platelets in most instances (Table 14–3). Additional treatment is discussed in Chapter 13.

Almazni I et al. Inherited thrombocytopenia: update on genes and genetic variants which may be associated with bleeding. *Front Cardiovasc Med.* 2019;6:80. [PMID: 31275945]

Noris P et al. Hereditary thrombocytopenias: a growing list of disorders. *Hematology Am Soc Hematol Educ Program.* 2017; 2017:385. [PMID: 29222283]

2. Bone Marrow Infiltration

Replacement of the normal bone marrow elements by leukemic cells, plasma cell myeloma, lymphoma, or nonhematologic tumors or by infections (such as mycobacterial disease or ehrlichiosis) may cause thrombocytopenia; however, abnormalities in other blood cell lines are usually present. These entities are easily diagnosed after examining the bone marrow biopsy and aspirate or determining the infecting organism from an aspirate specimen, and they often lead to a leukoerythroblastic peripheral blood smear (left-shifted myeloid lineage cells, nucleated red blood cells, and teardrop-shaped red blood cells). Treatment of thrombocytopenia is directed at eradication of the underlying infiltrative disorder, but platelet transfusion may be required if clinically significant bleeding is present.

3. Chemotherapy & Irradiation

Chemotherapeutic agents and irradiation may lead to thrombocytopenia by direct toxicity to megakaryocytes, hematopoietic progenitor cells, or both. The severity and duration of chemotherapy-induced depressions in the platelet count are determined by the specific regimen used, although the platelet count typically resolves more slowly following a chemotherapeutic insult than does neutropenia or anemia, especially if multiple cycles of treatment have been given. Until recovery occurs, patients may be supported with transfused platelets if bleeding is present or the risk of bleeding is high (Table 14–3). Initial studies suggest that that platelet growth factors, such as eltrombopag and romiplostim, may help prevent chemotherapy-induced thrombocytopenia and allow patients to receive their full chemotherapy doses on schedule. Checkpoint inhibitors can also lead to thrombocytopenia that mimics immune thrombocytopenic purpura.

Soff GA et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. *J Clin Oncol.* 2019;37:2892. [PMID: 31545663]

Wang Z et al. Recombinant human thrombopoietin (rh-TPO) for the prevention of severe thrombocytopenia induced by high-dose cytarabine: a prospective, randomized, self-controlled study. *Leuk Lymphoma.* 2018;59:2821. [PMID: 29909708]

4. Nutritional Deficiencies

Thrombocytopenia, typically in concert with anemia, may be observed with a deficiency of folate (that may accompany alcoholism) or vitamin B₁₂ (concomitant neurologic findings may be manifest). In addition, thrombocytopenia can occur in very severe iron deficiency, albeit rarely, whereas thrombocytosis is far more common. Replacing the deficient vitamin or mineral results in improvement in the platelet count.

5. Cyclic Thrombocytopenia

Cyclic thrombocytopenia is a rare disorder that produces cyclic oscillations of the platelet count, usually with a periodicity of 3–6 weeks. The pathophysiologic mechanism responsible for the condition is unclear. Severe thrombocytopenia and bleeding typically occur at the platelet nadir. Oral contraceptive medications, androgens, azathioprine, and thrombopoietic growth factors have been used successfully in the management of cyclic thrombocytopenia.

INCREASED PLATELET DESTRUCTION

1. Immune Thrombocytopenia



ESSENTIALS OF DIAGNOSIS

- ▶ Isolated thrombocytopenia (rule out pseudo-thrombocytopenia by review of peripheral smear).
- ▶ Assess for any new causative medications and HIV, hepatitis B, hepatitis C, and *Helicobacter pylori* infections.
- ▶ ITP is a diagnosis of exclusion.

General Considerations

ITP is an autoimmune condition in which pathogenic antibodies bind platelets, accelerating their clearance from the circulation. Growing evidence suggests additional pathophysiological mechanisms, including a role for T cells. Many patients with ITP also lack appropriate compensatory platelet production, thought, at least in part, to reflect the antibody's effect on megakaryocytopoiesis and thrombopoiesis. ITP is primary (idiopathic) in most adult patients, although it can be secondary (ie, associated with autoimmune disease, such as systemic lupus erythematosus [SLE]; lymphoproliferative disease, such as lymphoma; medications; and infections caused by hepatitis C virus, HIV, and *H pylori*). Antiplatelet antibody targets include glycoproteins IIb/IIIa and Ib/IX on the platelet membrane, although antibodies are demonstrable in only two-thirds of patients; testing for such antibodies is not standard of care given the significant false-positive and false-negative results. In addition to production of antiplatelet antibodies, HIV and hepatitis C virus may lead to thrombocytopenia through

additional mechanisms (for instance, by direct suppression of platelet production [HIV] and cirrhosis-related decreased thrombopoietin [TPO] production and secondary splenomegaly [hepatitis C virus]).

► Clinical Findings

A. Symptoms and Signs

Mucocutaneous bleeding may be present, depending on the platelet count. Clinically relevant spontaneous bruising, epistaxis, gingival bleeding, or other types of hemorrhage generally do not occur until the platelet count has fallen below $10,000\text{--}20,000/\text{mCL}$ ($10\text{--}20 \times 10^9/\text{L}$). Individuals with secondary ITP (such as due to autoimmune disease, HIV or HCV infection, SLE, or lymphoproliferative malignancy) may have additional disease-specific findings.

B. Laboratory Findings

Typically, patients have isolated thrombocytopenia. If substantial bleeding has occurred, anemia may also be present. Hepatitis B and C viruses and HIV infections should be excluded by serologic testing. *H pylori* infections can sometimes cause isolated thrombocytopenia.

Bone marrow should be examined in patients with unexplained cytopenias in two or more lineages, in patients older than 40 years with isolated thrombocytopenia, or in those who do not respond to primary ITP-specific therapy. A bone marrow biopsy is not necessary in all cases to make an ITP diagnosis in younger patients. Megakaryocyte morphologic abnormalities and hypocellularity or hypercellularity are not characteristic of ITP. ITP patients often have increased numbers of bone marrow megakaryocytes. If there are clinical findings suggestive of a lymphoproliferative malignancy, a CT scan should be performed. In the absence of such findings, otherwise asymptomatic patients younger than 40 years lacking the above infections and with unexplained isolated thrombocytopenia of recent onset may be considered to have ITP.

► Treatment

Individuals with platelet counts less than $25,000\text{--}30,000/\text{mCL}$ ($25\text{--}30 \times 10^9/\text{L}$) or those with significant bleeding should be treated; the remainder may be monitored serially for progression, but that is a patient-specific decision. The mainstay of initial treatment of new-onset primary ITP is a short course of prednisone with or without intravenous immunoglobulin (IVIG) or anti-D (WinRho) (Figure 14–1). A short course of high-dose dexamethasone is also an option for initial treatment. Response to corticosteroids is generally seen within 3–7 days of initiating treatment, with responses to IVIG typically seen in 24–36 hours. Platelet transfusions may be given concomitantly if active bleeding is present. Adding the anti-B cell monoclonal antibody rituximab to corticosteroids as first-line treatment may improve the initial response rate, but it is

associated with increased toxicity and is not regarded as standard first-line therapy in most centers.

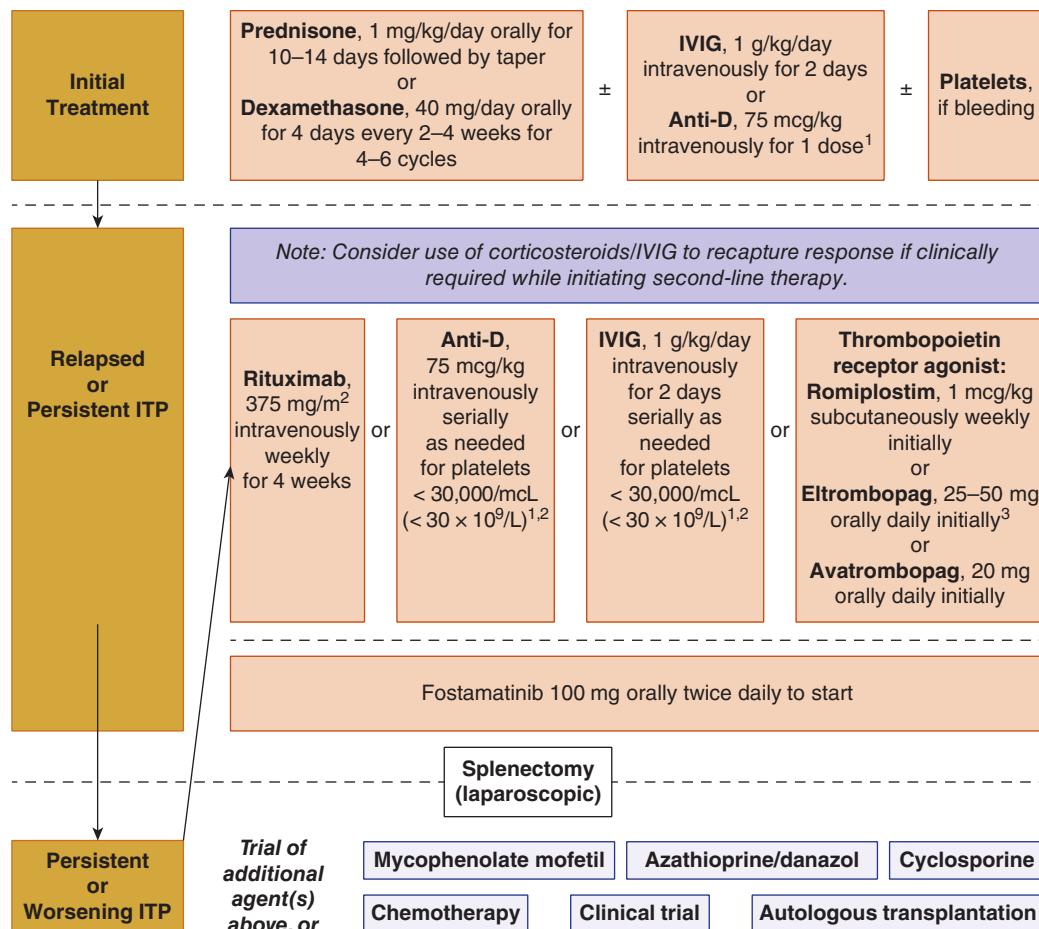
Although over two-thirds of patients with ITP respond to initial treatment with oral corticosteroids, most relapse following reduction of the corticosteroid dose. Patients with a persistent platelet count less than $30,000/\text{mCL}$ ($30 \times 10^9/\text{L}$) or clinically significant bleeding are appropriate candidates for second-line treatments (Figure 14–1). These treatments are chosen empirically, bearing in mind potential toxicities and patient preference. IVIG or anti-D (WinRho) temporarily increases platelet counts (duration, up to 3 weeks, rarely longer). Serial IVIG or anti-D treatment is an option for some adult patients while alternate safe treatment is pursued. Rituximab leads to clinical responses in about 50% of adults with corticosteroid-refractory chronic ITP, which decreases to about 20% at 5 years. The TPO-mimetics romiplostim (administered subcutaneously weekly), eltrombopag (taken orally daily), and avatrombopag (taken orally daily) are approved for use in adult patients with chronic ITP who have not responded durably to corticosteroids, IVIG, or splenectomy. Romiplostim, eltrombopag, or avatrombopag can be taken indefinitely to maintain the platelet response and can be used as second-line therapy. The Syk inhibitor fostamatinib represents a novel mechanism of action to treat ITP patients who do not respond to corticosteroids, TPO-mimetics, or rituximab. Splenectomy has a durable response rate of over 50% and may be considered for cases of severe ITP that fail to respond durably to initial treatment or are refractory to second-line agents; patients should receive pneumococcal, *Haemophilus influenzae* type b, and meningococcal vaccination at least 2 weeks before therapeutic splenectomy. If available, laparoscopic splenectomy is preferred. Additional treatments for ITP are found in Figure 14–1.

Management goals for pregnancy-associated ITP are a platelet count of $10,000\text{--}30,000/\text{mCL}$ ($10\text{--}30 \times 10^9/\text{L}$) in the first trimester, greater than or equal to $30,000/\text{mCL}$ ($30 \times 10^9/\text{L}$) during the second or third trimester, and greater than $50,000/\text{mCL}$ ($50 \times 10^9/\text{L}$) prior to cesarean section or vaginal delivery. Moderate-dose oral prednisone or intermittent IVIG infusions are standard treatment options. Splenectomy is reserved for failure to respond to these therapies and may be performed in the first or second trimester. Management requires close interaction between obstetrician and hematologist. TPO-mimetics are not approved for use during pregnancy.

For thrombocytopenia associated with HIV or hepatitis C virus, effective treatment of either infection leads to an amelioration of thrombocytopenia in most cases; refractory thrombocytopenia may require the use of IVIG, splenectomy, TPO-mimetic, or anti-CD20 therapy. Occasionally, ITP treatment response is impaired due to *H pylori* infection, which should be ruled out in the appropriate situation.

► When to Refer

All patients with ITP need to be managed by a hematologist because of the complexity of the decision making.



¹Use in non-splenectomized, Rh blood type-positive, non-anemic patients only.

²May need to repeat infusion every 2–6 weeks to maintain platelet response.

³Recommended starting dose in Asians is 25 mg daily.

▲ **Figure 14–1.** Management of immune thrombocytopenia (ITP), a simplified overview.

► When to Admit

Patients with major hemorrhage or very severe thrombocytopenia associated with bleeding should be admitted and monitored in-hospital until the platelet count has consistently risen to more than 20,000–30,000/mcL (20–30 × 10⁹/L) and hemodynamic stability has been achieved.

Bussel J et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. *Am J Hematol.* 2018;93:921. [PMID: 29696684]

Chaturvedi S et al. Splenectomy for immune thrombocytopenia: down but not out. *Blood.* 2018;131:1172. [PMID: 29295846]

Neumert C et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv.* 2019;3:3829. [PMID: 31794604]

Yang R et al. Therapeutic options for adult patients with previously treated immune thrombocytopenia—a systematic review and network meta-analysis. *Hematology.* 2019;24:290. [PMID: 30661482]

2. Thrombotic Microangiopathy

ESSENTIALS OF DIAGNOSIS

- ▶ Microangiopathic hemolytic anemia and thrombocytopenia, without another plausible explanation, are sufficient for a presumptive diagnosis of thrombotic microangiopathy (TMA).
- ▶ Fever, neurologic impairment, and kidney disease may occur but are not required for diagnosis.
- ▶ Kidney injury is more common and more severe in hemolytic-uremic syndrome (HUS).

► General Considerations

The TMAs include, but are not limited to, thrombotic thrombocytopenic purpura (TTP) and HUS. These

disorders are characterized by thrombocytopenia due to the incorporation of platelets into fibrin thrombi in the microvasculature, and microangiopathic hemolytic anemia, which results from shearing of erythrocytes in fibrin networks in the microcirculation.

In idiopathic TTP, autoantibodies against ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 repeat, member 13), also known as the von Willebrand factor (vWF) cleaving protease (vWFCP), lead to accumulation of ultra-large vWF multimers. The ultra-large multimers bridge and aggregate platelets in the absence of hemostatic triggers, which in turn leads to the vessel obstruction and various organ dysfunctions seen in TTP. In some cases of pregnancy-associated TMA, an antibody to ADAMTS-13 is present. In contrast, the activity of the ADAMTS-13 in congenital TTP is decreased due to a mutation in the gene encoding the molecule. Classic HUS, called Shiga toxin-mediated HUS, is thought to be secondary to toxin-mediated endothelial damage and is often contracted through the ingestion of undercooked ground beef contaminated with *Escherichia coli* (especially types O157:H7 or O145).

Complement-mediated HUS (formerly called atypical HUS) is not related to Shiga toxin. Patients with complement-mediated HUS often have genetic defects in proteins that regulate complement activity. Damage to endothelial cells—such as the damage that occurs in endemic HUS due to presence of toxins from *E. coli* (especially type O157:H7 or O145) or in the setting of cancer, hematopoietic stem cell transplantation, or HIV infection—may also lead to TMA. Certain drugs (eg, cyclosporine, quinine, ticlopidine, clopidogrel, mitomycin C, and bleomycin) are

associated with the development of TMA, possibly by promoting injury to endothelial cells, although inhibitory antibodies to ADAMTS-13 have been demonstrated in some cases.

Clinical Findings

A. Symptoms and Signs

Microangiopathic hemolytic anemia and thrombocytopenia are presenting signs in all patients with TTP and most patients with HUS; in a subset of patients with HUS, the platelet count remains in the normal range. Only about 25% of patients with TMA manifest all components of the original pentad of findings (microangiopathic hemolytic anemia, thrombocytopenia, fever, kidney disease, and neurologic abnormalities) (Table 14–4). Most patients (especially children) with HUS have a recent or current diarrheal illness, often bloody. Neurologic manifestations, including headache, somnolence, delirium, seizures, paresis, and coma, may result from deposition of microthrombi in the cerebral vasculature.

B. Laboratory Findings

Laboratory features of TMA include those associated with microangiopathic hemolytic anemia (anemia, elevated lactate dehydrogenase [LD], elevated indirect bilirubin, decreased haptoglobin, schistocytes on the blood smear, elevated reticulocyte count, and a negative direct anti-globulin test); thrombocytopenia; elevated creatinine; positive stool culture for *E. coli* O157:H7 or stool assays for Shiga toxin; reductions in ADAMTS-13 activity with the

Table 14–4. Presentation and management of thrombotic microangiopathies.

	TTP	Complement-Mediated HUS	Shiga Toxin–Mediated HUS
Patient population	Adults	Children (occasionally adults)	Usually children, often following bloody diarrhea
Pathogenesis	Acquired auto-antibody to ADAMTS-13	Some cases: heritable deficiency in function of complement regulatory proteins	Bacterial (such as enterotoxigenic <i>Escherichia coli</i> ; Shiga toxin)
Thrombocytopenia	Typically severe, except in very early clinical course	Variable	May be mild/absent in a minority of patients
Fever	Typical	Variable	Atypical
Kidney disease	Typical, but may be mild	Typical	Typical
Neurologic impairment	Variable	Less than half of cases	Less than half of cases
Laboratory investigation	Decreased activity of ADAMTS-13; inhibitor usually identified	Defects in complement regulatory proteins	Typically normal ADAMTS-13 activity Positive stool culture for <i>E. coli</i> O157:H7 or detectable antibody to Shiga toxin
Management	TPE Hemodialysis for severe kidney disease Caplizumab (selected patients) Platelet transfusions contraindicated unless TPE underway	Immediate TPE initially in most cases Eculizumab Supportive care Hemodialysis for severe kidney disease	Hemodialysis for severe kidney disease Supportive care TPE rarely beneficial (exception: selected cases in adults)

ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HUS, hemolytic-uremic syndrome; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.

presence (acquired TTP) or absence (inherited TTP) of ADAMTS-13 inhibitor; and mutations of genes encoding complement proteins (complement-mediated HUS; specialized laboratory assessment). Routine coagulation studies (prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen) are within the normal range in most patients with TTP or HUS.

► Treatment

With the exception of children or adults with endemic diarrhea-associated HUS, who generally recover with supportive care only, plasma exchange must be initiated as soon as the diagnosis of TMA is suspected and in all cases of TTP. Immediate administration of plasma exchange is essential in most cases of TTP because the mortality rate without treatment is over 95%. Plasma exchange usually is administered once daily until the platelet count and LD have returned to normal for at least 2 days, after which the frequency of treatments may be tapered slowly while the platelet count and LD are monitored for relapse. In cases of insufficient response to once-daily plasma exchange, twice-daily treatments can be considered. Fresh frozen plasma (FFP) may be administered if immediate access to plasma exchange is not available or in cases of familial TMA. *Platelet transfusions are contraindicated* in the treatment of TMA due to reports of worsening TMA, possibly due to propagation of platelet-rich microthrombi. In cases of documented life-threatening bleeding, however, platelet transfusions may be given slowly and preferably after plasma exchange is underway. Red blood cell transfusions may be administered in cases of clinically significant anemia. Hemodialysis should be considered for patients with significant kidney injury. Caplacizumab, a bi-specific antibody that targets the A1 domain of vWF and prevents vWF interaction with the platelet glycoprotein Ib-IX-V receptor, can reduce the time to platelet count normalization and 30-day mortality. The role of caplacizumab in the treatment of TTP remains controversial given its high cost and limited benefit, despite its inclusion in 2020 guidelines.

In cases of TTP relapse following initial treatment, plasma exchange should be reinstated. If ineffective, or in cases of primary refractoriness, second-line treatments including rituximab (which has shown efficacy when administered preemptively in selected cases of relapsing TTP), corticosteroids, IVIG, vincristine, cyclophosphamide, and splenectomy should be used. Idiopathic TTP is a relapsing autoimmune disorder (antibody inhibitor to ADAMTS-13) for most patients; careful monitoring of the ADAMTS-13 activity and inhibitor status and use of rituximab can prevent dangerous relapses.

Cases of complement-mediated HUS may respond to plasma infusion initially; however, once this diagnosis is strongly suspected, apheresis is typically stopped and serial infusions of the anti-complement C5 antibody eculizumab are given, which have produced sustained remissions in some patients. If irreversible kidney injury has occurred, hemodialysis or kidney transplantation may be necessary.

► When to Refer

Consultation by a hematologist or transfusion medicine specialist familiar with plasma exchange is required at the time of presentation. Patients with TMA and TTP require ongoing care by a hematologist.

► When to Admit

All patients with newly suspected or diagnosed TMA should be hospitalized immediately.

George JN et al. Syndromes of thrombotic microangiopathy associated with pregnancy. *Hematology Am Soc Hematol Educ Program*. 2015;2015:644. [PMID: 26637783]

Scully M et al; HERCULES Investigators. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;380:335. [PMID: 30625070]

Zheng XL et al. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2486. [PMID: 32914582]

Zheng XL et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2496. [PMID: 32914526]

3. Heparin-Induced Thrombocytopenia



ESSENTIALS OF DIAGNOSIS

- ▶ Thrombocytopenia within 5–14 days of exposure to heparin.
- ▶ Decline in baseline platelet count of $\geq 50\%$.
- ▶ Thrombosis occurs in up to 50% of cases; bleeding is uncommon.

► General Considerations

Heparin-induced thrombocytopenia (HIT) is an acquired disorder that affects approximately 3% of patients exposed to unfractionated heparin and ~0.6% of patients exposed to low-molecular-weight heparin (LMWH). The condition results from formation of IgG antibodies to heparin-platelet factor 4 (PF4) complexes; the antibody/heparin-PF4 complex binds to and activates platelets independent of physiologic hemostasis, which leads to thrombocytopenia and thromboses. von Willebrand factor has been postulated to play a role in the thrombotic events that take place long after heparin is cleared from the patient's system.

► Clinical Findings

A. Symptoms and Signs

Patients are often asymptomatic, and due to the prothrombotic nature of HIT, bleeding usually does not occur. Thrombosis (at any venous or arterial site), however, may be detected in up to 50% of patients, up to 30 days post diagnosis. If thrombosis has not already been detected, the use of duplex Doppler ultrasound of the lower extremities should be considered to rule out subclinical deep venous thrombosis (DVT).

B. Laboratory Findings

A presumptive diagnosis of HIT is made when new-onset thrombocytopenia is detected in a patient (typically a hospitalized patient) within 5–14 days of initial exposure to heparin; other presentations (eg, rapid-onset HIT) are less common and reflect recent prior heparin exposure. A decline of 50% or more from the baseline platelet count is typical. The 4T score (<http://www.qxmd.com/calculate-online/hematology/hit-heparin-induced-thrombocytopenia-probability>) is a clinical prediction rule for assessing pretest probability for HIT. Low 4T scores have been shown to be more predictive of excluding HIT than are intermediate or high scores of predicting its presence. Once HIT is clinically suspected, the clinician must establish the diagnosis by performing a screening PF4-heparin antibody enzyme-linked immunosorbent assay (ELISA). If the PF4-heparin antibody ELISA is positive, the diagnosis must be confirmed using a functional assay (such as serotonin release assay). The magnitude of a positive ELISA result correlates with the clinical probability of HIT, but even high ELISA optical density values may be falsely positive. The confirmatory functional assay is essential.

► Treatment

Treatment should be initiated as soon as the diagnosis of HIT is suspected, before results of laboratory testing are available.

Management of HIT (Table 14–5) involves the immediate discontinuation of all forms of heparin. Despite thrombocytopenia, platelet transfusions are rarely necessary and should be avoided. Due to the substantial frequency of thrombosis among HIT patients, an alternative anticoagulant should be administered immediately while awaiting confirmatory testing. A direct thrombin inhibitor (DTI), such as argatroban or bivalirudin, is preferred in critical illness because of the shorter duration of action. The use of the subcutaneous indirect anti-Xa inhibitor fondaparinux for initial treatment of HIT is a reasonable option in clinically stable patients. For confirmed HIT, the DTI should be continued until the platelet count has recovered to at least 100,000/mcL ($100 \times 10^9/L$), at which point treatment with a vitamin K antagonist (warfarin) may be initiated. The DTI should be continued until therapeutic anticoagulation with the vitamin K antagonist warfarin has been achieved (ie, international normalized ratio [INR] of 2.0–3.0); the infusion of argatroban must be temporarily discontinued before the INR is obtained so that it reflects the anticoagulant effect of warfarin alone. There is a growing acceptance for using oral anti-Xa agents instead of vitamin K antagonists in selected patients. In all patients with HIT, some form of anticoagulation (warfarin or other) should be continued for at least 30 days, due to a persistent risk of thrombosis even after the platelet count has recovered, but in patients in whom thrombosis has been documented, anticoagulation should continue for 3–6 months.

Subsequent exposure to heparin should be avoided in all patients with a prior history of HIT, if possible. If its use is regarded as necessary for a procedure, it should be withheld until PF4-heparin antibodies are no longer detectable

Table 14–5. Management of suspected or proven HIT.

I.	Discontinue all forms of heparin. Send PF4-heparin ELISA. Send confirmatory serotonin release assay if positive ELISA.	
II.	Begin treatment with direct thrombin inhibitor, or in some circumstances, fondaparinux.	
	Agent	Indication
	Argatroban	Prophylaxis or treatment of HIT
	Bivalirudin	Percutaneous coronary intervention ²
	Fondaparinux	Treatment of HIT
III.	Perform Doppler ultrasound of lower extremities to rule out subclinical thrombosis (if indicated).	
IV.	Follow platelet counts daily until recovery occurs.	
V.	When platelet count has recovered, transition anticoagulation to warfarin or fondaparinux; treat for 30 days (HIT) or 3–6 months (HITT).	
VI.	Document heparin allergy in medical record (confirmed cases).	

¹Liver insufficiency: initial infusion rate = 0.5 mcg/kg/min.

²Not approved for HIT/HITT.

ACT, activated clotting time; aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia and thrombosis; PF4, platelet factor 4.

by ELISA (usually as of 100 days following an episode of HIT), and exposure should be limited to the shortest time period possible. A common example is a cardiac catheterization. The heparin is gone before the antibody returns, so HIT is avoided.

► When to Refer

Due to the tremendous thrombotic potential of the disorder and the complexity of use of the DTI, all patients with HIT should be evaluated by a hematologist.

► When to Admit

Most patients with HIT are hospitalized at the time of detection of thrombocytopenia. Admission is a clinical decision for an outpatient in whom HIT is suspected and who is a candidate for subcutaneous fondaparinux. Other outpatients should be admitted because the DTIs must be administered by continuous intravenous infusion. Regardless, a hematologist needs to be involved as soon as the diagnosis is suspected or treatment is indicated.

Cuker A et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv.* 2018;2:3360. [PMID: 30482768]

Schindewolf M et al. Use of fondaparinux off-label or approved anticoagulants for management of heparin-induced thrombocytopenia. *J Am Coll Cardiol.* 2017;70:2636. [PMID: 29169470]

Warkentin TE. Laboratory diagnosis of heparin-induced thrombocytopenia. *Int J Lab Hematol.* 2019;41:15. [PMID: 31069988]

Warkentin TE et al. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. *Blood.* 2017;130:1104. [PMID: 28646118]

severe form of DIC with a particularly high mortality rate that occurs in peripartum women, include elevated liver transaminases and kidney injury due to gross hemoglobinuria and pigment nephropathy. Malignancy-related DIC may feature normal platelet counts and coagulation studies, but clinicians often see a dropping platelet count and fibrinogen, with a rising INR, highlighting the importance of serial laboratory values to help make the diagnosis.

Treatment

The underlying causative disorder must be treated (eg, antimicrobials, chemotherapy, surgery, or delivery of conceptus). If clinically significant bleeding is present, hemostasis must be achieved (Table 14–6).

Blood products are administered if clinically significant hemorrhage has occurred or is thought likely to occur without intervention based on progressively increasing PT and PTT and decreasing fibrinogen and platelets levels (Table 14–6). The goal of platelet therapy for most cases is greater than 20,000/mcL ($20 \times 10^9/L$) or greater than 50,000/mcL ($50 \times 10^9/L$) for serious bleeding, such as intracranial bleeding. FFP is typically given only to patients with a prolonged aPTT and PT and significant bleeding. Cryoprecipitate may be given for bleeding or for fibrinogen levels less than 80–100 mg/dL. The clinician should correct the fibrinogen level with cryoprecipitate prior to giving FFP for prolonged PT and aPTT to see if the

ESSENTIALS OF DIAGNOSIS

- ▶ Cancer, infection, trauma, and obstetric patients.
- ▶ Prolonged PT and aPTT, and low/declining fibrinogen.
- ▶ Thrombocytopenia.

General Considerations

Disseminated intravascular coagulation (DIC) is caused by uncontrolled local or systemic activation of coagulation, which leads to depletion of coagulation factors and fibrinogen, and often results in thrombocytopenia as platelets are activated and consumed.

Numerous disorders are associated with DIC, including sepsis (in which coagulation is activated by presence of lipopolysaccharide), cancer, trauma, burns, and pregnancy-associated complications (in which tissue factor is released). Aortic aneurysm and cavernous hemangiomas may promote localized intravascular coagulation, and snake bites may result in DIC due to the introduction of exogenous toxins.

Clinical Findings

A. Symptoms and Signs

Bleeding in DIC usually occurs at multiple sites, such as intravenous catheters or incisions, and may be widespread (purpura fulminans). Malignancy-related DIC may manifest principally as thrombosis (Trousseau syndrome).

B. Laboratory Findings

In early DIC, the platelet count and fibrinogen levels often remain within the normal range, albeit reduced from baseline levels. There is progressive thrombocytopenia (rarely severe), prolongation of the PT, decrease in fibrinogen levels, and eventually elevation in the aPTT. D-dimer levels typically are elevated due to the activation of coagulation and diffuse cross-linking of fibrin followed by fibrinolysis. Schistocytes on the blood smear, due to shearing of red cells through the microvasculature, are present in 10–20% of patients. Laboratory abnormalities in the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), a

Table 14–6. Management of DIC.

I. Assess for underlying cause of DIC and treat.	
II. Establish baseline platelet count, PT, aPTT, D-dimer, fibrinogen.	
III. Transfuse blood products only if ongoing bleeding or high risk of bleeding.	<p>Platelets: goal > 20,000/mcL ($20 \times 10^9/L$) (most patients) or > 50,000/mcL ($50 \times 10^9/L$) (severe bleeding, eg, intracranial hemorrhage)</p> <p>Cryoprecipitate: goal fibrinogen level > 80–100 mg/dL</p>
	<p>Fresh frozen plasma: goal PT and aPTT < 1.5 × normal</p> <p>Packed red blood cells: goal hemoglobin > 8 g/dL or improvement in symptomatic anemia</p>
IV. Follow platelets, aPTT, PT, fibrinogen every 4–12 hours as clinically indicated.	
V. If persistent bleeding due to severe consumption or consumption that requires excessive blood product use, consider use of heparin ¹ (initial infusion, 5 units/kg/h) and titrate to desired clinical goals; do not administer bolus.	
VI. Follow laboratory parameters every 4–12 hours as clinically indicated until DIC resolves	

¹Contraindicated if platelets cannot be maintained at > 50,000/mcL ($50 \times 10^9/L$), in cases of gastrointestinal or central nervous system bleeding, in conditions that may require surgical management, or placental abruption.

aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; PT, prothrombin time.

fibrinogen replacement alone corrects the PT and aPTT. The PT, aPTT, fibrinogen, and platelet count should be monitored at least every 6–8 hours in acutely ill patients with DIC.

In some cases of refractory bleeding despite replacement of blood products, administration of low doses of heparin can be considered. The clinician must remember that DIC is primarily a disorder of excessive clotting with secondary fibrinolysis, and that heparin can interfere with thrombin generation, which leads to less consumption of coagulation proteins and platelets. An infusion of 5 units/kg/h (no bolus) may be used with appropriate clinical judgement, uptitrated as clinically indicated. *Heparin, however, can be contraindicated if the platelet count cannot be maintained above 50,000/mcL (50 × 10⁹/L) and in cases of central nervous system hemorrhage, gastrointestinal bleeding, placental abruption, and any other condition that is likely to require imminent surgery.* Fibrinolysis inhibitors may be considered in select DIC patients with bleeding, but this can promote dangerous clotting and should be undertaken with great caution and only in consultation with a hematologist.

The treatment of HELLP syndrome must include evacuation of the uterus (eg, delivery of a term or near-term infant or removal of retained placental or fetal fragments). Patients with Trousseau syndrome require treatment of the underlying malignancy and administration of unfractionated heparin or subcutaneous therapeutic-dose LMWH as treatment of thrombosis, since warfarin typically is ineffective at secondary prevention of thromboembolism in the disorder. Typically, the heparin or LMWH treatment will gradually return the fibrinogen, PT (INR), aPTT, and platelet count back to normal, but it can take many days. Oral anti-Xa agents or oral DTIs can be considered once stabilized with parenteral heparin or LMWH, but extended LMWH is often used in this setting.

Immediate initiation of medical treatment (usually within 24 hours of diagnosis) is required for patients with acute promyelocytic leukemia (APL)-associated DIC, along with administration of blood products as clinically indicated.

► When to Refer

- Diffuse bleeding unresponsive to administration of blood products should be evaluated by a hematologist.
- All patients with DIC should be cared for by a hematologist prior to starting treatment with heparin or LMWH.

► When to Admit

Most patients with DIC are hospitalized when DIC is detected.

Cuker A et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv.* 2018;2:3360. [PMID: 30482768]

Levi M et al. Disseminated intravascular coagulation: an update on pathogenesis and diagnosis. *Expert Rev Hematol.* 2018; 11:663. [PMID: 29999440]

Levi M. Pathogenesis and diagnosis of disseminated intravascular coagulation. *Int J Lab Hematol.* 2018;40:15. [PMID: 29741245]
Warkentin TE et al. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. *Blood.* 2017;130:1104. [PMID: 28646118]

OTHER CONDITIONS CAUSING THROMBOCYTOPENIA

1. Drug-Induced Thrombocytopenia

Drug-induced thrombocytopenia is often immune-mediated but can also be due to marrow suppression. Table 14–7 lists medications associated with thrombocytopenia. The typical presentation of drug-induced, antibody-mediated thrombocytopenia is severe thrombocytopenia and

Table 14–7. Selected medications causing drug-associated thrombocytopenia.¹

Class	Examples
Chemotherapy	Most agents
Antiplatelet agents	Abciximab, eptifibatide, tirofiban Anagrelide Ticlopidine
Antimicrobial agents	Adefovir, indinavir, ritonavir Fluconazole Isoniazid Linezolid Penicillins Remdesivir Rifampin Sulfa drugs Vancomycin
Cardiovascular agents	Amiodarone Atorvastatin, simvastatin Captopril Digoxin Hydrochlorothiazide Procainamide
Gastrointestinal agents	Cimetidine, famotidine
Neuropsychiatric agents	Carbamazepine Haloperidol Methyldopa Phenytoin
Analgesic agents	Acetaminophen Diclofenac, ibuprofen, naproxen, sulindac
Anticoagulant agents	Heparin Low-molecular-weight heparin
Immunomodulator agents	Interferon-alpha Rituximab
Immunosuppressant agents	Mycophenolate mofetil Tacrolimus
Other agents	Immunizations Iodinated contrast dye

¹See also <https://www.ouhsc.edu/platelets/>.

mucocutaneous bleeding 5–14 days after exposure to a new drug, although a range of presentations is possible. Discontinuation of the offending agent leads to resolution of thrombocytopenia within 3–7 days in most cases, but recovery kinetics depend on rate of drug clearance, which can be affected by liver and kidney function. Patients with severe thrombocytopenia should be given platelet transfusions with or without IVIG. The University of Oklahoma Health Sciences center maintains a useful website for drug-induced thrombocytopenia (<https://www.ouhsc.edu/platelets/>).

2. Posttransfusion Purpura

Posttransfusion purpura (PTP) is a rare disorder of sudden-onset thrombocytopenia that occurs within 1 week after transfusion of red cells, platelets, or plasma. Antibodies against the human platelet antigen PL^{A1} are detected in most individuals with PTP. Patients with PTP often are either multiparous women or persons who have received transfusions previously. Severe thrombocytopenia and bleeding are typical. Initial treatment consists of administration of IVIG (1 g/kg/day for 2 days), which should be administered as soon as the diagnosis is suspected. Platelets are not indicated unless severe bleeding is present, but if they are to be administered, HLA-matched PL^{A1}-negative platelets are preferred. A second course or IVIG, plasma exchange, corticosteroids, TPO-mimetics, or splenectomy may be required in case of refractoriness. PL^{A1}-negative or washed blood products are preferred for subsequent transfusions, but data supporting various treatment options are limited.

3. Von Willebrand Disease Type 2B

von Willebrand disease (vWD) type 2B leads to chronic, characteristically mild to moderate thrombocytopenia via an abnormal vWF molecule that binds platelets with increased affinity, resulting in aggregation and clearance.

4. Platelet Sequestration

One-third of the platelet mass is typically sequestered in the spleen. Splenomegaly, due to a variety of conditions, may lead to thrombocytopenia of variable severity. When possible, treatment of the underlying disorder should be pursued, but splenectomy, splenic embolization, or splenic irradiation may be considered in selected cases.

5. Pregnancy

Gestational thrombocytopenia is thought to result from progressive expansion of the blood volume that typically occurs during pregnancy, leading to hemodilution. Cytophenias result even though blood cell production is normal or increased. Platelet counts less than 100,000/mcL ($100 \times 10^9/L$), however, are observed in less than 10% of pregnant women in the third trimester; decreases to less than 70,000/mcL ($70 \times 10^9/L$) should prompt consideration of pregnancy-related ITP as well as preeclampsia or a pregnancy-related thrombotic microangiopathy.

6. Infection or Sepsis

Both immune- and platelet production-mediated defects are possible, and there may be significant overlap with concomitant DIC. Regardless, the platelet count typically improves with effective antimicrobial treatment or after the infection has resolved. Hemophagocytosis may occur in some critically ill patients; a defect in immunomodulation may lead to bone marrow macrophages (histiocytes) engulfing cellular components of the marrow. The phenomenon typically resolves with resolution of the infection, but with certain infections (Epstein-Barr virus) immunosuppression may be required. Hemophagocytosis also may occur with malignancy, in which case the disorder is usually unresponsive to treatment with immunosuppression and requires treatment of the malignancy. Sepsis-related thrombocytopenia may be at least in part due to increased hepatic clearance of platelets caused by loss of asialoglycoprotein moieties on the platelet surface.

7. Pseudothrombocytopenia

Pseudothrombocytopenia results from ethylenediamine-tetraacetic acid (EDTA) anticoagulant-induced platelet clumping; the phenomenon typically disappears when blood is collected in a tube containing citrate anticoagulant. Pseudothrombocytopenia diagnosis requires review of the peripheral blood smear and is not associated with bleeding.

Koyama K et al. Time course of immature platelet count and its relation to thrombocytopenia and mortality in patients with sepsis. *PLoS One*. 2018;13:e0192064. [PMID: 29381746]

Menis M et al. Posttransfusion purpura occurrence and potential risk factors among the inpatient US elderly, as recorded in large Medicare databases during 2011 through 2012. *Transfusion*. 2015;55:284. [PMID: 25065878]

QUALITATIVE PLATELET DISORDERS

CONGENITAL DISORDERS OF PLATELET FUNCTION



ESSENTIALS OF DIAGNOSIS

- ▶ Usually diagnosed in childhood.
- ▶ Family history usually is positive.
- ▶ May be diagnosed in adulthood when there is excessive bleeding.

► General Considerations

Heritable qualitative platelet disorders are far less common than acquired platelet function disorders and lead to variably severe bleeding, often beginning in childhood. Occasionally, however, disorders of platelet function may go undetected until later in life when excessive bleeding occurs following a sufficient hemostatic challenge. Thus,

the true incidence of hereditary qualitative platelet disorders is unknown.

Bernard-Soulier syndrome (BSS) is a rare, autosomal recessive bleeding disorder due to reduced or abnormal platelet membrane expression of glycoprotein Ib/IX (vWF receptor).

Glanzmann thrombasthenia results from an abnormality in the platelet glycoprotein IIb/IIIa receptor on the platelet membrane. Glycoprotein IIb/IIIa is the fibrinogen receptor critical for linking platelets during initial platelet aggregation/platelet plug formation. Inheritance is autosomal recessive.

Under normal circumstances, activated platelets release the contents of platelet granules to reinforce the aggregatory response. Storage pool disease includes a spectrum of defects in release of alpha or dense (delta) platelet granules, or both (alpha-delta storage pool disease).

► Clinical Findings

A. Symptoms and Signs

Bleeding due to defective platelets is usually mucocutaneous, but it is not limited to mucocutaneous surfaces. The onset of bleeding with Glanzmann thrombasthenia is usually in infancy or childhood, but some forms are milder and present later in life. The degree of deficiency in IIb/IIIa may not correlate well with bleeding symptoms. Patients with storage pool disease are affected by variable bleeding, ranging from mild and trauma-related to spontaneous.

B. Laboratory Findings

In Bernard-Soulier syndrome, there are abnormally large platelets (approaching the size of red cells), moderate thrombocytopenia, and a prolonged bleeding time. Platelet aggregation studies show a marked defect in response to ristocetin, whereas aggregation in response to other agonists is normal; the addition of normal platelets corrects the abnormal aggregation. The diagnosis can be confirmed by platelet flow cytometry.

In Glanzmann thrombasthenia, platelet aggregation studies show marked impairment of aggregation in response to stimulation with various agonists, which reflects the critical role of the fibrinogen receptor in platelet plug formation.

Storage pool disease describes defects in the number, content, or function of platelet alpha or dense granules, or both. The gray platelet syndrome comprises abnormalities of platelet alpha granules, thrombocytopenia, and marrow fibrosis. The blood smear shows agranular platelets, and the diagnosis is confirmed with electron microscopy.

► Treatment

The mainstay of treatment (including periprocedural prophylaxis) is transfusion of normal platelets, although desmopressin acetate (DDAVP), antifibrinolytic agents, and recombinant human activated factor VII each have a role in selected clinical situations.

Orsini S et al; European Hematology Association-Scientific Working Group (EHA-SWG) on thrombocytopenias and platelet function disorders. Bleeding risk of surgery and its prevention in patients with inherited platelet disorders. *Hematologica*. 2017;102:1192. [PMID: 28385783]

ACQUIRED DISORDERS OF PLATELET FUNCTION

Platelet dysfunction is more commonly acquired than inherited; the widespread use of platelet-altering medications accounts for most of the cases of qualitative defects. In cases where platelet function is irreversibly altered, platelet inhibition typically recovers within 7–9 days following discontinuation of the drug, which is the time it takes to replace all of the impaired platelets with newly produced platelets. In cases where platelet function is non-irreversibly affected, platelet inhibition recovers with clearance of the drug from the system. Transfusion of platelets may be required if clinically significant bleeding is present.

Lee RH et al. Impaired hemostatic activity of healthy transfused platelets in inherited and acquired platelet disorders: mechanisms and implications. *Sci Transl Med*. 2019;11:eaay0203. [PMID: 31826978]

Zheng SL et al. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA*. 2019;321:277. [PMID: 30667501]

DISORDERS OF COAGULATION

CONGENITAL DISORDERS OF COAGULATION

1. Hemophilia A & B

► ESSENTIALS OF DIAGNOSIS

- **Hemophilia A:** congenital deficiency of coagulation factor VIII.
- **Hemophilia B:** congenital deficiency of coagulation factor IX.
- Recurrent hemarthroses and arthropathy.
- Risk of development of inhibitory antibodies to factor VIII or factor IX.
- Many older patients received blood products contaminated with HIV or hepatitis C virus.

► General Considerations

The frequency of hemophilia A is ~1 per 5000 live male births, whereas hemophilia B occurs in ~1 in 25,000 live male births. Inheritance is X-linked recessive, leading to affected males and carrier (affected) females with variable bleeding tendencies. Daughters of all affected males are obligate carriers. There is no race predilection. Factor

activity testing is indicated for male infants with a hemophilic maternal pedigree who are asymptomatic or who experience excessive bleeding, for all daughters of affected males (100% chance of being affected) and carrier mothers (50% chance of being affected), and for otherwise asymptomatic adolescents or adults who experience unexpected excessive bleeding with trauma or invasive procedures.

Inhibitors to factor VIII will develop in approximately 20–25% of patients with severe hemophilia A; inhibitors to factor IX will develop in less than 5% of patients with severe hemophilia B.

A substantial proportion of older patients with hemophilia acquired infection with HIV or HCV or both in the 1980s due to exposure to contaminated factor concentrates and blood products.

Clinical Findings

A. Symptoms and Signs

Severe hemophilia (factor VIII activity less than 1%) presents in infant males or in early childhood with spontaneous bleeding into joints, soft tissues, or other locations. Spontaneous bleeding is much less common in patients with mild hemophilia (factor VIII activity greater than 5%), but bleeding is common with provoked bleeding (eg, surgery, trauma). Intermediate clinical symptoms are seen in patients with moderate hemophilia (factor VIII activity 1–5%). Female carriers of hemophilia can have a wide range of factor VIII activity and therefore have variable bleeding tendencies.

Significant hemophilic arthropathy is usually avoided in patients who have received long-term prophylaxis with factor concentrate starting in early childhood, whereas destructive joint disease is common in adults who have experienced recurrent hemarthroses. Patients tend to have one or two “target” joints into which they bleed most often.

Inhibitor development to factor VIII or factor IX is characterized by bleeding episodes that are resistant to treatment with clotting factor VIII or IX concentrate, and by new or atypical bleeding.

B. Laboratory Findings

Hemophilia A or B is diagnosed by an isolated reproducibly low factor VIII or factor IX activity level, in the absence of other conditions. If the aPTT is prolonged, it typically corrects upon mixing with normal plasma. Depending on the level of residual factor VIII or factor IX activity, and the sensitivity of the thromboplastin used in the aPTT coagulation reaction, the aPTT may or may not be prolonged, although it typically is markedly prolonged in severe hemophilia. Hemophilia is classified according to the level of factor activity in the plasma. **Mild hemophilia** has greater than 5% factor activity; **moderate hemophilia** has 1–5% factor activity; and **severe hemophilia** has less than 1% factor activity. Female carriers may become symptomatic if significant lyonization has occurred favoring the defective factor VIII or factor IX gene, leading to factor VIII or factor IX activity level markedly less than 50%. Typically, a clinical bleeding diathesis occurs once the

factor activity is less than 20%, but this appears to be patient-specific, and bleeding can occur in trauma, surgery, and delivery if the factor activity is less than 50%.

In the presence of an inhibitor to factor VIII or factor IX, there is accelerated clearance of and suboptimal or absent rise in measured activity of infused factor, and the aPTT does not correct on mixing. The Bethesda assay measures the potency of the inhibitor.

Treatment

A. Factor VIII or IX Products

Plasma-derived or recombinant factor VIII or IX products are the mainstay of treatment. The standard of care for most individuals with severe hemophilia is primary prophylaxis: by the age of 4 years, most children with severe hemophilia have begun twice- or thrice-weekly infusions of factor to prevent the recurrent joint bleeding that otherwise would characterize the disorder and lead to severe musculoskeletal morbidity. In selected cases of less severe hemophilia, or as an adjunct to prophylaxis in severe hemophilia, treatment with factor products is given periprocedurally, prior to high-risk activities (such as sports), or as needed for bleeding episodes (Table 14–8). Recombinant factor VIII and factor IX molecules that are bioengineered to have an extended half-life may allow for extended dosing intervals in patients who are treated prophylactically. The decision to switch to a long-acting product is patient specific. The long-acting factor IX products have clear added value in reducing frequency of factor injections often to weekly or less. Long-acting factor VIII products have not achieved a similar degree of extended half-life. Patients with mild hemophilia A may respond to as-needed (on demand) intravenous or intranasal treatment with DDAVP. Antifibrinolytic agents may be useful in cases of mucosal bleeding and are commonly used adjunctively, such as following dental procedures.

B. Factor VIII or IX Inhibitors

Factor inhibitors (antibodies that interfere with activity or half-life) are a major clinical problem for patients with hemophilia. It may be possible to overcome low-titer inhibitors (less than 5 Bethesda units [BU]) by giving larger doses of factor, whereas treatment of bleeding in the presence of a high-titer inhibitor (more than 5 BU) requires infusion of an activated prothrombin complex concentrate (such as FEIBA [factor eight inhibitor bypassing activity]) or recombinant activated factor VII. Recombinant porcine factor VIII is also an option but is reserved for selective circumstances because of its cost. Inhibitor tolerance induction, achieved by giving large doses (50–300 units/kg intravenously of factor VIII daily) for 6–18 months, succeeds in eradicating the inhibitor in 70% of patients with hemophilia A and in 30% of patients with hemophilia B. Patients with hemophilia B who receive inhibitor tolerance induction, however, are at risk for development of nephrotic syndrome and anaphylactic reactions, making eradication of their inhibitors more problematic. Additional immunomodulation may allow for eradication in

Table 14–8. Treatment of bleeding in selected inherited disorders of hemostasis.

Disorder	Subtype	Treatment for Minor Bleeding	Treatment for Major Bleeding	Comment
Hemophilia A	Mild	DDAVP ¹	DDAVP ¹ or factor VIII product	Treat for 3–10 days for major bleeding or following surgery, keeping factor activity level 50–80% initially. Adjunctive EACA may be useful for mucosal bleeding or procedures
	Moderate or severe	Factor VIII product	Factor VIII product	
Hemophilia B	Mild, moderate, or severe	Factor IX product	Factor IX product	
von Willebrand disease	Type 1	DDAVP ¹	DDAVP ¹ , vWF product	
	Type 2	DDAVP ¹ , vWF product	vWF product	
	Type 3	vWF product	vWF product	
Factor XI deficiency	—	FFP or EACA	FFP	Adjunctive EACA should be used for mucosal bleeding or procedures

¹Mild hemophilia A and type 2A or 2B vWD patients: therapeutic trial must have previously confirmed an adequate response (ie, elevation of factor VIII or vWF activity level into the normal range) and (for type 2B) no exacerbation of thrombocytopenia. DDAVP is not typically effective for type 2M vWD. A vWF-containing factor VIII concentrate is preferred for treatment of type 2N vWD.

Notes:

DDAVP dose is 0.3 mcg/kg intravenously in 50 mL saline over 20 minutes, or nasal spray 300 mcg for weight > 50 kg or 150 mcg for < 50 kg, every 24 hours, maximum of three doses in a 72-hour period. If more than two doses are used in a 48-hour period, free water restriction and monitoring for hyponatremia is essential.

EACA dose is 50 mg/kg orally four times daily for 3–5 days; maximum 24 g/day, useful for mucosal bleeding/dental procedures.

Factor VIII product dose is 50 units/kg for severe hemophilia A intravenously initially followed by 25 units/kg every 8 hours followed by lesser doses at longer intervals once hemostasis has been established.

Factor IX product dose is 100 units/kg (120 units/kg if using Benefix) intravenously initially for severe hemophilia B followed by 50 units/kg (60 units/kg if using Benefix) every 8 hours followed by lesser doses at longer intervals once hemostasis has been established.

vWF-containing factor VIII product dose is 60–80 RCoF units/kg intravenously every 12 hours initially followed by lesser doses at longer intervals once hemostasis has been established.

FFP is typically administered in 4-unit boluses and may not need to be re-bolused after the initial administration due to the long half-life of factor XI.

DDAVP, desmopressin acetate; EACA, epsilon-aminocaproic acid; FFP, fresh frozen plasma; vWF, von Willebrand factor.

selected inhibitor tolerance induction–refractory patients. Emicizumab is a novel bi-specific antibody that brings activated factor IX and factor X together, effectively replacing the cofactor function of factor VIII in the clotting cascade, providing a major therapeutic advance for patients with inhibitors. Emicizumab has also been demonstrated to be an effective option for patients without inhibitors.

C. Gene Therapy

Gene therapy clinical trials for hemophilia A and B have shown great promise for patients with severe hemophilia A and B. For most patients, gene therapy has eliminated spontaneous bleeding as well as the need for factor replacement. While phase III clinical trials have been restricted to patients 18 years of age and older, the results look extremely promising. It is hoped that this potentially life-changing therapy will become an approved treatment outside of clinical trials in 2022.

D. Antiretroviral Therapy

Antiretroviral treatment should be administered to hemophilia patients with HIV infection. Patients with hepatitis C

infection should be referred for treatment to eradicate the virus.

► When to Refer

All patients with hemophilia should be seen regularly in a comprehensive hemophilia treatment center.

► When to Admit

- Major invasive procedures because of the need for serial infusions of clotting factor concentrate.
- Bleeding that is unresponsive to outpatient treatment.

George LA et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. *N Engl J Med.* 2017; 377:2215. [PMID: 29211678]

Mahlangu J et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med.* 2018;379:811. [PMID: 30157389]

Manco-Johnson MJ et al; Joint Outcomes Committee of the Universal Data Collection, US Hemophilia Treatment Center Network. Prophylaxis usage, bleeding rates, and joint outcomes of hemophilia, 1999 to 2010: a surveillance project. *Blood.* 2017;129:2368. [PMID: 28183693]

Oldenborg J et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med.* 2017;377:809. [PMID: 28691557]
 Pasi KJ et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *N Engl J Med.* 2020;382:29. [PMID: 31893514]

2. von Willebrand Disease



- The most common inherited bleeding disorder.
- vWF binds platelets to subendothelial surfaces, aggregates platelets, and prolongs the half-life of factor VIII.

► General Considerations

vWF is an unusually large multimeric glycoprotein that binds to subendothelial collagen and its platelet receptor, glycoprotein Ib, bridging platelets to the subendothelial matrix at the site of vascular injury and contributing to linking them together in the platelet plug. vWF also has a binding site for factor VIII, prolonging factor VIII half-life in the circulation.

Between 75% and 80% of patients with vWD have type 1, a quantitative abnormality of the vWF molecule that usually does not feature an identifiable causal mutation in the vWF gene.

Type 2 vWD is seen in 15–20% of patients with vWD. In type 2A or 2B vWD, a qualitative defect in the vWF molecule is causative. Type 2N and 2M vWD are due to defects in vWF that decrease binding to factor VIII or to platelets, respectively. Importantly, type 2N vWD can clinically resemble hemophilia A because factor VIII activity levels are decreased, and vWF activity and antigen (Ag) are normal. Type 2M vWD features a normal multimer pattern. Type 3 vWD is rare, and like type 1, is a quantitative defect, with mutational homozygosity or compound heterozygosity yielding very low levels of vWF and severe bleeding in infancy or childhood. Due to its factor VIII carrier function, a severely low vWF level leads to low factor VIII activity and prolonged aPTT.

► Clinical Findings

A. Symptoms and Signs

Patients with type 1 vWD usually have mild or moderate platelet-type bleeding (mucocutaneous) that may be evident in childhood. Heavier bleeding may occur with menes, surgery, or delivery. Patients with type 2 vWD usually have moderate to severe bleeding that presents in childhood or adolescence. Patient with type 3 vWD demonstrate a severe bleeding phenotype that typically manifests in childhood or infancy.

B. Laboratory Findings

In type 1 vWD, the vWF activity (ristocetin co-factor assay) and the vWF Ag are mildly depressed, whereas the vWF multimer pattern is normal (Table 14–9). Laboratory testing of type 2A or 2B vWD typically shows a ratio of vWF Ag:vWF activity of approximately 2:1 and a multimer pattern that lacks the highest molecular weight multimers. Thrombocytopenia is common in type 2B vWD due to a gain-of-function mutation of the vWF molecule, which leads to increased vWF binding to its receptor on platelets, resulting in platelet clearance; a ristocetin-induced platelet aggregation (RIPA) study shows an increase in platelet aggregation in response to low concentrations of ristocetin. Except in the more severe forms of vWD that feature a significantly decreased factor VIII activity, aPTT is most commonly normal in patients with vWD. The PT is not affected by vWD.

► Treatment

The treatment of vWD is outlined in Table 14–8. DDAVP is useful in the treatment of mild bleeding in most cases of type 1 and some cases of type 2 vWD. DDAVP causes release of vWF and factor VIII from storage sites (endothelial cells), leading to a two- to sevenfold increase in vWF and factor VIII. A therapeutic DDAVP trial to document sufficient rise in vWF level is critical prior to relying on DDAVP as a treatment option. Due to tachyphylaxis and the risk of significant hyponatremia secondary to fluid retention, DDAVP treatment is limited to one dose per 24 hours and no more than three doses over 5 days. vWF-containing factor VIII concentrates or recombinant VWF products are used in all other clinical scenarios, and when

Table 14–9. Laboratory diagnosis of von Willebrand disease.

Type		vWF Activity	vWF Antigen	Factor VIII	RIPA	Multimer Analysis
1		↓	↓	NI or ↓	↓	Normal pattern; uniform ↓ intensity of bands
2	A	↓↓	↓	↓	↓	Large and intermediate multimers decreased or absent
	B	↓↓	↓	↓	↑	Large multimers decreased or absent
	M	↓	↓	↓	↓	Normal pattern; uniform ↓ intensity of bands
	N	NI	NI	↓↓	NI	NI
3		↓↓↓	↓↓↓	↓↓↓	↓↓↓	Multimers absent

NI, normal; RIPA, ristocetin-induced platelet aggregation; vWF, von Willebrand factor.

bleeding is not controlled with DDAVP. Cryoprecipitate is no longer used as a source of vWD in clinical practice. Antifibrinolytic agents (eg, aminocaproic acid or tranexamic acid) may be used adjunctively for mucosal bleeding or procedures. Pregnant patients with type 1 vWD usually do not require treatment at the time of delivery because of the natural physiologic increase in vWF levels (up to threefold that of baseline) that are observed by parturition. However, levels need to be confirmed in late pregnancy, and if they are low or if excessive bleeding is encountered, vWF products may be given. Moreover, patients are at risk for significant bleeding 1–2 weeks postpartum when vWF levels fall secondary to the fall in estrogen levels and related return to baseline vWF levels.

Kouides PA. Present day management of inherited bleeding disorders in pregnancy. *Expert Rev Hematol.* 2016;9:987. [PMID: 27459638]

Sharma R et al. Advances in the diagnosis and treatment of Von Willebrand disease. *Blood.* 2017;130:2386. [PMID: 29187375]

3. Factor XI Deficiency

Factor XI deficiency (also called hemophilia C) is inherited in an autosomal recessive manner, leading to heterozygous, compound heterozygous, or homozygous defects. It is most prevalent among individuals of Ashkenazi Jewish descent, yet it is in the differential diagnosis of anyone with an unexplained prolonged aPTT. Levels of factor XI, while variably reduced, do not correlate well with bleeding symptoms. Mild bleeding is most common, and diagnosis is often made after unexpected, excessive bleeding following surgery or trauma. Importantly, factor XI deficiency that can lead to provoked excessive bleeding does not always prolong the aPTT. FFP is the mainstay of treatment when plasma-derived factor XI concentrate is not available. Administration of adjunctive aminocaproic acid or tranexamic acid is regarded as mandatory for procedures or bleeding episodes involving the mucosa (Table 14–8).

Vergheese L et al. Management of parturients with Factor XI deficiency—10 year case series and review of literature. *Eur J Obstet Gynecol Reprod Biol.* 2017;215:85. [PMID: 28622635]

4. Less Common Heritable Disorders of Coagulation

Congenital deficiencies of clotting factors II, V, VII, and X are rare and typically are inherited in an autosomal recessive pattern. A prolongation in the PT (and aPTT for factor X, factor V, and factor II deficiency) that corrects upon mixing with normal plasma is typical. Definitive diagnosis requires testing for specific factor activity. The treatment of factor II deficiency is with a prothrombin complex concentrate; factor V deficiency is treated with infusions of FFP or platelets (which contain factor V in alpha granules); factor VII deficiency is treated with recombinant human activated factor VII. Factor X deficiency is treated with an FDA-approved plasma-derived factor X product (Coagadex).

Deficiency of factor XIII characteristically leads to delayed bleeding that occurs hours to days after

a hemostatic challenge (such as surgery or trauma). The condition is usually life-long, and spontaneous intracranial hemorrhages as well as recurrent pregnancy loss appear to occur with increased frequency in these patients compared with other congenital deficiencies. Cryoprecipitate can be used to provide factor XIII, but if available, plasma-derived factor XIII concentrate (Corifact) is preferred to treat bleeding or for surgical prophylaxis. Regular prophylactic factor XIII replacement is indicated for patients with severe factor XIII deficiency. Factor XIII has an A and B subunit. Recombinant factor XIII A-subunit (Tretten) is an option for patients deficient in the factor XIII A subunit. Factor XIII deficiency does not cause a prolongation of the PT or aPTT.

Peyvandi F et al. Treatment of rare factor deficiencies in 2016. *Hematology Am Soc Hematol Educ Program.* 2016;2016:663. [PMID: 27913544]

ACQUIRED DISORDERS OF COAGULATION

1. Acquired Antibodies to Factor II

Patients with antiphospholipid antibodies occasionally have antibody specificity to coagulation factor II (prothrombin) that accelerates factor II clearances and can lead to severe hypoprothrombinemia and bleeding. Mixing studies may or may not reveal presence of an inhibitor, as the antibody typically binds a non-enzymatically active portion of the molecule leading to accelerated clearance, but characteristically the PT is prolonged and levels of factor II are low. FFP should be administered to treat bleeding. Treatment is immunosuppressive.

2. Acquired Antibodies to Factor V

Products containing bovine factor V (such as topical thrombin or fibrin glue, frequently used in surgical procedures) can lead to formation of an anti-factor V antibody that cross-reacts with human factor V. Clinicopathologic manifestations range from a prolonged PT in an otherwise asymptomatic individual to severe bleeding. Mixing studies suggest the presence of an inhibitor, and the factor V activity level is low. In cases of serious or life-threatening bleeding, IVIG or platelet transfusions, or both, should be administered, and immunosuppression (as for acquired inhibitors to factor VIII) may be offered.

3. Acquired Antibodies to Factor VIII

Acquired hemophilia A due to factor VIII inhibitors is the most common acquired factor-based bleeding disorder. Spontaneous antibodies to factor VIII (acquired hemophilia A) can occur in adults without a prior history of hemophilia; older adults and patients with lymphoproliferative malignancy or autoimmune disease and those who are postpartum or postsurgical are at highest risk. The clinical presentation, which should be viewed as a medical emergency, typically includes extensive soft tissue ecchymoses, hematomas, and mucosal bleeding, as opposed to hemarthrosis characteristic of congenital hemophilia A. The aPTT is typically prolonged and does not correct upon

mixing; factor VIII activity is low and a Bethesda assay reveals the titer of the inhibitor. Inhibitors of low titer (less than 5 BU) may often be overcome by infusion of high doses of factor VIII concentrates, whereas high-titer inhibitors (greater than 5 BU) must be treated with serial infusions of activated prothrombin complex concentrates, recombinant human activated factor VII, or recombinant porcine factor VIII. Along with establishment of hemostasis by one of these measures, immunosuppressive treatment with corticosteroids with or without oral cyclophosphamide or rituximab should be instituted. Treatment with IVIG and plasmapheresis can be considered in refractory cases. Unlike in congenital factor VIII deficiency, the patient's bleeding does not correlate well with the factor VIII activity level, so the clinician must be concerned with any elevation of aPTT secondary to acquired factor VIII inhibitor. All such patients require immediate referral to a hematologist.

Gibson CJ et al. Clinical problem-solving. A bruising loss. N Engl J Med. 2016;375:76. [PMID: 27406351]

4. Vitamin K Deficiency

Vitamin K deficiency may occur as a result of deficient dietary intake of vitamin K (from green leafy vegetables, soybeans, and other sources), malabsorption, or decreased production by intestinal bacteria (due to treatment with chemotherapy or antibiotics). Vitamin K is required for normal function of vitamin K epoxide reductase that assists in posttranslational gamma-carboxylation of the coagulation factors II, VII, IX, and X, which is necessary for their activity. Thus, mild to moderate vitamin K deficiency typically features a prolonged PT (activity of the vitamin K-dependent factors is more reflected than in the aPTT; aPTT is prolonged if the deficiency is more severe) that corrects upon mixing; activity levels of individual clotting factors II, VII, IX, and X typically are low. Importantly, a concomitantly low factor V activity level is not indicative of isolated vitamin K deficiency and may indicate an underlying defect in liver synthetic function. Hospitalized patients on broad-spectrum antibiotics and with poor or no oral intake are at high risk for vitamin K deficiency.

For treatment, vitamin K₁ (phytonadione) may be administered via intravenous or oral routes; the subcutaneous route is not recommended due to erratic absorption. The oral dose is 5–10 mg/day and absorption is typically excellent; at least partial improvement in the PT should be observed within 18–24 hours of administration. Intravenous administration results in faster normalization of a prolonged PT than oral administration; due to descriptions of anaphylaxis, parenteral doses should be administered at lower doses (1–5 mg/day) and slowly (eg, over 30 minutes) with concomitant monitoring. Overreplacement can make it difficult to resume warfarin when necessary.

5. Coagulopathy of Liver Disease

Impaired liver function due to cirrhosis or other causes leads to decreased synthesis of clotting factors, including factors II, V, VII, IX, X, and fibrinogen; whereas factor VIII

levels, largely made in endothelial cells, may be elevated despite depressed levels of other coagulation factors. The PT (and with advanced disease, the aPTT) is typically prolonged and usually corrects on mixing with normal plasma. A normal factor V level, in spite of decreases in the activity of factors II, VII, IX, and X, however, suggests vitamin K deficiency rather than liver disease. Qualitative and quantitative deficiencies of fibrinogen also are prevalent among patients with advanced liver disease, typically leading to a prolonged PT, thrombin time, and reptilase time.

The coagulopathy of liver disease usually does not require hemostatic treatment unless bleeding occurs. Infusion of FFP may be considered if active bleeding is present and the aPTT and PT are prolonged; however, the effect is transient and concern for volume overload may limit infusions. Patients with bleeding and a fibrinogen level consistently below 80–100 mg/dL should receive cryoprecipitate. Liver transplantation, if feasible, results in production of coagulation factors at normal levels. The use of recombinant human activated factor VII in patients with bleeding varices is controversial, although some patient subgroups may experience benefit. The coagulopathy of liver disease can predispose to bleeding or thrombosis, so caution and experience are needed for optimal management.

Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370:847. [PMID: 24571757]

Saner FH et al. Assessment and management of coagulopathy in critically-ill patients with liver failure. Curr Opin Crit Care. 2019;25:179. [PMID: 30855324]

Tripodi A et al. Changing concepts of cirrhotic coagulopathy. Am J Gastroenterol. 2017;112:274. [PMID: 27801884]

Tripodi A et al. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365:147. [PMID: 21751907]

6. Warfarin Ingestion

See Antithrombotic Therapy section, below.

7. Disseminated Intravascular Coagulation

See above.

8. Heparin/Fondaparinux/Direct-Acting Oral Anticoagulant Use

See Classes of Anticoagulants, below.

9. Lupus Anticoagulants

Lupus anticoagulants prolong the aPTT by interfering with interactions between the clotting cascade and the phospholipid surface on which they function, but they do not lead to bleeding. Rather, they predispose to thrombosis. Lupus anticoagulants were so named because of their early identification in patients with autoimmune disease, although they also occur with increased frequency in individuals with underlying infection, inflammation, or malignancy, and they also can occur in asymptomatic individuals in the general population. A prolongation in the aPTT is observed that does not correct completely on mixing but that normalizes with excessive phospholipid. Specialized testing such as a positive hexagonal phase phospholipid neutralization assay,

a prolonged dilute Russell viper venom time, and positive platelet neutralization assays can confirm the presence of a lupus anticoagulant. Rarely, the antibodies also interfere with factor II activity, and that tiny subset of lupus anticoagulant patients are at risk for bleeding.

OTHER CAUSES OF BLEEDING

Occasionally, abnormalities of the vasculature and integument may lead to bleeding despite normal hemostasis; congenital or acquired disorders may be causative. These abnormalities include Ehlers-Danlos syndrome, osteogenesis imperfecta, Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia) (see Chapter 40), and Marfan syndrome (heritable defects) and integumentary thinning due to prolonged corticosteroid administration or normal aging, amyloidosis, vasculitis, and scurvy (acquired defects). The bleeding time often is prolonged. If possible, treatment of the underlying condition should be pursued, but if this is not possible or feasible (ie, congenital syndromes), globally hemostatic agents such as DDAVP can be considered for treatment of bleeding.

ANTITHROMBOTIC THERAPY

The currently available anticoagulants include unfractionated heparin, LMWHs, fondaparinux, vitamin K antagonists (ie, warfarin), and direct-acting oral anticoagulants (DOACs) (ie, dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban). (For a discussion of the injectable DTIs, see section Heparin-Induced Thrombocytopenia above.)

► Classes of Anticoagulants

A. Unfractionated Heparin and LMWHs

Only about one-third of the molecules in a given preparation of unfractionated heparin contain the crucial pentasaccharide sequence necessary for binding of antithrombin and exerting its anticoagulant effect upon thrombin. The degree of anticoagulation with unfractionated heparin is typically monitored by aPTT or anti-Xa level in patients who are receiving the drug in therapeutic doses, although the pharmacokinetics of unfractionated heparin are poorly predictable. Only a fraction of an infused dose of heparin is metabolized by the kidneys, making it safe to use in most patients with significant kidney disease.

Due to less protein and cellular binding, the pharmacokinetics of the LMWHs are much more predictable than those of unfractionated heparin, allowing for fixed weight-based dosing. All LMWHs are principally renally cleared and must be avoided or used with extreme caution in individuals with creatinine clearance less than 30 mL/min. A longer half-life permits once- or twice-daily subcutaneous dosing, allowing for greater convenience and outpatient therapy in selected cases. Most patients do not require monitoring, although monitoring using the anti-Xa activity level is appropriate for patients with moderate kidney disease, those with elevated body mass index or low weight, and selected pregnant patients. LMWHs are associated with a lower frequency of heparin-induced thrombocytopenia and thrombosis (approximately 0.6%) than unfractionated heparin (3%).

B. Fondaparinux

Fondaparinux is a synthetic molecule consisting of the highly active pentasaccharide sequence found in LMWHs. As such, it exerts almost no thrombin inhibition and works to indirectly inhibit factor Xa through binding to anti-thrombin. Fondaparinux, like the LMWHs, is almost exclusively metabolized by the kidneys, and should be avoided in patients with creatinine clearance less than 30 mL/min. Predictable pharmacokinetics allow for weight-based dosing.

C. Vitamin K Antagonist (Warfarin)

The vitamin K antagonist warfarin inhibits the activity of the vitamin K-dependent carboxylase that is important for the posttranslational modification of coagulation factors II, VII, IX, and X. Although warfarin is taken orally, leading to a significant advantage over the heparins and heparin derivatives, interindividual differences in nutritional status, comorbid diseases, concomitant medications, and genetic polymorphisms lead to a poorly predictable anticoagulant response. Individuals taking warfarin must undergo periodic monitoring to verify the intensity of the anticoagulant effect, reported as the INR, which corrects for differences in potency of commercially available thromboplastin used to perform the PT.¹

D. Direct-Acting Oral Anticoagulants

Unlike warfarin, the DOACs (1) have a predictable dose effect and therefore do not require laboratory monitoring, (2) have anticoagulant activity independent of vitamin K with no need for dietary stasis, and (3) are renally metabolized to varying degrees so there are restrictions or dose reductions related to reduced kidney function (Table 14–10). While the DOACs have fewer drug interactions than warfarin, if DOACs are given with potentially interacting medications, there is no reliable way to measure the impact on anticoagulant activity of the concomitant administration. There is also no reliable way to measure adherence. Data remain limited on use of DOACs in morbidly obese patients (more than 120 kg or BMI greater than or equal to 40) in VTE treatment. The clinician must carefully consider kidney function, concomitant medications, indication for use, candidacy for lead-in parenteral therapy (as required for acute VTE treatment with edoxaban and dabigatran only) and anticipated patient adherence. Providers must be careful to dose each DOAC properly for the indication, kidney function, and weight of patient, and to check for drug interactions. (See Table 14–10 for details.) There is a reversal agent available for dabigatran and for the anti-Xa inhibitors apixaban and rivaroxaban (Table 14–11).

Routine monitoring is not recommended for patients taking DOACs. However, there are clinical scenarios where assessing anticoagulant activity may be helpful, including active bleeding, pending urgent

¹Importantly, because the INR is not standardized for abnormalities of factor V and fibrinogen, the INR should be used only in reference to anticoagulation in patients who are receiving warfarin.

Table 14–10. Direct-acting oral anticoagulants (DOACs) for VTE treatment and prevention.¹

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Approved uses for VTE	VTE treatment and secondary prevention VTE prophylaxis post-hip replacement	VTE treatment and secondary prevention VTE prophylaxis post-hip or knee replacement VTE prophylaxis in select adult patients hospitalized for acute medical illness	VTE treatment and secondary prevention VTE prophylaxis post-hip or knee replacement	VTE treatment and secondary prevention	Prophylaxis of VTE in select adults hospitalized for acute medical illness
Frequency of dosing for VTE	Twice daily	Twice daily for first 21 days of acute VTE therapy, then daily Once daily for DVT prophylaxis	Twice daily	Once daily	Once daily
Food	With or without food	With food (for 15- and 20-mg tablets)	With or without food	With or without food	With food
Crushable?	No	Can crush; do not administer via J tube	Can crush and administer orally or via NG tube	No data	
Renal clearance	80%	30–60%	25%	50%	15%
Kinetics	$t_{\frac{1}{2}} = 12\text{--}17\text{ hours}$; $t_{max} = 2\text{ hours}$	$t_{\frac{1}{2}} = 5\text{--}9\text{ hours}$; $t_{max} = 3\text{ hours}$	$t_{\frac{1}{2}} = 12\text{ hours}$; $t_{max} = 3\text{ hours}$	$t_{\frac{1}{2}} = 10\text{--}14\text{ hours}$; $t_{max} = 2\text{ hours}$	$t_{\frac{1}{2}} = 19\text{--}27\text{ hours}$; $t_{max} = 3\text{ hours}$
Impact on INR	↑ (or →)	↑↑ (or → at low concentrations)	↑ (or →)	↑	Unknown
Impact on aPTT	↑↑	↑	↑	↑	Unknown
Drug interactions (list not comprehensive)	Avoid rifampin, St John's wort, and possibly carbamazepine Caution with amiodarone, clarithromycin, dronedarone, ketoconazole, quinidine, verapamil No dose adjustment if CrCl > 50 mL/min Reduce dose to 75 mg orally twice daily if CrCl 30–50 mL/min and concurrent use of dronedarone or ketoconazole	Avoid carbamazepine, conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, phenytoin, rifampin, ritonavir, St John's wort Caution with the concurrent use of combined P-gp inhibitors and/or weak or moderate inhibitors of CYP3A4 (eg, amiodarone, azithromycin, diltiazem, dronedarone, erythromycin, felodipine, quinidine, ranolazine, verapamil) particularly in patients with impaired kidney function	Avoid carbamazepine, clarithromycin, phenytoin, rifampin, St John's wort, itraconazole, ketoconazole, and ritonavir in patients already taking apixaban even at a reduced dose of 2.5 mg twice daily Caution with clarithromycin, itraconazole, ketoconazole, and ritonavir	Avoid rifampin Reduce dose with certain P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin). Use has not been studied with many other P-gp inhibitors and inducers. Some experts recommend avoiding concurrent use altogether	Reduce dose to 40 mg orally daily with concurrent use of P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin)

Switching from DOAC to warfarin (per AC Forum Clinical Guidance: either approach [ie, stop DOAC then start LMWH and warfarin; or overlap warfarin with DOAC] can be used for all DOAC to warfarin transitions. If overlapping warfarin and DOAC, measure INR just before next DOAC dose and stop DOAC when INR ≥ 2.0)	Start warfarin and overlap with dabigatran; CrCl C50 mL/min, overlap 3 days CrCl 30–50 mL/min, overlap 2 days CrCl 15–30 mL/min, overlap 1 day	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0	For 60-mg dose, reduce dose to 30 mg and start warfarin concomitantly For 30-mg dose, reduce dose to 15 mg and start warfarin concomitantly Stop edoxaban when INR ≥ 2.0	No data available
Warfarin to DOAC	Start when INR < 2.0	Start when INR < 3.0	Start when INR < 2.0	Start when INR ≤ 2.5	Start when INR < 2.5
Special considerations	Dyspepsia is common and starts within first 10 days GI bleeding risk higher with dabigatran than with warfarin	GI bleeding risk higher with rivaroxaban than with warfarin		Do not use if CrCl < 15 mL/min	

¹Consult prescribing information for updated dosing. Dosing for atrial fibrillation is provided in Table 10–11.

APTT, activated partial thromboplastin time; CrCl, creatinine clearance; DOAC, direct-acting oral anticoagulant; GI, gastrointestinal; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NG, nasogastric; PCC, prothrombin complex concentrate; P-gp, P-glycoprotein; VTE, venous thromboembolism.

Table 14–11. Medications to consider for reversing anticoagulant effect during life-threatening bleeding.¹

Anticoagulants	Guidance
Parenteral	
Heparins	<p>Protamine provides total (for unfractionated heparin) or partial (for LMWHs) reversal of anticoagulant effect.</p> <ul style="list-style-type: none"> Administration: Very slow infusion Maximum dose: 50 mg intravenously Caution: risk of anaphylactoid reactions and true hypersensitivity reactions, especially if allergy to other protamine-containing medications (such as NPH insulin) or to fish (black box warning) Dosing depends on dose given and time elapsed Dosing calculator at https://clincalc.com/Protamine/
Unfractionated heparin	<p>Protamine (100% neutralization)</p> <ul style="list-style-type: none"> 1 mg protamine neutralizes approximately 100 units of heparin sulfate Monitor drug activity with aPTT and/or heparin anti-Xa activity
LMWH (enoxaparin, dalteparin)	<p>Protamine (approximately 60% neutralization)</p> <ul style="list-style-type: none"> Last dose < 8 hours ago: 1 mg protamine for each 100 units of dalteparin or 1 mg enoxaparin Last dose > 8 hours ago: 0.5 mg protamine for each 100 units of dalteparin or 1 mg enoxaparin Degree of reversal can be assessed with LMWH anti-Xa activity
Oral	
DOACs	<p>Guidance for all DOAC-associated major bleeding:</p> <ul style="list-style-type: none"> Supportive measures recommended for all patients If ingested within 2 hours, administer activated charcoal Reversal agent is recommended ONLY if bleeding is life-threatening or into a critical organ Reversal agent not recommended for DOAC overdose without bleeding
Dabigatran	<p>Idarucizumab 5 g intravenously once If idarucizumab is not available: administer APCC 50 units/kg intravenously</p>
Apixaban	<p>Andexanet alfa:</p> <ul style="list-style-type: none"> Last dose ≤ 5 mg AND within 8 hours: low dose² Last dose > 5 mg AND within 8 hours: high dose³ Last dose > 8 hours ago: low dose² <p>If andexanet alfa is not available: administer four-factor PCC 2000 units</p>
Rivaroxaban	<p>Andexanet alfa:</p> <ul style="list-style-type: none"> Last dose ≤ 10 mg AND within 8 hours: low dose² Last dose > 10 mg AND within 8 hours: high dose³ Last dose > 8 hours ago: low dose² <p>If andexanet alfa is not available: administer four-factor PCC 2000 units</p>
Warfarin	See Table 14–21

¹Guidance adopted from 2019 Anticoagulation Forum and American Society of Hematology 2019 guidelines.

²Low-dose andexanet alfa: initial 400 mg intravenous bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 min.

³High-dose andexanet alfa: initial 800 mg intravenous bolus at target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 min. Begin infusion within 2 minutes after intravenous bolus to prevent rebound anti-Xa activity.

APCC, three-factor prothrombin complex concentrate; DOACs, direct-acting oral anticoagulants; FFP, fresh frozen plasma; LMWH, low-molecular-weight heparin; PCC, four-factor prothrombin complex concentrate.

Data from Cuker A et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol. 2019;94(6):697–709; data from Witt DM et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2(22):3257–91.

surgery, suspected therapeutic failure, or concern for accumulation. Drug-specific anti-Xa levels are not widely available, and guidance is lacking regarding clinical approach to the results. DOACs have varying effects on the PT and aPTT. In the absence of drug-specific levels, a normal dilute thrombin time excludes the presence of clinically relevant dabigatran levels; an elevated aPTT suggests clinically relevant levels of dabigatran. An elevated PT suggests clinically relevant levels of rivaroxaban. However, a normal aPTT or normal PT does not rule out clinically significant amounts of dabigatran or rivaroxaban, respectively.

Douxfils J et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost. 2018;16:209. [PMID: 29193737]

► Prevention of Venous Thromboembolic Disease

The frequency of venous thromboembolic disease (VTE) among hospitalized patients ranges widely. Up to 60% of VTE cases occur during or after hospitalization, with especially high incidence among critical care patients and high-risk surgical patients.

Table 14–12. Risk stratification for DVT/VTE among surgical inpatients.

High risk ¹
Recent major orthopedic surgery/arthroplasty/fracture
Abdominal/pelvic cancer undergoing surgery
Spinal cord injury or major trauma within 90 days
More than three of the intermediate risk factors (see below)
Intermediate risk
Not ambulating independently outside of room at least twice daily
Active infectious or inflammatory process
Active malignancy
Major surgery (nonorthopedic)
History of VTE
Stroke
Central venous access or PICC line
Inflammatory bowel disease
Prior immobilization (> 72 hours) preoperatively
Obesity (BMI > 30)
Patient age > 50 years
Hormone replacement or oral contraceptive therapy
Hypercoagulable state
Nephrotic syndrome
Burns
Cellulitis
Varicose veins
Paresis
HF (systolic dysfunction)
COPD exacerbation
Low risk
Minor procedure and age < 40 years with no additional risk factors
Ambulatory with expected length of stay of < 24 hours or minor surgery

¹Risk is highest in first month and persists for up to 90 days. BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; HF, heart failure; PICC, peripherally inserted central catheter; VTE, venous thromboembolism.

Avoidance of fatal PE, which occurs in up to 5% of high-risk inpatients as a consequence of hospitalization or surgery, is a major goal of pharmacologic prophylaxis. Tables 14–12 and 14–13 provide risk stratification for DVT/VTE among hospitalized surgical and medical

Table 14–13. Padua Risk Assessment Model for VTE prophylaxis in hospitalized medical patients.

Condition	Points ¹
Active cancer, history of VTE, immobility, laboratory thrombophilia	3 points each
Recent (≤ 1 mo) trauma and/or surgery	2 points each
Age ≥ 70 , acute MI or CVA, acute infection, rheumatologic disorder, BMI ≥ 30 , hormonal therapy	1 point each

¹A score ≥ 4 connotes high risk of VTE in the noncritically ill medical patients and pharmacologic prophylaxis is indicated, absent absolute contraindications.

BMI, body mass index; CVA, cerebrovascular accident; MI, myocardial infarction; VTE, venous thromboembolism.

inpatients. Standard pharmacologic prophylactic regimens are listed in Table 14–14; prophylactic anticoagulation regimens differ in their recommended duration of use. Prophylactic strategies should be guided by individual risk stratification, with all moderate- and high-risk patients receiving pharmacologic prophylaxis, unless contraindicated. Contraindications to VTE prophylaxis for hospital inpatients at high risk for VTE are listed in Table 14–15. In patients at high risk for VTE with absolute contraindications to pharmacologic prophylaxis, mechanical devices such as intermittent pneumatic compression devices should be used, ideally in portable form with at least an 18-hour daily wear time.

It is recommended that VTE prophylaxis be used judiciously in hospitalized medical patients who are not critically ill since a comprehensive review of evidence suggested harm from bleeding in low-risk patients given low-dose heparin and skin necrosis in stroke patients given compression stockings. Risk assessment models like the Padua Risk Score (Table 14–13) and the IMPROVE risk score can help clinicians identify patients who may benefit from DVT prophylaxis. The IMPROVE investigators also developed a bleeding risk model that may aid in identifying acutely ill medical inpatients at increased risk for bleeding: https://www.outcomes.umassmed.org/IMPROVE/risk_score/index.html. While two of the anti-Xa oral anticoagulants (betrixaban and rivaroxaban) have been approved for extended duration prophylaxis after discharge for medically ill patients, how to identify those who will have clinical benefit from this practice is still unclear.

The Caprini score may help guide decisions in surgical patients about VTE prophylaxis (<https://www.mdcalc.com/caprini-score-venous-thromboembolism-2005>). In addition, certain high-risk surgical patients should be considered for extended-duration prophylaxis of up to 1 month, including those undergoing total hip replacement, hip fracture repair, and abdominal and pelvic cancer surgery. If bleeding is present, if the risk of bleeding is high, or if the risk of VTE is high for the inpatient (Table 14–12) and therefore combined prophylactic strategies are needed, some measure of thromboprophylaxis may be provided through mechanical devices such as intermittent pneumatic compression devices and graduated compression stockings.

A. Primary VTE Prevention in Patients with Active Cancer

Some ambulatory cancer patients undergoing chemotherapy who are at moderate to high risk of VTE (Khorana risk score ≥ 2) (<https://www.mdcalc.com/khorana-risk-score-venous-thromboembolism-cancer-patients>) may benefit from pharmacologic DVT prophylaxis, although bleeding risk is increased and caution should be taken, particularly in patients with gastrointestinal or intracranial malignancy, and other risk factors for anticoagulant-related bleeding (such as thrombocytopenia and kidney dysfunction). DOACs should be avoided when there are possible interactions with chemotherapeutic agents.

Table 14–14. Pharmacologic prophylaxis of VTE in selected clinical scenarios.¹

Anticoagulant	Dose	Frequency	Clinical Scenario	Comment
LMWH and Fondaparinux				
Enoxaparin	40 mg subcutaneously	Once daily	Most medical inpatients and critical care patients	—
			Surgical patients (moderate risk for VTE)	—
			Abdominal/pelvic cancer surgery	Consider continuing for 4 weeks total duration after abdominopelvic cancer surgery.
	30 mg subcutaneously	Twice daily	Bariatric surgery	Higher doses may be required.
			Orthopedic surgery ²	Give for at least 10 days. For THR, TKR, or HFS, consider continuing up to 1 month after surgery in high-risk patients.
			Major trauma	Not applicable to patients with isolated lower extremity trauma.
			Acute spinal cord injury	—
Dalteparin	2500 units subcutaneously	Once daily	Most medical inpatients	—
			Abdominal surgery (moderate risk for VTE)	Give for 5–10 days.
	5000 units subcutaneously	Once daily	Orthopedic surgery ²	First dose = 2500 units. Give for at least 10 days. For THR, TKR, or HFS, consider continuing up to 1 month after surgery in high-risk patients.
			Abdominal surgery (higher risk for VTE)	Give for 5–10 days. Consider continuing for 4 weeks total duration after abdominopelvic cancer surgery.
			Medical inpatients	—
Fondaparinux	2.5 mg subcutaneously	Once daily	Orthopedic surgery ²	Give for at least 10 days. For THR, TKR, or HFS, consider continuing up to 1 month after surgery in high-risk patients.
Direct-Acting Oral Anticoagulants				
Rivaroxaban	10 mg orally	Once daily	Orthopedic surgery: THR, TKR	Give for 12 days following TKR; give for 35 days following THR.
Apixaban	2.5 mg orally	Twice daily	Following THR or TKR	Give for 12 days following TKR; give for 35 days following THR.
Dabigatran	110 mg orally first day, then 220 mg	Once daily	Following THR	For patients with CrCl > 30 mL/min. Consider continuing up to 1 month after surgery in high-risk patients.
Betrixaban	160 mg orally first dose, then 80 mg with food Reduce dose for patients with severe renal impairment or taking P-gp inhibitors	Once daily	Medical inpatients with moderately to severely restricted mobility and other risk factors for VTE	Recommended duration of treatment is 35–42 days.
Unfractionated Heparin				
Unfractionated heparin	5000 units subcutaneously	Three times daily	Higher VTE risk with low bleeding risk	Includes gynecologic surgery for malignancy and urologic surgery, medical patients with multiple risk factors for VTE.
	5000 units subcutaneously	Twice daily	Hospitalized patients at intermediate risk for VTE	Includes gynecologic surgery (moderate risk).

(continued)

Table 14–14. Pharmacologic prophylaxis of VTE in selected clinical scenarios.¹ (continued)

Anticoagulant	Dose	Frequency	Clinical Scenario	Comment
			Patients with epidural catheters	LMWHs usually avoided due to risk of spinal hematoma.
			Patients with severe kidney disease ³	LMWHs contraindicated.
Warfarin and Aspirin				
Warfarin	(Variable) oral	Once daily	Orthopedic surgery ²	Titrate to goal INR = 2.5. Give for at least 10 days. For high-risk patients undergoing THR, TKR, or HFS, consider continuing up to 1 month after surgery.
Aspirin	81 mg orally	Twice daily	TKR, THR	For patients at otherwise low VTE risk following major orthopedic surgery. Give for at least 14 days.

¹All regimens administered subcutaneously, except for warfarin.

²Includes TKR, THR, and HFS.

³Defined as creatinine clearance < 30 mL/min.

CrCl, creatine clearance; HFS, hip fracture surgery; INR, international normalized ratio; LMWH, low-molecular-weight heparin; P-gp, P-glycoprotein; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolic disease.

B. Primary VTE Prevention, Diagnosis, and Treatment in Patients with Severe COVID-19

Patients with severe COVID-19 appear to have an increased incidence of thrombotic complications, including venous (DVT, PE) and arterial (stroke, limb occlusion) events. Risk is especially high in the critical care setting. Although

the reasons for this hypercoagulability are not yet well understood, the profound systemic inflammatory response associated with severe COVID-19 is thought to play a role. While the hypercoagulability in COVID-19 resembles DIC, laboratory and clinical findings are somewhat different. Laboratory findings in patients with severe COVID-19 may include markedly elevated D-dimer and modestly prolonged prothrombin time. However, patients with COVID-19 tend to have elevated fibrinogen levels; thrombocytopenia is rare and nonsevere; and bleeding complications are unusual. Thrombosis in patients with COVID-19 is associated with a poor prognosis and often occurs despite standard pharmacologic prophylaxis.

Table 14–15. Contraindications to VTE prophylaxis for medical or surgical hospital inpatients at high risk for VTE.

Absolute contraindications
Acute hemorrhage from wounds or drains or lesions
Intracranial hemorrhage within prior 24 hours
Heparin-induced thrombocytopenia (HIT): consider using fondaparinux
Severe trauma to head or spinal cord or extremities
Epidural anesthesia/spinal block within 12 hours of initiation of anticoagulation (concurrent use of an epidural catheter and anticoagulation other than low prophylactic doses of unfractionated heparin should require review and approval by service who performed the epidural or spinal procedure, eg, anesthesia/pain service, and in many cases, should be avoided entirely)
Currently receiving warfarin or heparin or LMWH or direct thrombin inhibitor for other indications
Relative contraindications
Coagulopathy (INR > 1.5)
Intracranial lesion or neoplasm
Severe thrombocytopenia (platelet count < 50,000/mcL [$50 \times 10^9/L$])
Intracranial hemorrhage within past 6 months
Gastrointestinal or genitourinary hemorrhage within past 6 months

INR, international normalized ratio; LMWH, low-molecular-weight heparin; VTE, venous thromboembolic disease.

Adapted from guidelines used at the Veterans Affairs Medical Center, San Francisco, CA.

1. Risk stratification and initial prognostication of patients with severe COVID-19—Given the prevalence and prognostic value of abnormal laboratory findings at presentation, patients with COVID-19 should have RP/INR, PTT, D-dimers, and fibrinogen measured. When results are abnormal, especially significantly elevated D-dimers or decreased fibrinogen, admission for monitoring should be considered even in patients who are otherwise clinically stable. Worsening laboratory parameters during hospitalization should prompt consideration of transfer to a higher level of care and heightened clinical suspicion for thrombosis.

2. VTE prophylaxis for patients with severe COVID-19—In the absence of strong contraindications, all patients hospitalized with COVID-19 should receive pharmacologic VTE prophylaxis. LMWH is preferred over unfractionated heparin to minimize staff exposure and the chance of heparin-induced thrombocytopenia.

For patients with a prior history of VTE who take an oral anticoagulant for secondary prevention at the time of admission, transition to LMWH should be considered due to its shorter half-life and potential anti-inflammatory properties.

For updated recommendations regarding pharmacologic dosing and post-discharge prophylaxis, refer to professional society guidance (links at end of this section) since guidance in this area is evolving rapidly.

3. Diagnosis and management of thromboembolic disease in patients with severe COVID-19—Logistical challenges complicate the diagnosis of thromboembolism in patients with COVID-19 due to patient instability and risks of staff exposures. D-dimers are generally elevated in hospitalized patients who have COVID-19. A substantial increase in D-dimers may suggest COVID-19-associated coagulopathy with or without thrombotic events. Clinicians should remain vigilant for signs and symptoms of thrombosis and consider obtaining surveillance laboratory testing at least every 3–4 days with low threshold for imaging. Ideally, thrombosis should be confirmed radiographically, but in situations where these studies cannot safely be obtained and clinical suspicion is very high, empiric treatment may be considered.

Guidance from the Anticoagulation Forum (<https://acforum.org/web/>), the International Society for Thrombosis and Haemostasis (<https://academy.isth.org/isth/#!menu=8&browseby=2&sortby=1&label=19794>), and the American Society for Hematology (<https://www.hematology.org/covid-19>) is evolving and should be frequently consulted.

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► Treatment of Venous Thromboembolic Disease

A. Anticoagulant Therapy

Treatment for VTE should be offered to patients with objectively confirmed DVT or PE, or to those in whom the clinical suspicion is high for the disorder but who have not yet undergone diagnostic testing (see Chapter 9). The management of VTE primarily involves administration of anti-coagulants; the goal is to prevent recurrence, extension and embolization of thrombosis and to reduce the risk of post-thrombotic syndrome. Suggested anticoagulation regimens are found in Table 14–16.

Table 14–16. Initial anticoagulation for VTE.¹

Anticoagulant	Dose/Frequency	Clinical Scenario					Comment
		DVT, Lower Extremity	DVT, Upper Extremity	PE	VTE, With Concomi- tant Severe Kidney Disease ²	VTE, Cancer- Related	
Unfractionated Heparin							
Unfractionated heparin	80 units/kg intravenous bolus, then continuous intravenous infusion of 18 units/kg/h	×	×	×	×		Bolus may be omitted if risk of bleeding is perceived to be elevated. Maximum bolus, 10,000 units. Requires aPTT or heparin anti-Xa monitoring. Most patients: begin warfarin at time of initiation of heparin.
	330 units/kg subcutaneously × 1, then 250 units/kg subcutaneously every 12 hours	×					

(continued)

Table 14–16. Initial anticoagulation for VTE.¹ (continued)

Anticoagulant	Dose/Frequency	Clinical Scenario					Comment
		DVT, Lower Extremity	DVT, Upper Extremity	PE	VTE, With Concomi- tant Severe Kidney Disease ²	VTE, Cancer- Related	
LMWH and Fondaparinux							
Enoxaparin ³	1 mg/kg subcutane- ously every 12 hours or 1.5 mg/kg subcutaneously daily	×	×	×			Most patients: begin warfarin at time of initiation of LMWH
Dalteparin ³	200 units/kg subcutaneously once daily for first month, then 150 units/kg/day	×	×	×		×	Preferred LMWH for cancer patients; administer for at least 3–6 months (no transition to warfarin)
Fondaparinux	5–10 mg subcutane- ously once daily; use 7.5 mg for body weight 50–100 kg; 10 mg for body weight > 100 kg	×	×	×			
Direct-Acting Oral Anticoagulants (DOACs)							
Rivaroxaban	15 mg orally twice daily with food for 21 days, then 20 mg orally daily with food	×	×	×		×	Contraindicated if CrCl < 30 mL/min Monotherapy without need for initial parenteral therapy Caution in luminal gastrointestinal or genitourinary cancer
Apixaban	10 mg orally twice daily for first 7 days, then 5 mg twice daily	×	×	×		×	Contraindicated if CrCl < 25 mL/min Monotherapy without need for initial parenteral therapy
Dabigatran	5–10 days of parenteral anticoagulation, then begin 150 mg orally twice daily	×	×	×			Contraindicated if CrCl < 15 mL/min Initial need for parenteral therapy
Edoxaban	5–10 days of parenteral anticoagulation, then 60 mg orally once daily; 30 mg once daily recommended if CrCl is between 15 and 50 mL/min, if weight ≤ 60 kg, or if certain P-gp inhibitors are present	×	×	×		×	Contraindicated if CrCl < 15 mL/min Initial need for parenteral therapy Caution in luminal gastrointestinal or genitourinary cancer

¹Obtain baseline hemoglobin, platelet count, aPTT, PT/INR, and creatinine prior to initiation of anticoagulation.

Anticoagulation is contraindicated in the setting of active bleeding.

²Defined as creatinine clearance < 30 mL/min.³If body weight < 50 kg, reduce dose and monitor anti-Xa levels.

CrCl, creatinine clearance; DVT, deep venous thrombosis; PE, pulmonary embolism; P-gp, P-glycoprotein; VTE, venous thromboembolic disease (includes DVT and PE).

Note: An “x” denotes appropriate use of the anticoagulant.

Table 14–17. Patient selection for outpatient treatment of DVT.

Patients considered appropriate for outpatient treatment	
No clinical signs or symptoms of PE and pain controlled	
Confirmed ability to pay for medication (either by insurance or out-of-pocket)	
Capable and willing to comply with frequent follow-up	
Initially, patients may need to be seen daily to weekly	
Potential contraindications for outpatient treatment	
DVT involving inferior vena cava, iliac, common femoral, or upper extremity vein (these patients might benefit from vascular intervention)	
Comorbid conditions requiring inpatient management	
Active peptic ulcer disease, GI bleeding in past 14 days, liver synthetic dysfunction	
Brain metastases, current or recent CNS or spinal cord injury/surgery in the last 10 days, CVA ≤ 4–6 weeks	
Familial bleeding diathesis	
Active bleeding from source other than GI	
Thrombocytopenia	
Creatinine clearance < 30 mL/min	
Weight < 55 kg (male) or < 45 kg (female)	
Recent surgery, spinal or epidural anesthesia in the past 3 days	
History of heparin-induced thrombocytopenia	
Inability to reliably take medication at home, recognize changes in health status, or understand or follow directions	

CNS, central nervous system; CVA, cerebrovascular accident; DVT, deep venous thrombosis; GI, gastrointestinal.

B. Selecting Appropriate Initial Anticoagulant Therapy

Most patients with DVT alone may be treated as outpatients, provided that their risk of bleeding is low and they have good follow-up. Table 14–17 outlines proposed selection criteria for outpatient treatment of DVT.

Among patients with PE, risk stratification at time of diagnosis should direct treatment and triage. Patients with persistent hemodynamic instability are classified as high-risk patients (previously referred to as having “massive PE”) and have an early PE-related mortality of more than 15%. These patients should be admitted to an intensive care unit and generally receive thrombolysis and anticoagulation with intravenous heparin. Intermediate-risk patients (previously, “submassive PE”) have a mortality rate of up to 15% and should be admitted to a higher level of inpatient care, with consideration of thrombolysis on a case-by-case basis. Catheter-directed techniques, if available, may be an option for patients who are poor candidates for systemic thrombolysis and/or in centers with expertise. Low-risk patients have a mortality rate less than 3% and are candidates for expedited discharge or outpatient therapy.

For hemodynamically stable patients, additional assessment focusing on right ventricular dysfunction is warranted to differentiate between low-risk, low-intermediate risk, and high-intermediate risk PE. The Bova score (<https://www.mdcalc.com/bova-score-pulmonary-embolism-complications>) and the simplified PE severity index accurately identify patients at low risk for 30-day PE-related mortality (Table 14–18) who are potential candidates for expedited

Table 14–18. Simplified Pulmonary Embolism Severity Index (PESI).

		Points		
		Age > 80 years old		
		1		
Cancer		1		
Chronic cardiopulmonary disease		1		
Systolic blood pressure < 100 mm Hg		1		
Oxygen saturation ≤ 90%		1		
		Severity Class	Points	30-Day Mortality
		Low risk	0	1%
		High risk	≥ 1	10%

Data from Jiménez D et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170:1383.

discharge or outpatient treatment. Because the Bova score includes serum troponin and evidence of right ventricular dysfunction (by CT or echocardiography), it also identifies patients with high-intermediate risk PE who warrant close monitoring and may require escalation of therapy. An RV/LV ratio less than 1.0 on chest CT angiogram has been shown to have good negative predictive value for adverse outcome but suffers from inter observer variability. Echocardiography may provide better assessment of right ventricular dysfunction when there is concern. Serum biomarkers such as B-type natriuretic peptide and troponin are most useful for their negative predictive value, and mainly in combination with other predictors.

Selection of an initial anticoagulant should be determined by patient characteristics (kidney function, immediate bleeding risk, weight) and the clinical scenario (eg, whether thrombolysis is being considered, active cancer, thrombosis location) as described in Table 14–16.

1. Parenteral anticoagulants—

HEPARINS—In patients in whom parenteral anticoagulation is being considered, LMWHs are more effective than unfractionated heparin in the immediate treatment of DVT and PE; they are preferred as initial treatment because of predictable pharmacokinetics, which allow for subcutaneous, once- or twice-daily dosing with no requirement for monitoring in most patients. Accumulation of LMWH and increased rates of bleeding have been observed among patients with severe kidney disease (creatinine clearance less than 30 mL/min), leading to a recommendation to use intravenous unfractionated heparin preferentially in these patients. *If concomitant thrombolysis is being considered, unfractionated heparin is indicated.* Patients with VTE and a perceived higher risk of bleeding (ie, post-surgery) may be better candidates for treatment with unfractionated heparin than LMWH given its shorter half-life and reversibility. Unfractionated heparin can be effectively neutralized with the positively charged protamine sulfate while protamine may only have partial reversal effect on LMWH. Use of unfractionated heparin leads to

heparin-induced thrombocytopenia and thrombosis in approximately 3% of patients, so daily complete blood counts are recommended during the initial 10–14 days of exposure.

Weight-based, fixed-dose daily subcutaneous fondaparinux (a synthetic factor Xa inhibitor) may also be used for the initial treatment of DVT and PE, with no increase in bleeding over that observed with LMWH. Its lack of reversibility, long half-life, and renal clearance limit its use in patients with an increased risk of bleeding or kidney disease.

2. Oral anticoagulants—

A. DIRECT-ACTING ORAL ANTICOAGULANTS—DOACs have a predictable dose effect, few drug-drug interactions, rapid onset of action, and freedom from laboratory monitoring (Table 14–10). Dabigatran, rivaroxaban, apixaban, and edoxaban are approved for treatment of acute DVT and PE. While rivaroxaban and apixaban can be used as monotherapy eliminating the need for parenteral therapy, patients treated with dabigatran or edoxaban must first receive 5–10 days of parenteral anticoagulation and then be transitioned to the oral agent per prescribing information. Unlike warfarin, DOACs do not require an overlap since these agents are immediately active; the DOAC is started when the parenteral agent is stopped. Compared to warfarin and LMWH, the DOACs are all noninferior with respect to prevention of recurrent VTE; both rivaroxaban and apixaban have a lower bleeding risk than warfarin with LMWH bridge. While DOACs are recommended as first-line therapy for acute VTE according to the CHEST 2016 VTE guidelines, agent selection should be individualized with consideration of kidney function, concomitant medication use, indication, ability to use LMWH bridge therapy, cost, and adherence.

B. WARFARIN—If warfarin is chosen as the oral anticoagulant it will be initiated along with the parenteral anticoagulant, which is continued until INR is in therapeutic range. Most patients require 5 mg of warfarin daily for initial treatment, but lower doses (2.5 mg daily) should be considered for patients of Asian descent, older adults, and those with hyperthyroidism, heart failure, liver disease, recent major surgery, malnutrition, certain polymorphisms for the CYP2C9 or the VKORC1 genes or who are receiving concurrent medications that increase sensitivity to warfarin. Conversely, individuals of African descent, those with larger body mass index or hypothyroidism, and those who are receiving medications that increase warfarin metabolism (eg, rifampin) may require higher initial doses (7.5 mg daily). Daily INR results should guide dosing adjustments in the hospitalized patient while at least biweekly INR results guide dosing in the outpatient during the initial period of therapy (Table 14–19). Web-based warfarin dosing calculators incorporating clinical and genetic factors are available to help clinicians choose appropriate starting doses (eg, see www.warfarindosing.org). Because an average of 5 days is required to achieve a steady-state reduction in the activity of vitamin K-dependent coagulation factors, the parenteral anticoagulant should be continued for at least 5 days and until the INR is more than 2.0. Meticulous follow-up should be

arranged for all patients taking warfarin because of the bleeding risk associated with initiation of therapy. Once stabilized, the INR should be checked at an interval no longer than every 6 weeks and warfarin dosing should be adjusted by guidelines (Table 14–20) since this strategy has been shown to improve the time patients spend in the therapeutic range and their clinical outcomes. Supratherapeutic INRs should be managed according to evidence-based guidelines (Table 14–21).

C. Duration of Anticoagulation Therapy

Recurrence rates of VTE after discontinuation of therapy—The clinical scenario in which the thrombosis occurred is the strongest predictor of recurrence and, in most cases, guides duration of anticoagulation (Table 14–22). In the first year after discontinuation of anticoagulation therapy, the frequency of recurrent VTE among individuals whose thrombosis occurred in the setting of a transient, major, reversible risk factor (such as surgery) is approximately 3% after completing 3 months of anticoagulation, compared with at least 8% for individuals whose thrombosis was unprovoked, and greater than 20% in patients with cancer. Men have a greater than twofold higher risk of recurrent VTE compared to women; recurrent PE is more likely to develop in patients with clinically apparent PE than in those with DVT alone and has a case fatality rate of nearly 10%; and proximal DVT has a higher recurrence risk than distal DVT.

1. Provoked versus unprovoked VTE—Patients with provoked VTE are generally treated with a minimum of 3 months of anticoagulation, whereas unprovoked VTE should prompt consideration of indefinite anticoagulation provided the patient is not at high risk for bleeding. Merely extending duration of anticoagulation beyond 3 months for unprovoked PE will not reduce risk of recurrence once anticoagulation is stopped; if anticoagulants are stopped after 3, 6, 12, or 18 months in such a patient, the risk of recurrence after cessation of therapy is similar. Individual risk stratification may help identify patients most likely to suffer recurrent disease and thus most likely to benefit from ongoing anticoagulation therapy. Normal D-dimer levels 1 month after cessation of anticoagulation are associated with lower recurrence risk, although some would argue not low enough to consider stopping anticoagulant therapy, particularly in men.

2. Risk scoring systems to guide therapy duration—The HERDOO2 risk scoring system uses body mass index, age, D-dimer, and post-phlebitic symptoms to identify women at lower risk for recurrence after unprovoked VTE (<https://www.mdcalc.com/herdoo2-rule-discontinuing-anticoagulation-unprovoked-vte>). The Vienna Prediction Model, a simple scoring system based on age, sex, D-dimer, and location of thrombosis, can help estimate an individual's recurrence risk to guide duration of therapy decisions.

3. Cancer-related VTE—LMWH has been the mainstay of treatment for cancer-related VTE based on lower VTE recurrence in cancer patients treated with dalteparin compared with warfarin. Studies have also shown that DOACs (edoxaban, rivaroxaban, and apixaban) are at

Table 14–19. Warfarin dosing adjustment guidelines for initiation of warfarin therapy.

Measurement Day	INR	Action
For Hospitalized Patients Newly Starting Therapy		
Day 1		5 mg (2.5 or 7.5 mg in select populations ¹)
Day 2	< 1.5	Continue dose
	≥ 1.5	Decrease or hold dose ²
Day 3	≤ 1.2	Increase dose ²
	> 1.2 and < 1.7	Continue dose
	≥ 1.7	Decrease dose ²
Day 4 until therapeutic	Daily increase < 0.2 units	Increase dose ²
	Daily increase 0.2–0.3 units	Continue dose
	Daily increase 0.4–0.6 units	Decrease dose ²
	Daily increase ≥ 0.7 units	Hold dose
For Outpatients Newly Starting Therapy		
Measure PT/INR on Day 1	Baseline	Start treatment with 2–7.5 mg
Measure PT/INR on Day 3–4	< 1.5	Increase weekly dose by 5–25%
	1.5–1.9	No dosage change
	2.0–2.5	Decrease weekly dose by 25–50%
	> 2.5	Decrease weekly dose by 50% or HOLD dose
Measure PT/INR on Day 5–7	< 1.5	Increase weekly dose by 10–25%
	1.5–1.9	Increase weekly dose by 0–20%
	2.0–3.0	No dosage change
	> 3.0	Decrease weekly dose by 10–25% or HOLD dose
Measure PT/INR on Day 8–10	< 1.5	Increase weekly dose by 15–35%
	1.5–1.9	Increase weekly dose by 5–20%
	2.0–3.0	No dosage change
	> 3.0	Decrease weekly dose by 10–25% or HOLD dose
Measure PT/INR on Day 11–14	< 1.6	Increase weekly dose by 15–35%
	1.6–1.9	Increase weekly dose by 5–20%
	2.0–3.0	No dosage change
	> 3.0	Decrease weekly dose by 5–20% or HOLD dose

¹See text.²In general, dosage adjustments should not exceed 2.5 mg or 50%.

Data from Kim YK et al. J Thromb Haemost. 2010;8:101. From Center for Health Quality, Outcomes, and Economic Research, VA Medical Center, Bedford, MA.

least as effective as LMWH for VTE treatment. The use of edoxaban and rivaroxaban is at the expense of increased bleeding, particularly for patients with gastrointestinal cancer. The International Society for Thrombosis and Haemostasis suggests use of specific DOACs for cancer patients with a diagnosis of acute VTE, no drug-drug interactions, and a low risk of bleeding but suggests use of LMWH for those with a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary tumor, and those at risk for bleeding from the genitourinary or gastrointestinal tract. For patients with intracranial malignancy and VTE, bleeding risk depends on tumor type (primary versus

metastatic) and other characteristics; whenever possible, interdisciplinary consultation is recommended to help determine risk of initiating anticoagulation. DOACs do not appear to confer higher bleeding risk compared to LMWH in patients with brain tumors. Clinicians must be aware that chemotherapeutic agents may interact with DOACs and their use should be avoided in cases of potential interactions because there is no easily accessible and reliable way to measure the anticoagulant effect of DOACs.

4. Thrombophilia workup in determining duration—

Laboratory workup for thrombophilia is not recommended routinely for determining duration of therapy because

Table 14–20. Warfarin-dosing adjustment guidelines for patients receiving long-term therapy, with target INR 2–3.

Patient INR	Weekly Dosing Change	
	Dose Change	Follow-Up INR
≤ 1.5	Increase by 10–15%	Within 1 week
1.51–1.79	If falling or low on two or more occasions, increase weekly dose by 5–10%.	7–14 days
1.80–2.29	Consider not changing the dose unless a consistent pattern has been observed.	7–14 days
2.3–3.0 (in range)	No change in dosage.	28 days (42 days if INR in range three times consecutively)
3.01–3.20	Consider not changing the dose unless a consistent pattern has been observed.	7–14 days
3.21–3.69	Do not hold warfarin. If rising or high on two or more occasions, decrease weekly dose by 5–10%.	7–14 days
3.70–4.99	Hold warfarin for 1 day and decrease weekly dose by 5–10%.	Within 1 week, sooner if clinically indicated
5.0–8.99	Hold warfarin. Clinical evaluation for bleeding. When INR is therapeutic, restart at lower dose (decrease weekly dose by 10–15%). Check INR at least weekly until stable.	Within 1 week, sooner if clinically indicated, then weekly until stabilized
≥ 9	See Table 14–21	

From Center for Health Quality, Outcomes, and Economic Research, VA Medical Center, Bedford, MA. Data from Kim YK et al. J Thromb Haemost. 2010;8:101. See also Van Spall HE et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation. 2012;126:2309.

clinical presentation is a much stronger predictor of recurrence risk. The workup may be pursued in patients younger than 50 years, with a strong family history, with a clot in unusual locations, or with recurrent thromboses (Table 14–23). In addition, a workup for thrombophilia may be considered in women of childbearing age in whom results may influence fertility and pregnancy outcomes and management or in those patients in whom results will influence duration of therapy. An important hypercoagulable state to identify is antiphospholipid syndrome because

these patients have a marked increase in recurrence rates, are at risk for both arterial and venous disease, in general receive bridge therapy during any interruption of anticoagulation, and should not receive DOACs as first-line antithrombotic therapy due to increased arterial events compared to warfarin. Due to effects of anticoagulants and acute thrombosis on many of the tests, the thrombophilia workup should be delayed in most cases until at least 3 months after the acute event, if indicated at all (Table 14–24). The benefit of anticoagulation must be weighed against the bleeding risks posed, and the benefit-risk ratio should be assessed at the initiation of therapy, at 3 months, and then at least annually in any patient receiving prolonged anticoagulant therapy. Bleeding risk scores, such as the Riete score (<https://www.mdcalc.com/riete-score-risk-hemorrhage-pulmonary-embolism-treatment>) have been developed to estimate risk of these complications. Their performance, however, may not offer any advantage over a clinician's subjective assessment, particularly in older individuals. Consideration of bleeding risk is of particular importance when identifying candidates for extended duration therapy for treatment of unprovoked VTE; it is recommended that patients with a high risk of bleeding receive a defined course of anticoagulation, rather than indefinite therapy, even if the VTE was unprovoked.

D. Secondary Prevention

Antithrombotic therapy offered after the initial 3–6 months of treatment should be considered in patients with VTE that is not majorly provoked; it is most compelling for those with unprovoked VTE. For most patients who continue to take a DOAC to prevent recurrence, the dose can be reduced to prophylactic intensity after the initial 6–12 months of therapy. In patients deemed poor candidates for ongoing DOAC or warfarin use but who warrant some secondary prevention, low-dose (81–100 mg) aspirin may be used; however, this will provide far less reduction in risk of recurrent VTE with similar bleeding risk.

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Li A et al. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. Thromb Res. 2019;173:158. [PMID: 29506866]

Table 14–21. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for the Management of Supratherapeutic INR.

Clinical Situation	INR	Recommendations
No significant bleed	Above therapeutic range but < 5.0	<ul style="list-style-type: none"> Lower dose or omit dose Monitor more frequently and resume at lower dose when INR falls within therapeutic range (if INR only slightly above range, may not be necessary to decrease dose) Hold next 1–2 doses
	≥ 5.0 but < 9.0	<ul style="list-style-type: none"> Monitor more frequently and resume therapy at lower dose when INR falls within therapeutic range <i>Patients at high risk for bleeding</i>¹: Hold warfarin and consider giving vitamin K₁ 1–2.5 mg orally; check INR in 24–48 h to ensure response to therapy Hold warfarin
		<ul style="list-style-type: none"> Vitamin K₁, 2.5–5 mg orally Monitor frequently and resume therapy at lower dose when INR within therapeutic range
Serious/life-threatening bleed		<ul style="list-style-type: none"> Hold warfarin and give 10 mg vitamin K by slow intravenous infusion supplemented by FFP, PCC, or recombinant factor VIIa (PCC preferred)

¹Patients at higher risk for bleeding include elderly people, and conditions that increase the risk of bleeding include kidney disease, hypertension, falls, liver disease, and history of gastrointestinal or genitourinary bleeding.

FFP, fresh frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrate.

Witt DM et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv.* 2018;2:3257. [PMID: 30482765]

E. Thrombolytic Therapy

Anticoagulation alone is appropriate treatment for most patients with PE; however, those with high-risk, massive PE, defined as PE with persistent hemodynamic instability,

have an in-hospital mortality rate that approaches 30% and, absent contraindications (Table 14–25), require immediate thrombolysis in combination with anticoagulation (Table 14–26). Systemic thrombolytic therapy has been used in carefully selected patients with intermediate-risk, submassive PE, defined as PE without hemodynamic instability but with evidence of right ventricular compromise and myocardial injury. Thrombolysis in this cohort decreases risk of hemodynamic compromise but increases the risk of major hemorrhage and stroke. A lower dose of

Table 14–22. Duration of treatment of VTE.

Scenario	Suggested Duration of Therapy	Comments
Provoked by major transient risk factor (eg, major surgery, major trauma, major hospitalization)	3 months	VTE prophylaxis upon future exposure to transient risk factors
Unprovoked	At least 3 months; consider indefinite if bleeding risk allows	May individually risk-stratify for recurrence with D-dimer, clinical risk scores, and clinical presentation Consider transition to DOAC secondary prevention dose after initial treatment period
Recurrent unprovoked	Indefinite	If recurrent despite therapeutic anticoagulation, consider hematology consultation for further evaluation and guidance
Cancer-related	≥ 3–6 months or as long as cancer is active, whichever is longer	LMWH or carefully selected DOAC recommended for initial treatment (see Table 14–16)
Underlying significant thrombophilia (eg, antiphospholipid antibody syndrome, antithrombin deficiency, protein C deficiency, protein S deficiency, ≥ two comitant thrombophilic conditions)	Indefinite	To avoid false positives, consider delaying investigation for laboratory thrombophilia until 3 months after event

DOAC, direct-acting anticoagulant; LMWH, low-molecular-weight heparin; VTE, venous thromboembolic disease.

Table 14–23. Candidates for thrombophilia workup if results will influence management.

Patients < 50 years of age
Strong family history of VTE
Clot in unusual locations
Recurrent thromboses
Women of childbearing age
Suspicion for APS (avoid DOACs if APS is strongly suspected or confirmed)

APS, antiphospholipid syndrome; DOACs, direct-acting anticoagulants; VTE, venous thromboembolism.

tPA commonly used for PE treatment has been evaluated in small trials but additional data are needed to recommend its use. Catheter-directed therapy for acute PE may be considered for high-risk or intermediate-risk PE when systemic thrombolysis has failed or as an alternative to systemic thrombolytic therapy.

In patients with large proximal iliofemoral DVT, data from randomized controlled trials are conflicting on the benefit of catheter-directed thrombolysis in addition to treatment with anticoagulation; the CaVenT trial showed some reduction in risk of postthrombotic syndrome, but the larger ATTRACT trial failed to show reduction in postthrombotic syndrome but did find an increased risk of major bleeding.

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Vedantham S et al; ATTRACT Trial Investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med.* 2017;377:2240. [PMID: 29211671]

F. Nonpharmacologic Therapy

1. Graduated compression stockings—Graduated compression stockings may provide symptomatic relief to selected patients with ongoing swelling but do not reduce risk of postthrombotic syndrome at 6 months. They are contraindicated in patients with peripheral vascular disease.

2. Inferior vena caval (IVC) filters—There is a paucity of data to support the use of IVC filters for the prevention of PE in any clinical scenario. There are two randomized, controlled trials of IVC filters for prevention of PE. In the first study, patients with documented DVT received full-intensity, time-limited anticoagulation with or without

Table 14–24. Laboratory evaluation of thrombophilia.

Hypercoagulable State	When to Suspect	Laboratory Workup	Influence of Anticoagulation and Acute Thrombosis
Antiphospholipid antibody syndrome	Unexplained DVT/PE CVA/TIA before age 50 years Recurrent thrombosis (despite anticoagulation) Thrombosis at an unusual site Arterial and venous thrombosis Livedo reticularis, Raynaud phenomenon, thrombocytopenia, recurrent early pregnancy loss	Anti-cardiolipin IgG and/or IgM medium or high titer (ie, > 40 GPL or MPL, or > the 99th percentile) ¹ Anti-beta-2 glycoprotein I IgG and/or IgM medium or high titer (> the 99th percentile) ¹ Lupus anticoagulant ¹	Lupus anticoagulant can be falsely positive or falsely negative on anticoagulation
Protein C, S, antithrombin deficiencies	Thrombosis < 50 years of age with family history of VTE	Screen with protein C activity, free protein S, antithrombin activity ² ; if free protein S is normal, check protein S activity	Acute thrombosis can result in decreased protein C, S and antithrombin activity. Warfarin can decrease protein C and S activity; heparin can decrease antithrombin activity. DOACs can increase protein C, S, and antithrombin activity
Factor V Leiden, prothrombin gene mutation	Thrombosis on OCPs, cerebral vein thrombosis, DVT/PE in White population	PCR for factor V Leiden or prothrombin gene mutation	No influence
Hyperhomocysteinemia		Fasting homocysteine	No influence

¹Detected on two occasions not < 12 weeks apart.

²Nephrotic syndrome and liver disease can reduce protein C, protein S, and antithrombin; pregnancy causes decreased free protein S. CVA/TIA, cerebrovascular accident/transient ischemic attack; DOACs, direct-acting oral anticoagulants; DVT/PE, deep venous thrombosis/pulmonary embolism; OCPs, oral contraceptives; PCR, polymerase chain reaction; VTE, venous thromboembolism.

Table 14–25. Contraindications to thrombolytic therapy for pulmonary embolism.**Absolute contraindication**

History of hemorrhagic stroke or stroke of unknown origin
Ischemic stroke in previous 6 months
Central nervous system neoplasm
Major trauma, surgery, or head injury in previous 3 weeks
Bleeding diathesis
Active bleeding

Relative contraindication

Transient ischemic attack in previous 6 months
Oral anticoagulation
Pregnancy or first postpartum week
Noncompressible puncture sites
Traumatic resuscitation
Refractory hypertension (systolic blood pressure > 180 mm Hg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer

Source: Modified, with permission, from Konstantinides SV et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543. © The European Society of Cardiology 2019.

placement of a permanent IVC filter. Patients with IVC filters had a lower rate of nonfatal asymptomatic PE at 12 days but an increased rate of DVT at 2 years. In the second study, patients with symptomatic PE and residual proximal DVT plus at least one additional risk factor for severity received full intensity anticoagulation with or without a retrievable IVC filter. IVC filter use did not reduce the risk of symptomatic recurrent PE at 3 months. Most experts agree with placement of an IVC filter in patients with acute proximal DVT and an absolute contraindication to anticoagulation despite lack of evidence to support this practice. While IVC filters were once commonly used to prevent VTE recurrence in the setting of

anticoagulation failure, many experts now recommend switching to an alternative agent or increasing the intensity of the current anticoagulant regimen instead. The remainder of the indications (submassive/intermediate-risk PE, free-floating iliofemoral DVT, perioperative risk reduction) are controversial. If the contraindication to anticoagulation is temporary (active bleeding with subsequent resolution), placement of a retrievable IVC filter may be considered so that the device can be removed once anticoagulation has been started and has been shown to be tolerated. Rates of IVC filter retrieval are very low, often due to failure to arrange for its removal. Thus, if a device is placed, removal should be arranged at the time of device placement.

Complications of IVC filters include local thrombosis, tilting, migration, fracture, and inability to retrieve the device. When considering placement of an IVC filter, it is best to consider both short- and long-term complications, since devices intended for removal may become permanent. To improve patient safety, institutions should develop systems that guide appropriate patient selection for IVC filter placement, tracking, and removal.

► When to Refer

- Presence of large iliofemoral VTE, unprovoked upper extremity DVT, IVC thrombosis, portal vein thrombosis, or Budd-Chiari syndrome for consideration of catheter-directed thrombolysis.
- High-risk PE for urgent embolectomy or catheter-directed therapies.
- Intermediate-risk PE if considering thrombolysis.
- History of HIT or prolonged PTT plus renal failure for alternative anticoagulation regimens.
- Consideration of IVC filter placement.
- Clots in unusual locations (eg, renal, hepatic, or cerebral vein), or simultaneous arterial and venous thrombosis, to assess possibility of a hypercoagulable state.
- Recurrent VTE while receiving therapeutic anticoagulation.

Table 14–26. Thrombolytic therapies for high risk (massive) pulmonary embolism.

Thrombolytic Agent	Dose	Frequency	Comment
Alteplase (r-TPA) (preferred)	100 mg	Continuous intravenous infusion over 2 hours	Follow with continuous intravenous infusion of unfractionated heparin (see Table 14–16 for dosage)
Urokinase	4400 international units/kg	Intravenous bolus × 1 followed by 4400 international units/kg continuous intravenous infusion for 12 hours	
Streptokinase	250,000 international units	250,000 international units intravenously loading dose over 30 min, followed by 100,000 international units/h over 12–24 h	

Source: Modified, with permission, from Konstantinides SV et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543. © The European Society of Cardiology 2019.

► When to Admit

- Documented or suspected intermediate- or high-risk PE, low-risk PE at high risk for bleeding, poor candidate for outpatient treatment.
- DVT with poorly controlled pain, high bleeding risk, or concerns about follow-up.
- Large iliofemoral DVT for consideration of thrombolysis.
- Acute DVT and absolute contraindication to anticoagulation for IVC filter placement.
- Venous thrombosis despite therapeutic anticoagulation.

- Suspected Paget-Schroetter syndrome (spontaneous upper extremity thrombosis related to thoracic outlet syndrome).

Bikdeli B et al. Systematic review of efficacy and safety of retrievable inferior vena caval filters. *Thromb Res.* 2018;165:79. [PMID: 29579576]

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15

Gastrointestinal Disorders

Kenneth R. McQuaid, MD

SYMPOTMS & SIGNS OF GASTROINTESTINAL DISEASE

DYSPEPSIA



ESSENTIALS OF DIAGNOSIS

- ▶ Predominant epigastric pain.
- ▶ May be associated with epigastric fullness, nausea, heartburn, or vomiting.
- ▶ Endoscopy is warranted in all patients age 60 years or older and selected younger patients with alarm features.
- ▶ In all other patients, testing for *Helicobacter pylori* is recommended; if positive, antibacterial treatment is given.
- ▶ Patients who are *H pylori* negative or do not improve after *H pylori* eradication should be prescribed a trial of empiric proton pump inhibitor therapy.
- ▶ Patients with refractory symptoms should be offered a trial of tricyclic antidepressant, prokinetic agent, or psychological therapy.

Etiology

A. Food or Drug Intolerance

Acute, self-limited “indigestion” may be caused by overeating, eating too quickly, eating high-fat foods, eating during stressful situations, or drinking too much alcohol or coffee. Prescription and nonprescription medications should be carefully reviewed since many may cause dyspepsia.

B. Functional Dyspepsia

Functional dyspepsia refers to dyspepsia for which no organic etiology has been determined by endoscopy or other testing. This is the most common cause of *chronic* dyspepsia, accounting for the majority of patients. Symptoms may arise from a complex interaction of increased visceral afferent sensitivity, gastric delayed emptying or impaired accommodation to food or psychosocial stressors or may develop de novo following an enteric infection. Although benign, these symptoms may be chronic and difficult to treat.

C. Luminal Gastrointestinal Tract Dysfunction

Peptic ulcer disease is present in 5–15% of patients with dyspepsia. Gastroesophageal reflux disease (GERD) is present in up to 20% of patients with dyspepsia, even without significant heartburn. Gastric or esophageal cancer is identified in less than 1% but is extremely rare in persons under age 60 years with uncomplicated dyspepsia. Other causes include gastroparesis (especially in diabetes mellitus) and parasitic infection (*Giardia*, *Strongyloides*, *Anisakis*).

D. *Helicobacter pylori* Infection

Chronic gastric infection with *H pylori* is an important cause of peptic ulcer disease and may cause dyspepsia in a small number of patients in the absence of peptic ulcer disease.

E. Pancreatic Disease

Pancreatic carcinoma and chronic pancreatitis may cause chronic epigastric pain that is more severe, sometimes

General Considerations

Dyspepsia refers to acute, chronic, or recurrent pain or discomfort centered in the upper abdomen. Predominant epigastric pain that is present for at least 1 month is clinically relevant. The epigastric pain may be associated with other symptoms of heartburn, nausea, fullness, or vomiting. Heartburn (retrosternal burning) should be distinguished from dyspepsia. When heartburn is the dominant complaint, gastroesophageal reflux is nearly always present. Dyspepsia occurs in 10–20% of the adult population and accounts for 3% of general medical office visits.

radiates to the back, and usually is associated with anorexia, rapid weight loss, steatorrhea, or jaundice.

F. Biliary Tract Disease

The abrupt onset of epigastric or right upper quadrant pain due to cholelithiasis or choledocholithiasis should be readily distinguished from dyspepsia.

G. Other Conditions

Diabetes mellitus, thyroid disease, chronic kidney disease, myocardial ischemia, intra-abdominal malignancy, gastric volvulus or paraesophageal hernia, chronic gastric or intestinal ischemia, and pregnancy are sometimes accompanied by acute or chronic epigastric pain or discomfort.

► Clinical Findings

A. Symptoms and Signs

Given the nonspecific nature of dyspeptic symptoms, the history has limited diagnostic utility. It should clarify the chronicity, location, and quality of the epigastric pain, and its relationship to meals. The pain may be accompanied by one or more upper abdominal symptoms including post-prandial fullness, heartburn, nausea, or vomiting. Concomitant weight loss, persistent vomiting, constant or severe pain, progressive dysphagia, hematemesis, or melena warrants endoscopy or abdominal CT imaging. Potentially offending medications and excessive alcohol use should be identified and discontinued if possible. The patient's reason for seeking care should be determined. Recent changes in employment, marital discord, physical and sexual abuse, anxiety, depression, and fear of serious disease may all contribute to the development and reporting of symptoms. Patients with functional dyspepsia often are younger, report a variety of abdominal and extragastrointestinal complaints, show signs of anxiety or depression, or have a history of use of psychotropic medications.

The symptom profile alone does not differentiate between functional dyspepsia and organic gastrointestinal disorders. Based on the clinical history alone, primary care clinicians misdiagnose nearly half of patients with peptic ulcers or gastroesophageal reflux.

The physical examination is rarely helpful. Signs of serious organic disease such as weight loss, organomegaly, abdominal mass, or fecal occult blood are to be further evaluated.

B. Laboratory Findings

In patients younger than age 60 with uncomplicated dyspepsia (in whom gastric cancer is rare), initial noninvasive strategies should be pursued. In patients older than age 60 years, initial laboratory work should include a complete blood count, serum electrolytes, liver enzymes, calcium, and thyroid function tests. The cost-effectiveness of routine laboratory studies is uncertain. In most patients younger than age 60, a noninvasive test for *H pylori* (urea breath test, fecal antigen test) should be performed first. Although serologic tests are inexpensive, performance characteristics are poor in low-prevalence populations, whereas breath and fecal antigen

tests have 95% accuracy. If *H pylori* breath test or fecal antigen test results are negative in a patient not taking nonsteroidal anti-inflammatory drugs (NSAIDs), peptic ulcer disease is virtually excluded.

C. Upper Endoscopy

Upper endoscopy is mainly indicated to look for upper gastric or esophageal malignancy in patients over age 60 years with new-onset dyspepsia (in whom there is increased malignancy risk) and in selected younger patients with "alarm" features. In patients under age 60, the risk of malignancy is less than 1%—even among patients with reported "alarm" features. Recent guidelines therefore recommend against routine endoscopy for younger patients—even those with "alarm" features. However, endoscopy should be performed in patients with prominent "alarm" features, such as progressive weight loss, rapidly progressive dysphagia, severe vomiting, evidence of bleeding or anemia, or jaundice. It is also helpful for selected patients who are excessively concerned about serious underlying disease. For patients born in regions in which there is a higher incidence of gastric cancer, such as Central or South America, China and Southeast Asia, or Africa, an age threshold of 45 years may be more appropriate.

Endoscopic evaluation may also be warranted when symptoms fail to respond to initial empiric management strategies or when frequent symptom relapse occurs after discontinuation of empiric therapy.

D. Other Tests

In patients with refractory symptoms or progressive weight loss, antibodies for celiac disease or stool testing for ova and parasites or *Giardia* antigen, fat, or elastase may be considered. Abdominal imaging (ultrasonography or CT scanning) is performed only when pancreatic, biliary tract, vascular disease, or volvulus is suspected. Gastric emptying studies may be useful in patients with recurrent nausea and vomiting who have not responded to empiric therapies.

► Treatment

Initial empiric treatment is warranted for patients who are younger than age 60 years and who lack severe or worrisome "alarm" features. All other patients as well as patients whose symptoms do not respond to or relapse after empiric treatment should undergo upper endoscopy with subsequent treatment directed at the specific disorder identified (eg, peptic ulcer, gastroesophageal reflux, cancer). When endoscopy is performed, gastric biopsies should be obtained to test for *H pylori* infection. If infection is present, antibacterial treatment should be given.

A. Empiric Therapy

H pylori-negative patients most likely have functional dyspepsia or atypical GERD and can be treated with an antisecretory agent (proton pump inhibitor) for 4 weeks. For patients who have symptom relapse after discontinuation of the proton pump inhibitor, intermittent or long-term proton pump inhibitor therapy may be considered.

For patients in whom test results are positive for *H pylori*, antibiotic therapy proves definitive for patients with underlying peptic ulcers and may improve symptoms in a small subset (less than 10%) of infected patients with functional dyspepsia. Patients with persistent dyspepsia after *H pylori* eradication can be given a trial of proton pump inhibitor therapy.

B. Treatment of Functional Dyspepsia

Patients who have no significant findings on endoscopy as well as patients under age 60 who do not respond to *H pylori* eradication or empiric proton pump inhibitor therapy are presumed to have functional dyspepsia. Patients with mild, intermittent symptoms may respond to reassurance and lifestyle or dietary changes. A food diary, in which patients record their food intake, symptoms, and daily events, may reveal dietary or psychosocial precipitants of pain. Herbal therapies (peppermint, caraway) may offer benefit with little risk of adverse effects.

Antisecretory drugs (proton pump inhibitors or H₂-receptor antagonists) have demonstrated limited efficacy in the treatment of functional dyspepsia. A small number of patients (less than 10%) derive benefit from *H pylori* eradication therapy. Low doses of antidepressants (eg, desipramine or nortriptyline, 25–50 mg orally at bedtime) benefit some patients, possibly by moderating visceral afferent sensitivity. Doses should be increased slowly to minimize side effects. Although some prokinetics have demonstrated modest improvement in global symptoms compared to placebo in controlled trials, the more effective agents are either not available in the United States (domperidone) or were removed from the market due rare but serious adverse events (cisapride). Metoclopramide (5–10 mg three times daily) may improve symptoms but cannot be recommended for long-term use due to the risk of tardive dyskinesia.

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central pattern generator) within the medulla that coordinate emesis. It may be stimulated by four different sources of afferent input: (1) Afferent vagal fibers from the gastrointestinal viscera are rich in serotonin 5-HT₃ receptors; these may be stimulated by biliary or gastrointestinal distention, mucosal or peritoneal irritation, or infections. (2) Fibers of the vestibular system, which have high concentrations of histamine H₁ and muscarinic cholinergic receptors. (3) Higher central nervous system centers (amygdala); here, certain sights, smells, or emotional experiences may induce vomiting. For example, patients receiving chemotherapy may start vomiting in anticipation of its administration. (4) The chemoreceptor trigger zone, located outside the blood-brain barrier in the area postrema of the medulla, which is rich in opioid, serotonin 5-HT₃, neurokinin 1 (NK₁), and dopamine D₂ receptors. This region may be stimulated by drugs and chemotherapeutic agents, toxins, hypoxia, uremia, acidosis, and radiation therapy. Although the causes of nausea and vomiting are many, a simplified list is provided in Table 15–1.

Clinical Findings

A. Symptoms and Signs

Acute symptoms without abdominal pain are typically caused by food poisoning, infectious gastroenteritis, drugs, or systemic illness. A 2020 American Gastroenterological Association (AGA) meta-analysis reported a pooled prevalence of nausea or vomiting (usually mild) in 7.8% of patients with acute COVID-19. Up to 16% of patients may present with gastrointestinal symptoms (anorexia, nausea, diarrhea) in the absence of respiratory symptoms. Inquiry should be made into recent changes in medications, diet, other intestinal symptoms, or similar illnesses in family members. The acute onset of severe pain and vomiting suggests peritoneal irritation, acute gastric or intestinal obstruction, or pancreaticobiliary disease. Persistent vomiting suggests pregnancy, gastric outlet obstruction, gastroparesis, intestinal dysmotility, psychogenic disorders, and central nervous system or systemic disorders. Vomiting that occurs in the morning before breakfast is common with pregnancy, uremia, alcohol intake, and increased intracranial pressure. Inquiry should be made into use of cannabis products. Suspect cannabinoid hyperemesis syndrome in patients with prolonged use, especially in those who report compulsive showering or bathing. Vomiting immediately after meals strongly suggests bulimia or psychogenic causes. Vomiting of undigested food one to several hours after meals is characteristic of gastroparesis or a gastric outlet obstruction; physical examination may reveal a succussion splash. Patients with acute or chronic symptoms should be asked about neurologic symptoms (eg, headache, stiff neck, vertigo, and focal paresthesias or weakness) that suggest a central nervous system cause.

B. Special Examinations

With vomiting that is severe or protracted, serum electrolytes should be obtained to look for hypokalemia, azotemia, or metabolic alkalosis resulting from loss of gastric contents. Flat and upright abdominal radiographs or abdominal CT are obtained in patients with severe pain or

NAUSEA & VOMITING

Nausea is a vague, intensely disagreeable sensation of sickness or “queasiness” and is distinguished from anorexia. Vomiting often follows, as does retching (spasmodic respiratory and abdominal movements). Vomiting should be distinguished from regurgitation, the effortless reflux of liquid or food stomach contents; and from rumination, the chewing and swallowing of food that is regurgitated voluntarily after meals.

The brainstem vomiting center is composed of a group of neuronal areas (area postrema, nucleus tractus solitarius, and

Table 15–1. Causes of nausea and vomiting.

Visceral afferent stimulation	<p>Infections</p> <p>Mechanical obstruction</p> <ul style="list-style-type: none"> Gastric outlet obstruction: peptic ulcer disease, malignancy, gastric volvulus Small intestinal obstruction: adhesions, hernias, volvulus, Crohn disease, carcinomatosis <p>Dysmotility</p> <ul style="list-style-type: none"> Gastroparesis: diabetic, postviral, postvagotomy Small intestine: systemic sclerosis (scleroderma), amyloidosis, chronic intestinal pseudo-obstruction, familial myoneuropathies <p>Peritoneal irritation</p> <ul style="list-style-type: none"> Peritonitis: perforated viscus, appendicitis, spontaneous bacterial peritonitis Viral gastroenteritis: Norwalk agent, rotavirus, COVID-19 "Food poisoning": toxins from <i>Bacillus cereus</i>, <i>Staphylococcus aureus</i>, <i>Clostridium perfringens</i> Acute systemic infections <p>Hepatobiliary or pancreatic disorders</p> <ul style="list-style-type: none"> Acute or chronic pancreatitis Cholecystitis or choledocholithiasis <p>Topical gastrointestinal irritants</p> <ul style="list-style-type: none"> Alcohol, NSAIDs, oral antibiotics <p>Postoperative</p> <p>Other</p> <ul style="list-style-type: none"> Cardiac disease: acute myocardial infarction, heart failure Urologic disease: stones, pyelonephritis Vascular: chronic mesenteric ischemia, superior mesenteric artery syndrome
Vestibular disorders	<p>Vestibular disorders</p> <ul style="list-style-type: none"> Labyrinthitis, Ménière syndrome, motion sickness
CNS disorders	<p>Increased intracranial pressure</p> <ul style="list-style-type: none"> CNS tumors, subdural or subarachnoid hemorrhage <p>Migraine</p> <p>Cyclical vomiting syndrome</p> <p>Infections</p> <ul style="list-style-type: none"> Meningitis, encephalitis <p>Psychogenic</p> <ul style="list-style-type: none"> Anticipatory vomiting, anorexia nervosa and bulimia, psychiatric disorders
Irritation of chemoreceptor trigger zone	<p>Antitumor chemotherapy</p> <p>Medications and drugs</p> <ul style="list-style-type: none"> Opioids Marijuana Anticonvulsants Antiparkinsonism drugs Beta-blockers, antiarrhythmics, digoxin Oral contraceptives Cholinesterase inhibitors Diabetes medications (metformin, acarbose, pramlintide, exenatide) <p>Radiation therapy</p> <p>Systemic disorders</p> <ul style="list-style-type: none"> Diabetic ketoacidosis Uremia Adrenocortical crisis Parathyroid disease Hypothyroidism Pregnancy Paraneoplastic syndrome

CNS, central nervous system; COVID-19, coronavirus disease 2019; NSAIDs, nonsteroidal anti-inflammatory drugs.

suspicion of mechanical obstruction to look for free intra-peritoneal air or dilated loops of small bowel. The cause of gastric outlet obstruction is best demonstrated by upper endoscopy, and the cause of small intestinal obstruction is best demonstrated with abdominal CT imaging. Gastroparesis is confirmed by nuclear scintigraphic studies or

¹³C-octanoic acid breath tests, which show delayed gastric emptying and either upper endoscopy or barium upper gastrointestinal series showing no evidence of mechanical gastric outlet obstruction. Abnormal liver biochemical tests or elevated amylase or lipase suggest pancreaticobiliary disease, which may be investigated with an abdominal

sonogram or CT scan. Central nervous system causes are best evaluated with either head CT or MRI.

Complications

Complications include dehydration, hypokalemia, metabolic alkalosis, aspiration, rupture of the esophagus (Boerhaave syndrome), and bleeding secondary to a mucosal tear at the gastroesophageal junction (Mallory-Weiss syndrome).

Treatment

A. General Measures

Most causes of acute vomiting are mild, self-limited, and require no specific treatment. Patients should ingest clear liquids (broths, tea, soups, carbonated beverages) and small quantities of dry foods (soda crackers). Ginger may be an effective nonpharmacologic treatment. For more severe acute vomiting, hospitalization may be required. Patients unable to eat and losing gastric fluids may become dehydrated, resulting in hypokalemia with metabolic alkalosis. Intravenous 0.45% saline solution with 20 mEq/L of potassium chloride is given in most cases to maintain hydration. A nasogastric suction tube for gastric or mechanical small bowel obstruction improves patient comfort and permits monitoring of fluid loss.

B. Antiemetic Medications

Medications may be given either to prevent or to control vomiting. Combinations of drugs from different classes may provide better control of symptoms with less toxicity in some patients. Table 15–2 outlines common antiemetic dosing regimens.

1. Serotonin 5-HT₃-receptor antagonists—Ondansetron, granisetron, dolasetron, and palonosetron are effective in preventing chemotherapy- and radiation-induced emesis when initiated prior to treatment. Due to its prolonged half-life and internalization of the 5-HT₃-receptor, palonosetron is superior to other 5-HT₃-receptor antagonists for the prevention of acute and delayed chemotherapy-induced emesis from moderately or highly emetogenic chemotherapeutic regimens. Although 5-HT₃-receptor antagonists are effective as single agents for the prevention of chemotherapy-induced nausea and vomiting, their efficacy is enhanced by combination therapy with a corticosteroid (dexamethasone) and an NK₁-receptor antagonist. Serotonin antagonists increasingly are used for the prevention of postoperative nausea and vomiting because of increased restrictions on the use of other antiemetic agents (such as droperidol).

2. Corticosteroids—Corticosteroids (eg, dexamethasone) have antiemetic properties, but the basis for these effects is unknown. These agents enhance the efficacy of serotonin receptor antagonists for preventing acute and delayed nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy regimens.

3. Neurokinin receptor antagonists—Aprepitant, fosaprepitant, and rolapitant are highly selective antagonists for NK₁-receptors in the area postrema. They are

used in combination with corticosteroids and serotonin antagonists for the prevention of acute and delayed nausea and vomiting with highly emetogenic chemotherapy regimens. Netupitant is another oral NK₁-receptor antagonist that is administered in a fixed-dose combination with palonosetron. Combined therapy with a neurokinin-1 receptor antagonist prevents acute emesis in 80–90% and delayed emesis in more than 70% of patients treated with highly emetogenic regimens.

4. Dopamine antagonists—The phenothiazines, butyrophenones, and substituted benzamides (eg, prochlorperazine, promethazine) have antiemetic properties that are due to dopaminergic blockade as well as to their sedative effects. High doses of these agents are associated with anti-dopaminergic side effects, including extrapyramidal reactions and depression. With the advent of more effective and safer antiemetics, these agents are infrequently used, mainly in outpatients with minor, self-limited symptoms. The atypical antipsychotic agent olanzapine has potent antiemetic properties that may be mediated by blockade of both dopamine and serotonin neurotransmitters. It may be used in patients with poor control of chemotherapy-induced nausea and vomiting.

5. Antihistamines and anticholinergics—These drugs (eg, meclizine, dimenhydrinate, transdermal scopolamine) may be valuable in the prevention of vomiting arising from stimulation of the labyrinth, ie, motion sickness, vertigo, and migraines. They may induce drowsiness. A combination of oral vitamin B₆ and doxylamine is recommended by the American College of Obstetricians and Gynecologists as first-line therapy for nausea and vomiting during pregnancy.

6. Cannabinoids—Marijuana has been used widely as an appetite stimulant and antiemetic. Some states allow the use of medical marijuana with a clinician's certification. Strains of medical marijuana with different proportions of various naturally occurring cannabinoids (primarily THC and cannabidiol [CBD]) can be chosen to minimize its psychoactive effects. Excessive cannabinoid may cause nausea, vomiting, and abdominal pain (cannabinoid hyperemesis syndrome), which may be temporarily relieved with hot showers or bathing.

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Table 15–2. Common antiemetic dosing regimens.

	Dosage	Route
Serotonin 5-HT₃ Antagonists		
Ondansetron	Doses vary: 4–8 mg twice daily for postoperative nausea and vomiting 8 mg twice daily for moderately or highly emetogenic chemotherapy	Intravenously, orally Intravenously, orally
Granisetron	1 mg once daily 1–2 mg once daily	Intravenously Orally
Dolasetron	12.5 mg postoperatively 100 mg once daily	Intravenously Orally
Palonosetron	0.25 mg once as a single dose 30 min before start of chemotherapy 0.5 mg once as single dose	Intravenously Orally
Corticosteroids		
Dexamethasone	4–12 mg once pre-induction for prevention of postoperative nausea and vomiting 8 mg once daily for chemotherapy	Intravenously, orally Intravenously, orally
Methylprednisolone	40–100 mg once daily	Intravenously, intramuscularly, orally
Dopamine Receptor Antagonists		
Metoclopramide	10–20 mg or 0.5 mg/kg every 6–8 hours 10–20 mg every 6–8 hours	Intravenously Orally
Prochlorperazine	5–10 mg every 4–6 hours 25 mg suppository every 6 hours	Intravenously, intramuscularly, orally Per rectum
Promethazine	12.5–25 mg every 6–8 hours 25 mg every 6–8 hours	Intravenously, orally Per rectum
Trimethobenzamide	200 mg every 6–8 hours 250–300 mg every 6–8 hours	Orally Intravenously, orally
Olanzapine	5–10 mg once daily on days 1–4 for chemotherapy	
Neurokinin Receptor Antagonists¹		
Aprepitant	125 mg once before chemotherapy; then 80 mg on days 1 and 2 after chemotherapy	Orally
Fosaprepitant	150 mg once 30 min before chemotherapy	Intravenously
Rolapitant	180 mg once before chemotherapy	Orally
Netupitant/palonosetron	Netupitant 300 mg/palonosetron 0.50 mg once before chemotherapy	Orally

¹Neurokinin receptor antagonists are used solely for highly emetogenic chemotherapy regimens in combination with 5-HT₃ antagonists or dexamethasone or both.

HICCUPS

Though usually a benign and self-limited annoyance, hiccups may be persistent and a sign of serious underlying illness. In patients on mechanical ventilation, hiccups can trigger a full respiratory cycle and result in respiratory alkalosis.

Causes of benign, self-limited hiccups include gastric distention (carbonated beverages, air swallowing, overeating), sudden temperature changes (hot then cold liquids, hot then cold shower), alcohol ingestion, and states of heightened emotion (excitement, stress, laughing). There are over 100 causes of recurrent or persistent hiccups due to gastrointestinal, central nervous system, cardiovascular, and thoracic disorders.

► Clinical Findings

Evaluation of the patient with persistent hiccups should include a detailed neurologic examination, serum creatinine, liver chemistry tests, and a chest radiograph. When the cause remains unclear, CT or MRI of the head, chest, and abdomen, echocardiography, and upper endoscopy may help.

► Treatment

A number of simple remedies may be helpful in patients with acute benign hiccups. (1) Irritation of the nasopharynx by tongue traction, lifting the uvula with a spoon, catheter stimulation of the nasopharynx, or eating 1 teaspoon (tsp)

(7 g) of dry granulated sugar. (2) Interruption of the respiratory cycle by breath holding, Valsalva maneuver, sneezing, gasping (fright stimulus), or rebreathing into a bag. (3) Stimulation of the vagus by carotid massage. (4) Irritation of the diaphragm by holding knees to chest or by continuous positive airway pressure during mechanical ventilation. (5) Relief of gastric distention by belching or insertion of a nasogastric tube.

A number of drugs have been promoted as being useful in the treatment of hiccups. Chlorpromazine, 25–50 mg orally or intramuscularly, is most commonly used. Other agents reported to be effective include anticonvulsants (phenytoin, carbamazepine), benzodiazepines (lorazepam, diazepam), metoclopramide, baclofen, gabapentin, and occasionally general anesthesia.

Adam E. A systematic review of the effectiveness of oral baclofen in the management of hiccups in adult palliative care patients. *J Pain Palliat Care Pharmacother.* 2020;34:43. [PMID: 31910072]

Jeon YS et al. Management of hiccups in palliative care patients. *BMJ Support Palliat Care.* 2018;8:1. [PMID: 28705925]

CONSTIPATION

Constipation occurs in 15% of adults and up to one-third of elderly adults and is a common reason for seeking medical attention. It is more common in women. Older individuals are predisposed due to comorbid medical conditions, medications, poor eating habits, decreased mobility, and in some cases, inability to sit on a toilet (bed-bound patients). The first step in evaluating the patient is to determine what is meant by “constipation.” Patients may define constipation as infrequent stools (fewer than three in a week), hard or lumpy stools, excessive straining, or a sense of incomplete evacuation. Table 15–3 summarizes the many causes of constipation, which are discussed below.

Etiology

A. Primary Constipation

Most patients have constipation that cannot be attributed to any structural abnormalities or systemic disease. Approximately 40% of these patients have normal colonic transit time, 20% slow transit, and 40% defecatory disorders (with or without slow colonic transit). Normal colonic transit time is approximately 35 hours; more than 72 hours is significantly abnormal. Slow colonic transit is commonly idiopathic but may be part of a generalized gastrointestinal dysmotility syndrome. Normal defecation requires coordination between relaxation of the anal sphincter and pelvic floor musculature while abdominal pressure is increased. Patients with defecatory disorders (also known as dyssynergic defecation)—women more often than men—have impaired relaxation or paradoxical contraction of the anal sphincter and/or pelvic floor muscles during attempted defecation that impedes the bowel movement. This problem may be acquired during childhood or adulthood. Patients may complain of excessive straining, sense of incomplete evacuation, need for digital manipulation, or adoption of a non-sitting (eg, standing) position during defecation. Patients

Table 15–3. Causes of constipation in adults.

Most common	Inadequate fiber or fluid intake Poor bowel habits
Systemic disease	Endocrine: hypothyroidism, hyperparathyroidism, diabetes mellitus Metabolic: hypokalemia, hypercalcemia, uremia, porphyria Neurologic: Parkinson disease, multiple sclerosis, sacral nerve damage (prior pelvic surgery, tumor), paraplegia, autonomic neuropathy
Medications	Opioids Diuretics Calcium channel blockers Anticholinergics Psychotropics Calcium and iron supplements NSAIDs Clonidine Cholestyramine
Structural abnormalities	Anorectal: rectal prolapse, rectocele, rectal intussusception, anorectal stricture, anal fissure, solitary rectal ulcer syndrome Perineal descent Colonic mass with obstruction: adenocarcinoma Colonic stricture: radiation, ischemia, diverticulosis Hirschsprung disease Idiopathic megarectum
Slow colonic transit	Idiopathic: isolated to colon Psychogenic Eating disorders Chronic intestinal pseudo-obstruction
Pelvic floor dyssynergia	
Irritable bowel syndrome	

NSAIDs, nonsteroidal anti-inflammatory drugs.

with predominant complaints of abdominal pain or bloating with chronic idiopathic constipation are more appropriately given a diagnosis of irritable bowel syndrome (IBS) with constipation.

B. Secondary Constipation

Constipation may be caused by systemic disorders, medications, or obstructing colonic lesions. Systemic disorders can cause constipation because of neurologic gut dysfunction, myopathies, endocrine disorders, or electrolyte abnormalities (eg, hypercalcemia or hypokalemia); medication side effects are often responsible (eg, anticholinergics or opioids). Colonic lesions that obstruct fecal passage, such as neoplasms and strictures, are an uncommon cause but important in new-onset constipation. Such lesions should be excluded in patients older than age 50 years, in patients with “alarm” symptoms or signs (hematochezia, weight loss, anemia, or positive fecal occult blood tests [FOBT] or fecal immunochemical tests [FIT]), and in patients with a family history of colon cancer or inflammatory bowel disease. Defecatory difficulties also can be due to a variety of anorectal problems that impede or obstruct

flow (perineal descent, rectal prolapse, rectocele), some of which may require surgery, and to Hirschsprung disease (usually suggested by lifelong constipation).

► Clinical Findings

A. Symptoms and Signs

All patients should undergo a history and physical examination to distinguish primary from secondary causes of constipation. Physical examination should include digital rectal examination with assessment for anatomic abnormalities, such as anal stricture, rectocele, rectal prolapse, or perineal descent during straining as well as assessment of pelvic floor motion during simulated defecation (ie, the patient's ability to "expel the examiner's finger"). Further diagnostic tests should be performed in patients with any of the following: age 50 years or older, severe constipation, signs of an organic disorders, alarm symptoms (hematochezia, weight loss, positive FOBT or FIT), or a family history of colon cancer or inflammatory bowel disease. These tests should include laboratory studies (complete blood count; serum electrolytes, calcium, glucose, and thyroid-stimulating hormone) and a colonoscopy or flexible sigmoidoscopy.

B. Special Examinations

Patients with refractory constipation not responding to routine medical management warrant further diagnostic studies. Anorectal manometry including a balloon expulsion test should be performed first to evaluate for defecatory disorders. Inability to expel a balloon (attached to a 16F indwelling urinary catheter) filled with 50 mL of warm water within 1–2 minutes while sitting on a toilet is strongly suggestive of pelvic floor dyssynergia. Defecography to further assess pelvic floor function may be considered in selected patients. Subsequent colon transit studies are recommended only after defecatory disorders have been excluded. Colon transit time may be assessed by radiopaque markers, scintigraphy, or wireless motility capsule.

► Treatment

A. Chronic Constipation

1. Dietary and lifestyle measures—Patients should be instructed on normal defecatory function and optimal toileting habits, including regular timing, proper positioning, and abdominal pressure. Adequate dietary fluid and fiber intake should be emphasized. A trial of soluble fiber supplements (ie, psyllium) is recommended (Table 15–4). Increased dietary fiber may cause distention or flatulence, which often diminishes over several days. Response to fiber therapy is not immediate and increases in dosage should be made gradually over 7–10 days. Fiber is most likely to benefit patients with normal colonic transit, but it may not benefit patients with colonic inertia, defecatory disorders, opioid-induced constipation, or IBS; it may even exacerbate symptoms in these patients. Regular exercise is associated with a decreased risk of constipation. When possible, discontinue medications that may be causing or contributing to constipation. Probiotics are widely

promoted to patients in direct advertising for treatment of constipation. A 2014 meta-analysis of randomized controlled trials suggests probiotics improve stool frequency and consistency; however, more study is needed.

2. Laxatives—Laxatives may be given on an intermittent or chronic basis for constipation that does not respond to dietary and lifestyle changes (Table 15–4). In a 2020 survey of US adults with constipation symptoms (hard, lumpy, or infrequent stools or straining), 45% were taking fibers supplements or nonprescription laxatives; only 3% were taking prescription laxatives. There is no evidence that long-term use of these agents is harmful.

A. OSMOTIC LAXATIVES—Treatment usually is initiated with regular (daily) use of an osmotic laxative. Nonabsorbable osmotic agents increase secretion of water into the intestinal lumen, thereby softening stools and promoting defecation. Magnesium hydroxide, nondigestible carbohydrates (sorbitol, lactulose), and polyethylene glycol are all efficacious and safe for treating acute and chronic cases. The dosages are adjusted to achieve soft to semi-liquid movements. Magnesium-containing saline laxatives should not be given to patients with chronic renal insufficiency. Nondigestible carbohydrates may induce bloating, cramps, and flatulence. Polyethylene glycol 3350 (MiraLAX) is a component of solutions traditionally used for colonic lavage prior to colonoscopy and does not cause flatulence. When used in conventional doses, the onset of action of these osmotic agents is generally within 24 hours. For more rapid treatment of acute constipation, purgative laxatives may be used, such as magnesium citrate. Magnesium citrate may cause hypermagnesemia.

B. STIMULANT LAXATIVES—For patients with incomplete response to osmotic agents, stimulant laxatives may be prescribed as needed as a "rescue" agent or on a daily basis. These agents stimulate fluid secretion and colonic contraction, resulting in a bowel movement within 6–12 hours after oral ingestion or 15–60 minutes after rectal administration. Oral agents are usually administered once daily at bedtime. Common nonprescription preparations include bisacodyl and senna (Table 15–4).

C. SECRETAGOGUES—Several agents stimulate intestinal chloride secretion either through activation of chloride channels (lubiprostone) or guanylycyclase C (linaclotide and plecanatide), resulting in increased intestinal fluid and accelerated colonic transit. In multicenter controlled trials, patients treated with lubiprostone 24 mcg orally twice daily, linaclotide 145 mcg once daily, or plecanatide 3 mg once daily increased the number of bowel movements compared with patients treated with placebo. Because these agents are expensive, they should be reserved for patients who have suboptimal response or side effects with less expensive agents.

D. SEROTONIN 5-HT₄-RECEPTOR AGONIST—Stimulation of 5-HT₄-receptors in the colon leads to increased release of acetylcholine within smooth muscle of the intestinal tract, which stimulates high-amplitude peristaltic contractions in the proximal colon. Prucalopride is a high-affinity 5-HT₄-agonist that is approved in the United States for the

Table 15–4. Pharmacologic management of constipation.

Agent	Dosage	Onset of Action	Comments
Fiber Laxatives			
Psyllium	1–3 tsp once or twice daily	Days	(Metamucil; Perdiem)
Methylcellulose	1–3 tsp once or twice daily	Days	(Citrucel) Less gas, flatulence
Calcium polycarbophil	1 or 2 tablets once or twice daily	12–24 hours	(FiberCon) Does not cause gas; pill form
Guargum	1 tbsp once or twice daily	Days	(Benefiber) Non-gritty, tasteless, less gas
Stool Surfactants			
Docusate sodium	100 mg once or twice daily	12–72 hours	(Colace) Marginal benefit
Mineral oil	15–45 mL once or twice daily	6–8 hours	May cause lipid pneumonia if aspirated
Osmotic Laxatives			
Magnesium hydroxide	15–30 mL orally once or twice daily	6–24 hours	(Milk of magnesia; Epsom salts) May cause hypermagnesemia if chronic kidney disease
Lactulose or 70% sorbitol	15–60 mL orally once daily to three times daily	6–48 hours	Cramps, bloating, flatulence
Polyethylene glycol (PEG 3350)	17 g in 8 oz liquid once or twice daily	6–24 hours	(MiraLAX) Less bloating than lactulose, sorbitol
Stimulant Laxatives			
Bisacodyl	5–20 mg orally as needed	6–8 hours	May cause cramps; avoid daily use if possible
Bisacodyl suppository	10 mg per rectum as needed	1 hour	
Senna	17.2–34.4 mg orally	8–12 hours	(ExLax; Senekot; SennaS) May cause cramps; avoid daily use if possible
Lubiprostone	24 mcg orally twice daily	12–48 hours	Expensive; may cause nausea. Contraindicated in pregnancy
Linaclotide	72–145 mcg orally once daily		Expensive; contraindicated in pediatric patients
Plecanatide	3–6 mg once daily		Expensive; contraindicated in pediatric patients
Enemas			
Tap water	500 mL per rectum	5–15 minutes	
Sodium phosphate enema	120 mL per rectum	5–15 minutes	Commonly used for acute constipation or to induce movement prior to medical procedures
Mineral oil enema	100–250 mL per rectum	5–15 minutes	To soften and lubricate fecal impaction
Agents Used for Acute Purgative or to Clean Bowel Prior to Medical Procedures			
Polyethylene glycol (PEG 3350)	4 L orally administered over 2–4 hours	< 4 hours	(GoLYTELY; CoLYTE; NuLYTE, MoviPrep) Used to cleanse bowel before colonoscopy
Magnesium citrate	10 oz orally	3–6 hours	Lemon-flavored

treatment of chronic constipation (2 mg once daily). In six clinical trials, 19–38% of patients treated with prucalopride experienced at least three spontaneous bowel movements per week, which was 5–23% more than with placebo. In contrast to prior, less-selective 5-HT₄-agonists (cisapride, tegaserod), which were removed from the market due to adverse cardiovascular events, prucalopride does not have affinity for hERG K⁺ channels and does not appear to have any cardiovascular risk.

E. OPIOID-RECEPTOR ANTAGONISTS—Long-term use of opioids can cause constipation by inhibiting peristalsis and

increasing intestinal fluid absorption. Methylnaltrexone (450 mg orally once daily), naloxegol (12.5–25 mg orally once daily), and naldemedine (0.2 mg orally once daily) are mu-opioid receptor antagonists that block peripheral opioid receptors (including in the gastrointestinal tract) without affecting central analgesia. They are approved for the treatment of opioid-induced constipation in patients receiving opioids for chronic noncancer pain (see Chapter 5). A subcutaneous formulation of methylnaltrexone also is approved for treatment of patients receiving palliative care for advanced illness who have not responded to conventional laxative regimens.

B. Fecal Impaction

Severe impaction of stool in the rectal vault may result in obstruction to further fecal flow, leading to partial or complete large bowel obstruction. Predisposing factors include medications (eg, opioids), severe psychiatric disease, prolonged bed rest, neurogenic disorders of the colon, and spinal cord disorders. Clinical presentation includes decreased appetite, nausea and vomiting, and abdominal pain and distention. There may be paradoxical “diarrhea” as liquid stool leaks around the impacted feces. Firm feces are palpable on digital examination of the rectal vault. Initial treatment is directed at relieving the impaction with enemas (saline, mineral oil, or diatrizoate) or digital disruption of the impacted fecal material. Long-term care is directed at maintaining soft stools and regular bowel movements (as above).

► When to Refer

- Patients with refractory constipation for anorectal testing.
- Patients with defecatory disorders may benefit from biofeedback therapy.
- Patients with alarm symptoms or who are over age 50 should be referred for colonoscopy.
- Rarely, surgery (subtotal colectomy) is required for patients with severe colonic inertia.

Bharucha AE et al. Mechanisms, evaluation, and management of chronic constipation. *Gastroenterology*. 2020;18:1232. [PMID: 31945360]

Bandler J et al. Pretest and post-test probabilities of diagnoses of rectal evacuation disorders based on symptoms, rectal exam, and basic tests: a systematic review. *Clin Gastroenterol Hepatol*. 2020;18:2479. [PMID: 31811949]

Crockett SD et al. American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology*. 2019;156:218. [PMID: 30340754]

Luthra P et al. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2019;4:831. [PMID: 31474542]

Oh SJ et al. Chronic constipation in the United States: results from a population-based survey assessing healthcare seeking and use of pharmacotherapy. *Am J Gastroenterol*. 2020;115:895. [PMID: 32324606]

patients with other complaints such as dysphagia, heartburn, early satiety, or vomiting.

Chronic excessive belching is almost always caused by supragastric belching (voluntary diaphragmatic contraction, followed by upper esophageal relaxation with air inflow to the esophagus) or true air swallowing (aerophagia), both of which are behavioral disorders that are more common in patients with anxiety or psychiatric disorders. These patients may benefit from referral to a behavioral or speech therapist.

Pauwels A et al. A randomized, double-blind, placebo-controlled, cross-over study using baclofen in the treatment of rumination syndrome. *Am J Gastroenterol*. 2018;113:97. [PMID: 29206813]

2. Bloating & Flatus

Bloating is a complaint of increased abdominal pressure that may or may not be accompanied by visible distention. Organic causes of acute bloating with distention, vomiting, and/or pain include ascites, gastrointestinal obstruction (gastric fundoplication, gastric outlet obstruction, small intestine or colon obstruction, and constipation). Complaints of chronic abdominal distention or bloating are common. Some patients swallow excess air (aerophagia, poorly fitting dentures, sleep apnea, and rapid eating) or produce excess gas (excessive FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides, and polyols] ingestion and malabsorption). Others have impaired gas propulsion or expulsion, increased bowel wall tension, enhanced visceral sensitivity, or altered viscerosomatic reflexes leading to abdominal protrusion. Many of these patients have an underlying functional gastrointestinal disorder such as IBS or functional dyspepsia. Constipation should be treated, and exercise (which accelerates gas propulsion) is recommended. Medications that inhibit gastrointestinal motility should be avoided (opioids and calcium channel blockers).

Healthy adults pass **flatus** up to 20 times daily and excrete up to 750 mL. Flatus is derived from two sources: swallowed air (primarily nitrogen) and bacterial fermentation of undigested carbohydrate (which produces H₂, CO₂, and methane). A number of short-chain carbohydrates (FODMAPs) are incompletely absorbed in the small intestine and pass into the colon. These include lactose (dairy products); fructose (fruits, corn syrups, and some sweeteners); polyols (stone-fruits, mushrooms, and some sweeteners); and oligosaccharides (legumes, lentils, cruciferous vegetables, garlic, onion, pasta, and whole grains). Abnormal gas production may be caused by increased ingestion of these carbohydrates or, less commonly, by disorders of malabsorption. Foul odor may be caused by garlic, onion, eggplant, mushrooms, and certain herbs and spices.

Determining abnormal from normal amounts of flatus is difficult. Patients who report excess flatus may also complain of bloating, cramping, and altered stool habits (diarrhea or constipation). Patients with a long-standing history of flatulence and no other symptoms or signs of malabsorption disorders can be treated conservatively. Gum chewing and carbonated beverages should be avoided to reduce air swallowing. Lactose intolerance may be assessed

GASTROINTESTINAL GAS

1. Belching

Belching (eructation) is the involuntary or voluntary release of gas from the stomach or esophagus. It occurs most frequently after meals, when gastric distention results in transient lower esophageal sphincter (LES) relaxation. Belching is a normal reflex and does not itself denote gastrointestinal dysfunction. Virtually all stomach gas comes from swallowed air. With each swallow, 2–5 mL of air is ingested, and excessive amounts may result in distention, flatulence, and abdominal pain. This may occur with rapid eating, gum chewing, smoking, and the ingestion of carbonated beverages. Evaluation should be restricted to

by a 2-week trial of a lactose-free diet or by a hydrogen breath test. A list of foods containing FODMAPs should be provided and high FODMAP foods eliminated for 2–4 weeks. If symptoms improve, FODMAP groups may be sequentially introduced to identify triggers. Multiple low-FODMAP dietary guides are available; however, referral to a knowledgeable dietician may be helpful.

The nonprescription agent Beano (alpha-d-galactosidase enzyme) reduces gas caused by foods containing galactooligosaccharides (legumes, chickpeas, lentils) but not other FODMAPs. Activated charcoal may afford relief. Simethicone has no proven benefit.

Many patients report reduced flatus production with use of probiotics, although there has been limited controlled study of these agents for this purpose.

Lacy BE et al. Management of chronic abdominal distention and bloating. *Clin Gastroenterol Hepatol*. 2021;19:219. [PMID: 32246999]

Scarlata K. Low FODMAP diet: what your patients need to know. *Am J Gastroenterol*. 2019;114:189. [PMID: 30356177]

DIARRHEA

Diarrhea can range in severity from an acute self-limited episode to a severe, life-threatening illness. To properly evaluate the complaint, the clinician must determine the patient's normal bowel pattern and the nature of the current symptoms.

Approximately 10 L/day of fluid enter the duodenum of which all but 1.5 L/day are absorbed by the small intestine. The colon absorbs most of the remaining fluid, with less than 200 mL/day lost in the stool. Although diarrhea sometimes is defined as a stool weight of more than 200–300 g/24 h, quantification of stool weight is necessary only in some patients with chronic diarrhea. In most cases, the physician's working definition of diarrhea is increased stool frequency (more than three bowel movements per day) or liquidity of feces.

The causes of diarrhea are myriad. In clinical practice, it is helpful to distinguish acute from chronic diarrhea, as the evaluation and treatment are entirely different (Tables 15–5 and 15–6).

1. Acute Diarrhea



ESSENTIALS OF DIAGNOSIS

- Diarrhea of < 2 weeks' duration is most commonly caused by invasive or noninvasive pathogens and their enterotoxins.

Acute noninflammatory diarrhea

- Watery, nonbloody.
- Usually mild, self-limited.
- Caused by a virus or noninvasive bacteria.
- Diagnostic evaluation is limited to patients with diarrhea that is severe or persists beyond 7 days.

Acute inflammatory diarrhea

- Blood or pus, fever.
- Usually caused by an invasive or toxin-producing bacterium.
- Diagnostic evaluation requires routine stool bacterial testing (including *E coli* O157:H5 and O157:H7) in all and testing as clinically indicated for *Clostridioides difficile* and parasites.

► Etiology & Clinical Findings

Diarrhea acute in onset and persisting for less than 2 weeks is most commonly caused by infectious agents, bacterial toxins (either preformed or produced in the gut), or medications. Community outbreaks (including norovirus and SARS-CoV-2 in nursing homes, schools, cruise ships) suggest a viral etiology or a common food source. Among patients with COVID-19 infection, watery diarrhea (usually mild) occurs in 7.7% and it may be the presenting symptom. Similar recent illnesses in family members suggest an infectious origin. Ingestion of improperly stored or prepared food implicates food poisoning. Pregnant women have an increased risk of developing listeriosis. Day care attendance or exposure to unpurified water (camping, swimming) may result in infection with *Giardia* or *Cryptosporidium*. Large *Cyclospora* outbreaks have been traced to contaminated produce. Recent travel abroad suggests "traveler's diarrhea" (see Chapter 30). Antibiotic

Table 15–5. Causes of acute infectious diarrhea.

Noninflammatory Diarrhea	Inflammatory Diarrhea
Viral Noroviruses, astrovirus, adenovirus, rotavirus, sapovirus, coronavirus SARS-CoV-2	Viral <i>Cytomegalovirus</i>
Protozoal <i>Giardia lamblia</i> <i>Cryptosporidium</i> <i>Cyclospora</i>	Protozoal <i>Entamoeba histolytica</i>
Bacterial 1. Preformed enterotoxin production <i>Staphylococcus aureus</i> <i>Bacillus cereus</i> <i>Clostridium perfringens</i> 2. Enterotoxin production Enterotoxigenic <i>Escherichia coli</i> (ETEC) <i>Vibrio cholera</i> , <i>Vibrio vulnificus</i>	Bacterial 1. Cytotoxin production <i>Enterohemorrhagic E. coli</i> O157:H5 and O157:H7 (EHEC) <i>Vibrio parahaemolyticus</i> <i>Clostridioides difficile</i> <i>Plesiomonas shigelloides</i> 2. Mucosal invasion <i>Shigella</i> <i>Campylobacter jejuni</i> <i>Salmonella</i> <i>Enteroinvasive E. coli</i> (EIEC) <i>Aeromonas</i> <i>Yersinia enterocolitica</i> <i>Chlamydia</i> <i>Neisseria gonorrhoeae</i> <i>Listeria monocytogenes</i>

Table 15–6. Causes of chronic diarrhea.

Osmotic diarrhea	Malabsorption syndromes
CLUES: Stool volume decreases with fasting; increased stool osmotic gap <ol style="list-style-type: none"> Medications: antacids, lactulose, sorbitol Disaccharidase deficiency: lactose intolerance Factitious diarrhea: magnesium (antacids, laxatives) 	CLUES: Weight loss, abnormal laboratory values; fecal fat > 10 g/24 h <ol style="list-style-type: none"> Small bowel mucosal disorders: celiac disease, tropical sprue, Whipple disease, eosinophilic gastroenteritis, small bowel resection (short bowel syndrome), Crohn disease Lymphatic obstruction: lymphoma, carcinoid, infectious (tuberculosis, MAI), Kaposi sarcoma, sarcoidosis, retroperitoneal fibrosis Pancreatic disease: chronic pancreatitis, pancreatic carcinoma Bacterial overgrowth: motility disorders (diabetes, vagotomy), systemic sclerosis (scleroderma), fistulas, small intestinal diverticula
Secretory diarrhea	Motility disorders
CLUES: Large volume (> 1 L/day); little change with fasting; normal stool osmotic gap <ol style="list-style-type: none"> Hormonally mediated: VIPoma, carcinoid, medullary carcinoma of thyroid (calcitonin), Zollinger-Ellison syndrome (gastrin) Factitious diarrhea (laxative abuse); phenolphthalein, senna Villous adenoma Bile salt malabsorption (idiopathic, ileal resection; Crohn ileitis; postcholecystectomy) Medications 	CLUES: Systemic disease or prior abdominal surgery <ol style="list-style-type: none"> Postsurgical: vagotomy, partial gastrectomy, blind loop with bacterial overgrowth Systemic disorders: systemic sclerosis (scleroderma), diabetes mellitus, hyperthyroidism Irritable bowel syndrome
Inflammatory conditions	Chronic infections
CLUES: Fever, hematochezia, abdominal pain <ol style="list-style-type: none"> Ulcerative colitis Crohn disease Microscopic colitis Malignancy: lymphoma, adenocarcinoma (with obstruction and pseudodiarrhea) Radiation enteritis 	<ol style="list-style-type: none"> Parasites: <i>Giardia lamblia</i>, <i>Entamoeba histolytica</i>, <i>Strongyloides stercoralis</i>, <i>Capillaria philippinensis</i> AIDS-related: Viral: Cytomegalovirus; Bacterial: <i>Clostridioides difficile</i>, <i>Mycobacterium avium complex</i>; Protozoal: Microsporidia (<i>Enterocytozoon bieneusi</i>), <i>Cryptosporidium</i>, <i>Cystoisospora belli</i> (formerly <i>Isospora belli</i>)
Medications	Factitious
Common offenders: SSRIs, cholinesterase inhibitors, NSAIDs, proton pump inhibitors, angiotensin II receptor blockers, metformin, allopurinol	See Osmotic and Secretory diarrhea above

MAI, *Mycobacterium avium-intracellulare*; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

administration within the preceding several weeks increases the likelihood of *C difficile* colitis. Finally, risk factors for HIV infection or sexually transmitted diseases should be determined. (AIDS-associated diarrhea is discussed in Chapter 31; infectious proctitis is discussed later in this chapter under Anorectal Infections.) Persons engaging in anal intercourse or oral-anal sexual activities are at risk for a variety of infections that cause proctitis, including gonorrhea, syphilis, lymphogranuloma venereum, and herpes simplex.

The nature of the diarrhea helps distinguish among different infectious causes (Table 15–5).

A. Noninflammatory Diarrhea

Watery, nonbloody diarrhea associated with perumbilical cramps, bloating, nausea, or vomiting suggests a small bowel source caused by either a virus (rotavirus, norovirus, adenovirus, coronavirus), a toxin-producing bacterium (enterotoxigenic *E coli* [ETEC], *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*, *Plesiomonas shigelloides*), or another agent (*Giardia*) that disrupts normal absorption and secretory process in the small intestine. Prominent vomiting suggests viral enteritis or *S aureus* food poisoning. Although typically mild, the diarrhea (which originates in the small intestine) can be voluminous and result in dehydration with hypokalemia and metabolic

acidosis (eg, cholera). Because tissue invasion does not occur, fecal leukocytes are not present.

B. Inflammatory Diarrhea

The presence of fever and bloody diarrhea (dysentery) indicates colonic tissue damage caused by invasion (shigellosis, salmonellosis, *Campylobacter* or *Yersinia* infection, amebiasis) or a toxin (*C difficile*, *Aeromonas*, Shiga-toxin-producing *E coli* [STEC; also known as enterohemorrhagic *E coli*]}. Because these organisms predominantly involve the colon, the diarrhea is small in volume (less than 1 L/day) and associated with left lower quadrant cramps, urgency, and tenesmus. Fecal leukocytes or lactoferrin usually are present in infections with invasive organisms. *E coli* O157:H7 is a Shiga-toxin-producing noninvasive organism most commonly acquired from contaminated meat that has resulted in several outbreaks of an acute, often severe hemorrhagic colitis. A major complication of STEC is hemolytic-uremic syndrome, which develops in 6–22% of cases. In immunocompromised and HIV-infected patients, cytomegalovirus (CMV) can cause intestinal ulceration with watery or bloody diarrhea.

Infectious dysentery must be distinguished from acute ulcerative colitis, which may also present acutely with fever, abdominal pain, and bloody diarrhea. Diarrhea that persists for more than 14 days is not attributable to bacterial

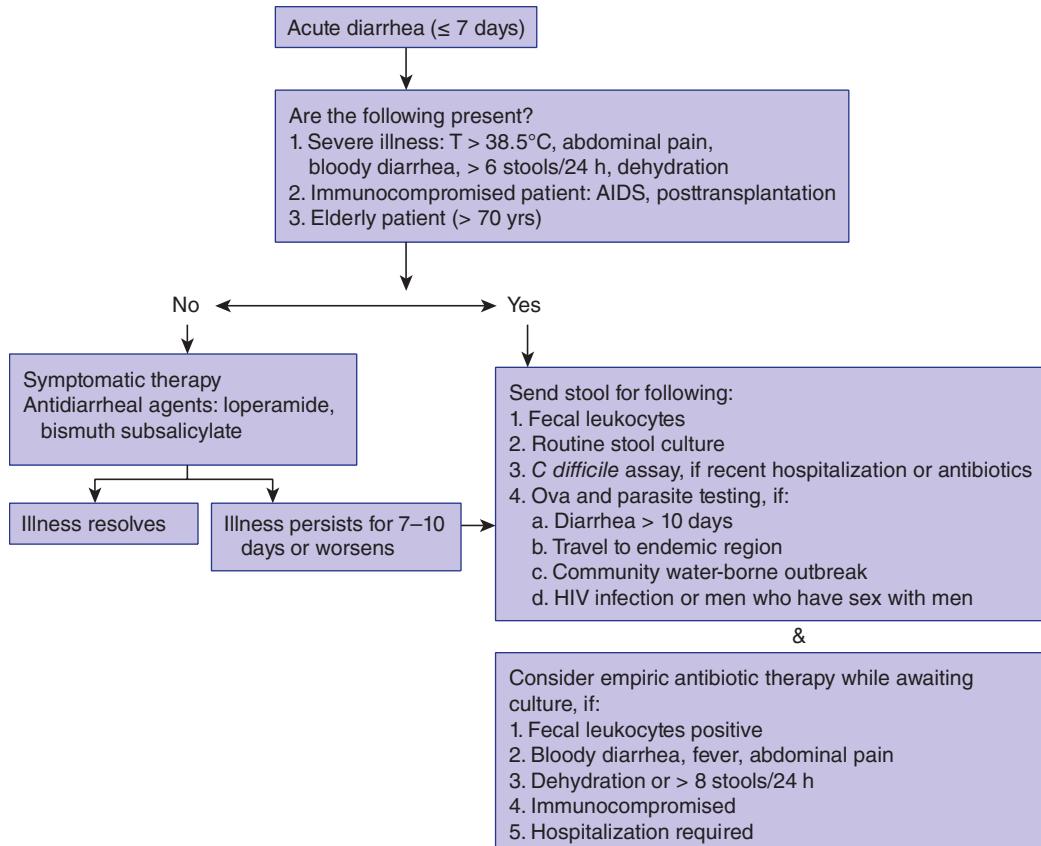


Figure 15–1. Evaluation of acute diarrhea.

pathogens (except for *C difficile*) and should be evaluated as chronic diarrhea.

Evaluation

In over 90% of patients with acute noninflammatory diarrhea, the illness is mild and self-limited, responding within 5 days to simple rehydration therapy or antidiarrheal agents. The isolation rate of bacterial pathogens from stool cultures in patients with acute noninflammatory diarrhea is under 3%; therefore, diagnostic investigation is unnecessary except in suspected outbreaks or in patients at high risk for spreading infection to others.

The goal of initial evaluation of acute diarrhea is to distinguish patients with mild disease from those with more serious illness. Prompt medical evaluation is indicated in the following situations (Figure 15–1): (1) signs of inflammatory diarrhea manifested by any of the following: fever (higher than 38.5°C), WBC 15,000/mcL ($15 \times 10^9/L$) or more, bloody diarrhea, or severe abdominal pain; (2) the passage of six or more unformed stools in 24 hours; (3) profuse watery diarrhea and dehydration; (4) frail older patients or nursing home residents; (5) immunocompromised patients (AIDS, posttransplantation); (6) exposure to antibiotics; (7) hospital-acquired diarrhea (onset following at least 3 days of hospitalization); or (8) systemic illness.

Physical examination pays note to the patient's level of hydration, mental status, and the presence of abdominal tenderness or peritonitis. Peritoneal findings may be present in infection with *C difficile* or STEC. Hospitalization is required in patients with severe dehydration, organ failure, marked abdominal pain, or altered mental status.

Stool should be sent for microbial assessment when patients have dysentery (bloody stools), severe illness, or persistent diarrhea beyond 7 days. Until recently, stool specimens were sent for microscopy (to assess for fecal white cells and protozoa) and bacterial cultures. These traditional methods provided a positive diagnosis in 60–75% of patients with dysenteric diarrhea but required 48–72 hours. Currently, most centers perform microbial assessment using multiplex molecular techniques with nucleic acid amplification (eg, polymerase chain reaction [PCR] assays) that screen for a panel of pathogens, including viruses, protozoa, and bacteria, within 1–5 hours. In patients who are hospitalized or who have a history of antibiotic exposure, a stool sample should be tested for *C difficile*.

Treatment

A. Diet

Most mild diarrhea will not lead to dehydration provided the patient takes adequate oral fluids containing carbohydrates

and electrolytes. Patients find it more comfortable to rest the bowel by avoiding high-fiber foods, fats, milk products, caffeine, and alcohol. Frequent feedings of tea, “flat” carbonated beverages, and soft, easily digested foods (eg, soups, crackers, bananas, applesauce, rice, toast) are encouraged.

B. Rehydration

In more severe diarrhea, dehydration can occur quickly, especially in children and frail older adults. Oral rehydration with fluids containing glucose, Na^+ , K^+ , Cl^- , and bicarbonate or citrate is preferred when feasible. A convenient mixture is $\frac{1}{2}$ tsp salt (3.5 g), 1 tsp baking soda (2.5 g NaHCO_3), 8 tsp sugar (40 g), and 8 oz orange juice (1.5 g KCl), diluted to 1 L with water. Alternatively, oral electrolyte solutions (eg, Pedialyte, Gatorade) are readily available. Fluids should be given at rates of 50–200 mL/kg/24 h depending on the hydration status. Intravenous fluids (lactated Ringer injection) are preferred in patients with severe dehydration.

C. Antidiarrheal Agents

Antidiarrheal agents may be used safely in patients with mild to moderate diarrheal illnesses to improve patient comfort. Opioid agents help decrease the stool number and liquidity and control fecal urgency. However, they should not be used in patients with bloody diarrhea, high fever, or systemic toxicity and should be discontinued in patients whose diarrhea is worsening despite therapy. With these provisos, such drugs provide excellent symptomatic relief. Loperamide is preferred, in a dosage of 4 mg orally initially, followed by 2 mg after each loose stool (maximum: 8 mg/24 h).

Bismuth subsalicylate (Pepto-Bismol), two tablets or 30 mL orally four times daily, reduces symptoms in patients with traveler’s diarrhea by virtue of its anti-inflammatory and antibacterial properties. It also reduces vomiting associated with viral enteritis. Anticholinergic agents (eg, diphenoxylate with atropine) are contraindicated in acute diarrhea because of the rare precipitation of toxic megacolon.

D. Antibiotic Therapy

1. Empiric treatment—Empiric antibiotic treatment of patients with acute, community-acquired diarrhea generally is not indicated. Even patients with inflammatory diarrhea caused by invasive pathogens usually have symptoms that will resolve within several days without antimicrobials. In centers in which stool microbial testing with rapid molecular assays is not available, empiric treatment may be considered while the stool bacterial culture is incubating in certain patients: those with non-hospital-acquired diarrhea; those with moderate to severe fever, tenesmus, or bloody stools; and those with no suspicion of infection with STEC. It should also be considered in patients who are immunocompromised or who have significant dehydration. The oral drugs of choice for empiric treatment are the fluoroquinolones (eg, ciprofloxacin 500 mg, ofloxacin 400 mg, or levofloxacin 500 mg once daily) for 1–3 days. Alternatives include trimethoprim-sulfamethoxazole, 160/800 mg twice daily; or doxycycline, 100 mg twice daily. Macrolides and penicillins are no longer recommended because of

widespread microbial resistance to these agents. Rifaximin (200 mg three times daily for 3 days) and azithromycin (1000 mg single dose or 500 mg daily for 3 days) are approved for empiric treatment of noninflammatory traveler’s diarrhea (see Chapter 30).

2. Specific antimicrobial treatment—Antibiotics are not recommended in patients with nontyphoid *Salmonella*, *Campylobacter*, STEC, *Aeromonas*, or *Yersinia*, except in severe disease, because they do not hasten recovery or reduce the period of fecal bacterial excretion. The infectious bacterial diarrheas for which treatment is recommended are shigellosis, cholera, extraintestinal salmonellosis, listeriosis, and *C difficile*. The parasitic infections for which treatment is indicated are amebiasis, giardiasis, cryptosporidiosis, cyclosporiasis, and *Enterocytozoon bieneusi* infection. Therapy for traveler’s diarrhea, infectious (sexually transmitted) proctitis, and AIDS-related diarrhea is presented in Chapters 30 and 31.

► When to Admit

- Severe dehydration for intravenous fluids, especially if vomiting or unable to maintain sufficient oral fluid intake.
- Bloody diarrhea that is severe or worsening in order to distinguish infectious versus noninfectious cause.
- Severe abdominal pain, worrisome for toxic colitis, inflammatory bowel disease, intestinal ischemia, or surgical abdomen.
- Signs of severe infection or sepsis (temperature higher than 39.5°C, leukocytosis, rash).
- Severe or worsening diarrhea in patients who are older than 70 years or immunocompromised.
- Signs of hemolytic-uremic syndrome (acute kidney injury, thrombocytopenia, hemolytic anemia).

Siciliano V et al. Clinical management of infectious diarrhea. Rev Recent Clin Trials. 2020;15:298. [PMID: 32598272]

Sultan S et al. AGA Institute rapid review of the gastrointestinal and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the consultative management of patients with COVID-19. Gastroenterology. 2020;159:320. [PMID: 32407808]

2. Chronic Diarrhea



- Diarrhea present for > 4 weeks.
- Before embarking on extensive workup, common causes should be excluded, including medications, chronic infections, and IBS.

► Etiology

The causes of chronic diarrhea may be grouped into the following major pathophysiologic categories: medications, osmotic diarrheas, secretory conditions, inflammatory

conditions, malabsorptive conditions, motility disorders, chronic infections, and systemic disorders (Table 15–6).

A. Medications

Numerous medications can cause diarrhea. All medications should be carefully reviewed, and discontinuation of potential culprits should be considered.

B. Osmotic Diarrheas

As stool leaves the colon, fecal osmolality is equal to the serum osmolality, ie, approximately 290 mOsm/kg. Under normal circumstances, the major osmoles are Na^+ , K^+ , Cl^- , and HCO_3^- . The stool osmolality may be estimated by multiplying the stool ($\text{Na}^+ + \text{K}^+$) \times 2. The **osmotic gap** is the difference between the *measured* osmolality of the stool (or serum) and the *estimated* stool osmolality and is normally less than 50 mOsm/kg. An increased osmotic gap (greater than 75 mOsm/kg) implies that the diarrhea is caused by ingestion or malabsorption of an osmotically active substance. The most common causes are carbohydrate malabsorption (lactose, fructose, sorbitol), laxative abuse, and malabsorption syndromes. Osmotic diarrheas resolve during fasting. Those caused by malabsorbed carbohydrates are characterized by abdominal distention, bloating, and flatulence due to increased colonic gas production.

Carbohydrate malabsorption is common and should be considered in all patients with chronic, postprandial diarrhea. Patients should be asked about their intake of dairy products (lactose), fruits and artificial sweeteners (fructose and sorbitol), processed foods and soft drinks (high-fructose corn syrup), and alcohol. The diagnosis of carbohydrate malabsorption may be established by an elimination trial for 2–3 weeks or by hydrogen breath tests.

Ingestion of magnesium- or phosphate-containing compounds (laxatives, antacids) should be considered in enigmatic chronic diarrhea. The fat substitute olestra also causes diarrhea and cramps in occasional patients.

C. Secretory Conditions

Increased intestinal secretion or decreased absorption results in a high-volume watery diarrhea with a normal osmotic gap. There is little change in stool output during the fasting state, and dehydration and electrolyte imbalance may develop. Causes include endocrine tumors (stimulating intestinal or pancreatic secretion), bile salt malabsorption (stimulating colonic secretion), and microscopic colitis. Microscopic colitis is a common cause of chronic watery diarrhea in older adults (see Inflammatory Bowel Disease, below).

D. Inflammatory Conditions

Diarrhea is present in most patients with inflammatory bowel disease (ulcerative colitis, Crohn disease). A variety of other symptoms may be present, including abdominal pain, fever, weight loss, and hematochezia.

E. Malabsorptive Conditions

The major causes of malabsorption are small mucosal intestinal diseases, intestinal resections, lymphatic

obstruction, small intestinal bacterial overgrowth, and pancreatic insufficiency. Its characteristics are weight loss, osmotic diarrhea, steatorrhea, and nutritional deficiencies. Significant diarrhea in the absence of weight loss is not likely to be due to malabsorption. The physical and laboratory abnormalities related to deficiencies of vitamins or minerals are discussed in Chapter 29.

F. Motility Disorders (Including IBS)

IBS is the most common cause of chronic diarrhea in young adults (see Irritable Bowel Syndrome, below). It should be considered in patients with lower abdominal pain and altered bowel habits who have no other evidence of serious organic disease (weight loss, nocturnal diarrhea, anemia, or gastrointestinal bleeding). Abnormal intestinal motility secondary to systemic disorders, radiation enteritis, or surgery may result in diarrhea due to rapid transit or to stasis of intestinal contents with bacterial overgrowth, resulting in malabsorption.

G. Chronic Infections

Chronic parasitic infections may cause diarrhea through a number of mechanisms. Pathogens most commonly associated with diarrhea include the protozoans *Giardia*, *Entamoeba histolytica*, and *Cyclospora* as well as the intestinal nematodes. Strongyloidiasis and capillariasis should be excluded in patients from endemic regions, especially in the presence of eosinophilia. Bacterial infections with *C difficile* and, uncommonly, *Aeromonas* and *Plesiomonas* may cause chronic diarrhea.

Immunocompromised patients are susceptible to infectious organisms that can cause acute or chronic diarrhea (see Chapter 31), including microsporidia, *Cryptosporidium*, CMV, *Cystoisospora belli* (formerly *Isospora belli*), *Cyclospora*, and *Mycobacterium avium* complex.

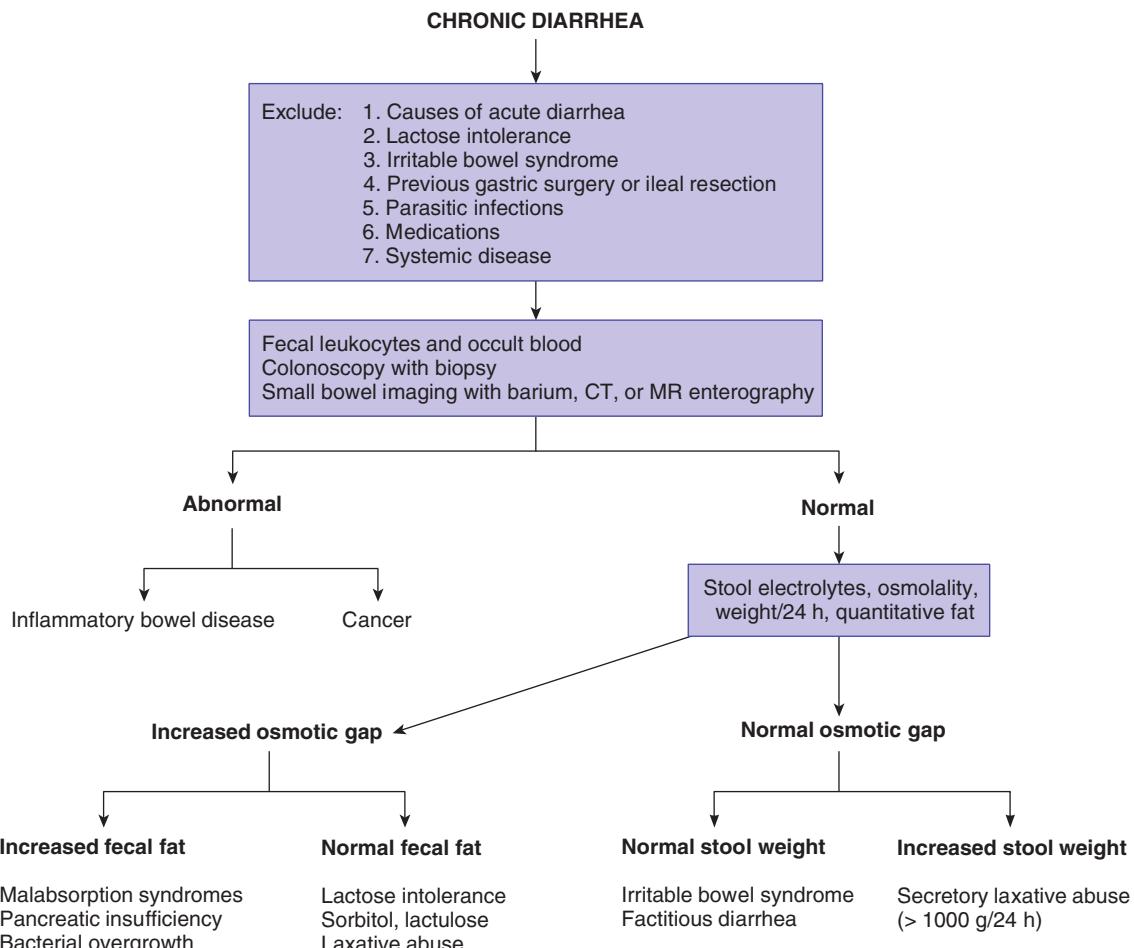
H. Systemic Conditions

Chronic systemic conditions, such as thyroid disease, diabetes, and collagen vascular disorders, may cause diarrhea through alterations in motility or intestinal absorption.

► Clinical Findings

The history and physical examination commonly suggest the underlying pathophysiology that guides the subsequent diagnostic workup (Figure 15–2). The clinician should establish whether the diarrhea is continuous or intermittent, its relationship to meals, and whether it occurs at night or during fasting. The stool appearance may suggest a malabsorption disorder (greasy or malodorous), inflammatory disorder (containing blood or pus), or a secretory process (watery). The presence of abdominal pain suggests IBS or inflammatory bowel disease. Medications, diet, and recent psychosocial stressors should be reviewed. Physical examination should assess for signs of malnutrition, dehydration, and inflammatory bowel disease.

Because chronic diarrhea is caused by so many conditions, the subsequent diagnostic approach is guided by the relative suspicion for the underlying cause, and no specific



▲ Figure 15–2. Decision diagram for diagnosis of causes of chronic diarrhea.

algorithm can be followed in all patients. Prior to embarking on an extensive evaluation, the most common causes of chronic diarrhea should be considered, including medications, IBS, and lactose intolerance. The presence of nocturnal diarrhea, weight loss, anemia, or positive results on FOBT are inconsistent with these disorders and warrant further evaluation. AIDS-associated diarrhea is discussed in Chapter 31.

A. Initial Diagnostic Tests

1. Routine laboratory tests—Complete blood count, serum electrolytes, liver chemistries, calcium, phosphorus, albumin, thyroid-stimulating hormone, vitamin A and D levels, prothrombin time with international normalized ratio (INR), erythrocyte sedimentation rate, and C-reactive protein should be obtained in most patients. Serologic testing for celiac disease with an IgA tissue transglutaminase (TG) test is recommended in the evaluation of most patients with chronic diarrhea even in the absence of signs of malabsorption. Anemia occurs in malabsorption syndromes (folate, iron deficiency, or vitamin B₁₂) as well as

inflammatory conditions. Hypoalbuminemia is present in malabsorption, protein-losing enteropathies, and inflammatory diseases. Hyponatremia and nonanion gap metabolic acidosis occur in secretory diarrheas. Increased erythrocyte sedimentation rate or C-reactive protein suggests inflammatory bowel disease.

2. Routine stool studies—Stool samples should be analyzed for ova and parasites, electrolytes (to calculate osmotic gap), qualitative staining for fat (Sudan stain), occult blood, and either leukocytes or fecal calprotectin or lactoferrin. Parasitic infections (*Giardia*, *E histolytica*, *Cryptosporidium*, and *Cyclospora*) may be diagnosed with stool multiplex PCR assays that test for a panel of pathogens within 1–5 hours, or, where PCR is unavailable, by microscopy with special stains. As discussed previously, an increased osmotic gap suggests an osmotic diarrhea or disorder of malabsorption. A positive fecal fat stain suggests a disorder of malabsorption. In patients with positive fecal fat or suspicion for chronic pancreatitis, a stool sample should be sent for measurement of pancreatic elastase, which is low with pancreatic insufficiency. The presence of

fecal leukocytes or elevated calprotectin or lactoferrin may suggest inflammatory bowel disease.

3. Endoscopic examination and mucosal biopsy—Most patients with chronic persistent diarrhea undergo colonoscopy with mucosal biopsy to exclude inflammatory bowel disease (including Crohn disease and ulcerative colitis), microscopic colitis, and colonic neoplasia. Upper endoscopy with small bowel biopsy is performed when a small intestinal malabsorptive disorder is suspected (celiac disease, Whipple disease) from abnormal laboratory studies or a positive fecal fat stain. It may also be done in patients with advanced AIDS to document *Cryptosporidium*, microsporidia, and *M avium-intracellulare* infection.

B. Further Studies

If the cause of diarrhea is still not apparent, further studies may be warranted.

1. 24-hour stool collection quantification of total weight and fat

A stool weight of less than 200–300 g/24 h excludes diarrhea and suggests a functional disorder such as IBS. A weight greater than 1000–1500 g suggests a significant secretory process, including neuroendocrine tumors. A fecal fat determination in excess of 10 g/24 h confirms a malabsorptive disorder. Fecal elastase less than 100 mcg/g may be caused by pancreatic insufficiency. (See Celiac Disease and specific tests for malabsorption, below.)

2. Other imaging studies—Calcification on a plain abdominal radiograph confirms a diagnosis of chronic pancreatitis, although abdominal CT and endoscopic ultrasonography are more sensitive for the diagnosis of chronic pancreatitis as well as pancreatic cancer. Small intestinal imaging with CT or MRI enterography is helpful in the diagnosis of Crohn disease, small bowel lymphoma, carcinoid, and jejunal diverticula. Neuroendocrine tumors may be localized using somatostatin receptor scintigraphy. Retention of less than 11% at 7 days of intravenous ⁷⁵Se-homotaurocholate on scintigraphy suggests bile salt malabsorption.

3. Laboratory tests

A. SEROLOGIC TESTS FOR NEUROENDOCRINE TUMORS

Secretory diarrheas due to neuroendocrine tumors are rare but should be considered in patients with chronic, high-volume watery diarrhea (greater than 1 L/day) with a normal osmotic gap that persists during fasting. Measurements of the secretagogues of various neuroendocrine tumors may be assayed, including serum chromogranin A (pancreatic neuroendocrine tumors), vasoactive intestinal peptide (VIP) (VIPoma), calcitonin (medullary thyroid carcinoma), gastrin (Zollinger-Ellison syndrome), and urinary 5-hydroxyindoleacetic acid (5-HIAA) (carcinoid).

B. BREATH TEST—The diagnosis of small bowel bacterial overgrowth is suggested by a noninvasive breath test (glucose or lactulose); however, a high rate of false-positive test results limits the utility of these tests. A definitive diagnosis of bacterial overgrowth is determined by aspirate of small intestinal contents for quantitative aerobic and anaerobic bacterial culture; however, this procedure is not available at most centers.

Treatment

A number of antidiarrheal agents may be used in certain patients with chronic diarrheal conditions and are listed below. Opioids are safe in most patients with chronic, stable symptoms.

Loperamide: 4 mg orally initially, then 2 mg after each loose stool (maximum: 16 mg/day).

Diphenoxylate with atropine: One tablet orally three or four times daily as needed.

Codeine and deodorized tincture of opium: Because of potential habituation, these drugs are avoided except in cases of chronic, intractable diarrhea. Codeine may be given in a dosage of 15–60 mg orally every 4 hours; tincture of opium, 0.3–1.2 mL orally every 6 hours as needed.

Clonidine: Alpha-2-adrenergic agonists inhibit intestinal electrolyte secretion. Clonidine, 0.1–0.3 mg orally twice daily, or a clonidine patch, 0.1–0.2 mg/day, may help in some patients with secretory diarrheas, diabetic diarrhea, or cryptosporidiosis.

Octreotide: This somatostatin analog stimulates intestinal fluid and electrolyte absorption and inhibits intestinal fluid secretion and the release of gastrointestinal peptides. It is given for secretory diarrheas due to neuroendocrine tumors (VIPomas, carcinoid). Effective doses range from 50 mcg to 250 mcg subcutaneously three times daily.

Bile salt binders: Cholestyramine 2–4 g or colestipol (1–2 g once to three times daily) or coleseveldam (625 mg, 1–3 tablets once or twice daily) may be useful in patients with bile salt-induced diarrhea, which may be idiopathic or secondary to intestinal resection or ileal disease.

Burgers K et al. Chronic diarrhea in adults: evaluation and differential diagnosis. Am Fam Physician. 2020;15:472. [PMID: 32293842]

Sadowski DC et al. Canadian Association of Gastroenterology clinical practice guideline on the management of bile acid diarrhea. Clin Gastroenterol Hepatol. 2020;18:24. [PMID: 31526844]

Smalley W et al. AGA clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology. 2019;157:851. [PMID: 31302098]

GASTROINTESTINAL BLEEDING

1. Acute Upper Gastrointestinal Bleeding



ESSENTIALS OF DIAGNOSIS

- ▶ Hematemesis (bright red blood or “coffee grounds”).
- ▶ Melena in most cases; hematochezia in massive upper gastrointestinal bleeds.
- ▶ Volume status to determine severity of blood loss; hematocrit is a poor early indicator of blood loss.
- ▶ Endoscopy diagnostic and may be therapeutic.

► General Considerations

There are over 250,000 hospitalizations a year in the United States for acute upper gastrointestinal bleeding. In the United States, the mortality rate for nonvariceal upper gastrointestinal bleeding has declined steadily over the past 20 years to 2.1% in 2009. Mortality is higher in patients who are older than age 60 years and in patients in whom bleeding develops during hospitalization. Patients seldom die of exsanguination but rather of complications from an underlying disease.

The most common presentation of upper gastrointestinal bleeding is hematemesis or melena. Hematemesis may be either bright red blood or brown “coffee grounds” material. Melena develops after as little as 50–100 mL of blood loss in the upper gastrointestinal tract, whereas hematochezia requires a loss of more than 1000 mL. Although hematochezia generally suggests a lower bleeding source (eg, colonic), severe upper gastrointestinal bleeding may present with hematochezia in 10% of cases.

Upper gastrointestinal bleeding is self-limited in 80% of patients; urgent medical therapy and endoscopic evaluation are obligatory in the rest. Patients with bleeding more than 48 hours prior to presentation have a low risk of recurrent bleeding.

► Etiology

Peptic ulcers account for 40% of major upper gastrointestinal bleeding with an overall mortality rate of less than 5%. In North America, the incidence of bleeding from ulcers is declining due to eradication of *H pylori* and prophylaxis with proton pump inhibitors in high-risk patients.

Portal hypertension accounts for 10–20% of upper gastrointestinal bleeding. Bleeding usually arises from esophageal varices and less commonly gastric or duodenal varices or portal hypertensive gastropathy. Approximately 25% of patients with cirrhosis have medium to large esophageal varices, of whom 30% experience acute variceal bleeding within a 2-year period. Due to improved care, the hospital mortality rate has declined over the past 20 years from 40% to 15%. Nevertheless, a mortality rate of 60–80% is expected at 1–4 years due to recurrent bleeding or other complications of chronic liver disease.

Lacerations of the gastroesophageal junction cause 5–10% of cases of upper gastrointestinal bleeding. Many patients report a history of heavy alcohol use or retching. Less than 10% have continued or recurrent bleeding.

Vascular anomalies are found throughout the gastrointestinal tract and may be the source of chronic or acute gastrointestinal bleeding. They account for 7% of cases of acute upper tract bleeding. The most common are **angioectasias** (angiodyplasias), which are 1–10 mm distorted, aberrant submucosal vessels caused by chronic, intermittent obstruction of submucosal veins. They have a bright red stellate appearance and occur throughout the gastrointestinal tract but most commonly in the right colon. **Telangiectasias** are small, cherry red lesions caused by dilation of venules that may be part of systemic conditions (hereditary hemorrhagic telangiectasia, CREST syndrome) or occur sporadically. The **Dieulafoy lesion** is an aberrant, large-caliber submucosal

artery, most commonly in the proximal stomach that causes recurrent, intermittent bleeding.

Gastric neoplasms result in 1% of upper gastrointestinal hemorrhages.

Erosive gastritis is superficial, so it is a relatively unusual cause of severe gastrointestinal bleeding (less than 5% of cases) and more commonly results in chronic blood loss. Gastric mucosal erosions are due to NSAIDs, alcohol, or severe medical or surgical illness (stress-related mucosal disease).

Severe erosive esophagitis due to chronic gastroesophageal reflux may rarely cause significant upper gastrointestinal bleeding, especially in patients who are bedbound long-term.

An aortoenteric fistula complicates 2% of abdominal aortic grafts or, rarely, can occur as the initial presentation of a previously untreated aneurysm. Unusual causes of upper gastrointestinal bleeding include hemobilia (from hepatic tumor, angioma, penetrating trauma), and pancreatic malignancy and pseudoaneurysm (hemosuccus pancreaticus).

► Initial Evaluation & Treatment

A. Stabilization

The initial step is assessment of the hemodynamic status. A systolic blood pressure lower than 100 mm Hg identifies a high-risk patient with severe acute bleeding. A heart rate over 100 beats/min with a systolic blood pressure over 100 mm Hg signifies moderate acute blood loss. A normal systolic blood pressure and heart rate suggest relatively minor hemorrhage. Postural hypotension and tachycardia are useful when present but may be due to causes other than blood loss. Because the hematocrit may take 24–72 hours to equilibrate with the extravascular fluid, it is not a reliable indicator of the severity of acute bleeding.

In patients with significant bleeding, two 18-gauge or larger intravenous lines should be started prior to further diagnostic tests. Blood is sent for complete blood count, prothrombin time with INR, serum creatinine, liver enzymes, and blood typing and screening (in anticipation of the possible need for transfusion). In patients without hemodynamic compromise or overt active bleeding, aggressive fluid repletion can be delayed until the extent of the bleeding is further clarified. Patients with evidence of hemodynamic compromise are given 0.9% saline or lactated Ringer infusion and cross-matched for 2–4 units of packed red blood cells. It is rarely necessary to administer type-specific or O-negative blood. Central venous pressure monitoring is desirable in some cases, but line placement should not interfere with rapid volume resuscitation.

Placement of a nasogastric tube is not routinely recommended in clinical guidelines but may be helpful in the initial assessment and triage of selected patients with suspected active upper tract bleeding. The aspiration of red blood or “coffee grounds” confirms an upper gastrointestinal source of bleeding, though up to 18% of patients with confirmed upper tract sources of bleeding have nonbloody aspirates—especially when bleeding originates in the duodenum. Erythromycin (250 mg) administered intravenously 30 minutes prior to upper

endoscopy promotes gastric emptying and may improve the quality of endoscopic evaluation when substantial amounts of blood or clot in the stomach is suspected. Efforts to stop or slow bleeding by gastric lavage with large volumes of fluid are of no benefit and expose the patient to an increased risk of aspiration.

B. Blood Replacement

The amount of fluid and blood products required is based on assessment of vital signs, evidence of active bleeding from nasogastric aspirate, and laboratory tests. Sufficient packed red blood cells should be given to maintain a hemoglobin of 7–9 g/dL, based on the patient's hemodynamic status, comorbidities (especially cardiovascular disease), and presence of continued bleeding. In the absence of continued bleeding, the hemoglobin should rise approximately 1 g/dL for each unit of transfused packed red cells. Transfusion of blood should not be withheld from patients with massive active bleeding regardless of the hemoglobin value. In patients with severe gastrointestinal bleeding, it is desirable to transfuse blood before the hemoglobin reaches 7 g/dL to prevent decreases below that level occurring from hemodilution with fluid resuscitation. In actively bleeding patients, platelets are transfused if the platelet count is under 50,000/mcL ($50 \times 10^9/L$) and considered if there is impaired platelet function due to aspirin or clopidogrel use (regardless of the platelet count). Uremic patients (who also have dysfunctional platelets) with active bleeding are given three doses of desmopressin (DDAVP), 0.3 mcg/kg intravenously, at 12-hour intervals. In patients with active bleeding who have been taking anticoagulation therapy, the benefits of reversal of anticoagulation (reduced bleeding and reduced need for blood products) must be weighed against the risks (thromboembolism, ischemia). In general, endoscopy may be performed safely and effective hemostasis treatment applied if the INR is less than 2.5. In patients taking warfarin, anticoagulation with active bleeding and INR greater than 2.5, either fresh frozen plasma or four factor prothrombin complex (Kcentra[®]) may be administered. In the face of massive bleeding, administration of four factor prothrombin complex concentrates is preferred (rather than fresh frozen plasma) because it is more rapid and effective at correcting the INR and requires a smaller volume. In patients receiving anticoagulation therapy with the direct thrombin inhibitor (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), restoration of normal anticoagulation usually requires 24–48 hours (presuming normal kidney and liver function). Therefore, reversal should only be considered in patients with life-threatening bleeding. Idarucizumab (an intravenous monoclonal antibody) is approved for the reversal of dabigatran, and andexanet alfa (a modified factor Xa decoy protein) is approved for the reversal of apixaban and rivaroxaban. For management of coagulation abnormalities in patients with cirrhosis and upper gastrointestinal bleeding, see Esophageal Varices.

C. Initial Triage

A preliminary assessment of risk based on several clinical factors aids in the resuscitation as well as the rational triage

of the patient. Clinical predictors of increased risk of rebleeding and death include age over 60 years, comorbid illnesses, systolic blood pressure less than 100 mm Hg, pulse greater than 100 beats/min, and bright red blood in the nasogastric aspirate or on rectal examination.

1. High risk—Patients with active bleeding manifested by hematemesis or bright red blood on nasogastric aspirate, shock, persistent hemodynamic derangement despite fluid resuscitation, serious comorbid medical illness, or evidence of advanced liver disease require admission to an intensive care unit (ICU). After adequate resuscitation, endoscopy should be performed within 12 hours in most patients but may be delayed in selected patients with serious comorbidities (eg, acute coronary syndrome) who do not have signs of continued bleeding.

2. Low to moderate risk—All other patients are admitted to a step-down unit or medical ward after appropriate stabilization for further evaluation and treatment. Patients without evidence of active bleeding undergo nonemergent endoscopy usually within 24 hours.

► Subsequent Evaluation & Treatment

Specific treatment of the various causes of upper gastrointestinal bleeding is discussed elsewhere in this chapter. The following general comments apply to most patients with bleeding.

The clinician's impression of the bleeding source is correct in only 40% of cases. Signs of chronic liver disease implicate bleeding due to portal hypertension, but a different lesion is identified in 25% of patients with cirrhosis. A history of dyspepsia, NSAID use, or peptic ulcer disease suggests peptic ulcer. Acute bleeding preceded by heavy alcohol ingestion or retching suggests a Mallory-Weiss tear, though most patients with Mallory-Weiss tears have neither.

A. Upper Endoscopy

Virtually all patients with upper tract bleeding should undergo upper endoscopy within 24 hours of arriving in the emergency department. The benefits of endoscopy in this setting are threefold.

1. To identify the source of bleeding—The appropriate acute and long-term medical therapy is determined by the cause of bleeding. Patients with portal hypertension will be treated differently from those with ulcer disease. If surgery or radiologic interventional therapy is required for uncontrolled bleeding, the source of bleeding identified at endoscopy will determine the approach.

2. To determine the risk of rebleeding and guide triage—Patients with a nonbleeding Mallory-Weiss tear, esophagitis, gastritis, and ulcers that have a clean, white base have a very low risk (less than 5%) of rebleeding. Patients with one of these findings who are younger than 60 years, without hemodynamic instability or transfusion requirement, without serious coexisting illness, and who have stable social support may be discharged from the emergency department or medical ward after endoscopy with outpatient follow-up. All others with one of these low-risk lesions

should be observed on a medical ward for 24–48 hours. Patients with ulcers that are actively bleeding or have a visible vessel or adherent clot, or who have variceal bleeding usually require at least a 3-day hospitalization with closer initial observation in an ICU or step-down unit.

3. To render endoscopic therapy—Hemostasis can be achieved in actively bleeding lesions with endoscopic modalities such as cautery, injection, or endoclips. About 90% of bleeding or nonbleeding varices can be effectively treated immediately with application of rubber bands to the varices. Similarly, 90% of bleeding ulcers, angiomas, or Mallory-Weiss tears can be controlled with either injection of epinephrine, direct cauterization of the vessel by a heater probe or multipolar electrocautery probe, or application of an endoclip. Certain nonbleeding lesions such as ulcers with visible blood vessels, and angioectasias are also treated with these therapies. Specific endoscopic therapy of varices, peptic ulcers, and Mallory-Weiss tears is dealt with elsewhere in this chapter.

B. Acute Pharmacologic Therapies

1. Acid inhibitory therapy—**Intravenous proton pump inhibitors** (esomeprazole or pantoprazole, 80 mg bolus, followed by 8 mg/h continuous infusion for 72 hours) reduce the risk of rebleeding in patients with peptic ulcers with high-risk features (active bleeding, visible vessel, or adherent clot) after endoscopic treatment. **Oral proton pump inhibitors** (omeprazole, esomeprazole, or pantoprazole 40 mg; lansoprazole or dexlansoprazole 30–60 mg) once or twice daily are sufficient for lesions at low-risk for rebleeding (eg, esophagitis, gastritis, clean-based ulcers, and Mallory-Weiss tears).

Administration of continuous intravenous proton pump inhibitor *before* endoscopy results in a decreased number of ulcers with lesions that require endoscopic therapy. It therefore is standard clinical practice at many institutions to administer either an intravenous or a high-dose oral proton pump inhibitor prior to endoscopy in patients with significant upper gastrointestinal bleeding. Based on the findings during endoscopy, the intravenous proton pump inhibitor may be continued or discontinued.

2. Octreotide—Continuous intravenous infusion of octreotide (100 mcg bolus, followed by 50–100 mcg/h) reduces splanchnic blood flow and portal blood pressures and is effective in the initial control of bleeding related to portal hypertension. It is administered promptly to all patients with active upper gastrointestinal bleeding and evidence of liver disease or portal hypertension until the source of bleeding can be determined by endoscopy. In countries where it is available, terlipressin may be preferred to octreotide for the treatment of bleeding related to portal hypertension because of its sustained reduction of portal and variceal pressures and its proven reduction in mortality.

C. Other Treatment

1. Intra-arterial embolization—Angiographic treatment is used in patients with persistent bleeding from ulcers, angiomas, or Mallory-Weiss tears who have failed endoscopic

therapy and are poor operative risks. Compared with surgical intervention for recurrent or refractory bleeding, embolization achieves equivalent clinical success rates with lower mortality.

2. Transvenous intrahepatic portosystemic shunts (TIPS)

(TIPS)—Placement of a wire stent from the hepatic vein through the liver to the portal vein provides effective decompression of the portal venous system and control of acute variceal bleeding. It is indicated in patients in whom endoscopic modalities have failed to control acute variceal bleeding.

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Stanley AJ et al. Management of acute upper gastrointestinal bleeding. BMJ. 2019;364:l536. [PMID: 30910853]

2. Acute Lower Gastrointestinal Bleeding

ESSENTIALS OF DIAGNOSIS

- ▶ Hematochezia usually present.
- ▶ Ten percent of cases of hematochezia due to upper gastrointestinal source.
- ▶ Evaluation with colonoscopy in stable patients.
- ▶ Massive active bleeding calls for evaluation with sigmoidoscopy, upper endoscopy, angiography, or nuclear bleeding scan.

► General Considerations

Lower gastrointestinal bleeding is defined as that arising below the ligament of Treitz, ie, the small intestine or colon; however, up to 95% of cases arise from the colon. The severity of lower gastrointestinal bleeding ranges from mild anorectal bleeding to massive, large-volume hematochezia. Bright red blood that drips into the bowl after a bowel movement or is mixed with solid brown stool signifies mild bleeding, usually from an anorectosigmoid source, and can be evaluated in the outpatient setting. In patients hospitalized with gastrointestinal bleeding, lower tract bleeding is one-third as common as upper gastrointestinal hemorrhage and tends to have a more benign course. Patients hospitalized with lower gastrointestinal tract bleeding are less likely to present with shock or orthostasis (less than 5%) or to require transfusions (less than 40%). Spontaneous cessation of bleeding occurs in over 75% of cases, and hospital mortality is approximately 1%.

► Etiology

The cause of these lesions depends on both the age of the patient and the severity of the bleeding. In patients under

50 years of age, the most common causes are infectious colitis, anorectal disease, and inflammatory bowel disease. In older patients, significant hematochezia is most often seen with diverticulosis, angiectasias, malignancy, or ischemia. There is an increased risk of lower gastrointestinal bleeding in patients taking aspirin, nonaspirin antiplatelet agents, and NSAIDs.

A. Diverticulosis

Hemorrhage occurs in 3–5% of all patients with diverticulosis and is the most common cause of major lower tract bleeding, accounting for over 50% of cases. Diverticular bleeding usually presents as acute, painless, large-volume maroon or bright red hematochezia in patients over age 50 years. More than 95% of cases require less than 4 units of blood transfusion. Bleeding subsides spontaneously in 80% but may recur in up to 25% of patients.

B. Angiectasias

Angiectasias (angiodyplasias) occur throughout the upper and lower intestinal tracts and cause painless bleeding ranging from melena or hematochezia to occult blood loss. They are responsible for 5% of cases of lower gastrointestinal bleeding, where they are most often seen in the cecum and ascending colon. They are flat, red lesions (2–10 mm) with ectatic peripheral vessels radiating from a central vessel, and are most common in patients over age 70 years and in those with chronic renal failure. Bleeding in younger patients more commonly arises from the small intestine.

Ectasias can be identified in up to 6% of persons over age 60 years, so the mere presence of ectasias does not prove that the lesion is the source of bleeding, since active bleeding is seldom seen.

C. Neoplasms

Benign polyps and malignant carcinomas are associated with chronic occult blood loss or intermittent anorectal hematochezia. Furthermore, they may cause up to 7% of acute lower gastrointestinal hemorrhage.

After endoscopic removal of colonic polyps, important bleeding may occur up to 2 weeks later in 0.1–1% of patients overall but in 3–10% following mucosal resection of large (greater than 2 cm) polyps. In up to one-half of cases, colonoscopy is required to treat postpolypectomy hemorrhage and minimize the need for transfusions.

D. Inflammatory Bowel Disease

Patients with inflammatory bowel disease (especially ulcerative colitis) often have diarrhea with variable amounts of hematochezia. Bleeding varies from occult blood loss to recurrent hematochezia mixed with stool. Symptoms of abdominal pain, tenesmus, and urgency are often present.

E. Anorectal Disease

Anorectal disease (hemorrhoids, fissures) usually results in small amounts of bright red blood noted on the toilet paper, streaking of the stool, or dripping into the toilet bowl; clinically significant blood loss can sometimes occur.

Hemorrhoids are the source in 10% of patients admitted with lower bleeding. Rectal ulcers may account for up to 8% of lower bleeding, usually in elderly or debilitated patients with constipation.

F. Ischemic Colitis

This condition is seen commonly in older patients, most of whom have atherosclerotic disease. Most cases occur spontaneously due to transient episodes of nonocclusive ischemia. Ischemic colitis may also occur in 5% of patients after surgery for ileo-aortic or abdominal aortic aneurysm. In younger patients, colonic ischemia may develop due to vasculitis, coagulation disorders, estrogen therapy, and long-distance running. Ischemic colitis results in hematochezia or bloody diarrhea associated with mild cramps. In most patients, the bleeding is mild and self-limited.

G. Others

Radiation-induced proctitis causes anorectal bleeding that may develop months to years after pelvic radiation. Endoscopy reveals multiple rectal telangiectasias. Acute infectious colitis (see Acute Diarrhea, above) commonly causes bloody diarrhea. Rare causes of lower tract bleeding include vasculitic ischemia, solitary rectal ulcer, NSAID-induced ulcers in the small bowel or right colon, small bowel diverticula, and colonic varices.

► Clinical Findings

A. Symptoms and Signs

The color of the stool helps distinguish upper from lower gastrointestinal bleeding, especially when observed by the clinician. Brown stools mixed or streaked with blood predict a source in the rectosigmoid or anus. Large volumes of bright red blood suggest a colonic source; maroon stools imply a lesion in the right colon or small intestine; and black stools (melena) predict a source proximal to the ligament of Treitz. Although 10% of patients admitted with self-reported hematochezia have an upper gastrointestinal source of bleeding (eg, peptic ulcer), this almost always occurs in the setting of massive hemorrhage with hemodynamic instability. Painless large-volume bleeding usually suggests diverticular bleeding. Bloody diarrhea associated with cramping abdominal pain, urgency, or tenesmus is characteristic of inflammatory bowel disease, infectious colitis, or ischemic colitis.

B. Diagnostic Tests

Important considerations in management include exclusion of an upper tract source, anoscopy and sigmoidoscopy, colonoscopy, nuclear bleeding scans and angiography, and small intestine push enteroscopy or capsule imaging.

1. Exclusion of an upper tract source—A nasogastric tube with aspiration should be considered, especially in patients with hemodynamic compromise. Aspiration of red blood or dark brown (“coffee grounds”) guaiac-positive material strongly implicates an upper gastrointestinal source of bleeding. Upper endoscopy should be performed in most

patients presenting with hematochezia and hemodynamic instability to exclude an upper gastrointestinal source before proceeding with evaluation of the lower gastrointestinal tract.

2. Anoscopy and sigmoidoscopy—In otherwise healthy patients without anemia under age 45 years with small-volume bleeding, anoscopy and sigmoidoscopy are performed to look for evidence of anorectal disease, inflammatory bowel disease, or infectious colitis. If a lesion is found, no further evaluation is needed immediately unless the bleeding persists or is recurrent. In patients over age 45 years with small-volume hematochezia, the entire colon must be evaluated with colonoscopy to exclude tumor.

3. Colonoscopy—In patients with acute, large-volume bleeding requiring hospitalization, colonoscopy is the preferred initial study in most cases. A meta-analysis of four randomized trials comparing colonoscopy within 24 hours versus elective colonoscopy found that colonoscopy within 24 hours did not reduce length of stay, rebleeding, or mortality. Thus, for patients with stable vital signs and whose lower gastrointestinal bleeding appears to have stopped (more than 75% of patients), colonoscopy can be performed electively within 24–36 hours of admission after appropriate resuscitation and bowel cleansing. For patients who are resuscitated and hemodynamically stable but have signs of continued active bleeding (less than 25% of patients), earlier colonoscopy (within 12–24 hours) can be considered after oral administration of colonic lavage solution (4–8 L of GoLyteLy, CoLYTE, or NuLyte) over 2–5 hours to clear the bowel of clots. The probable site of bleeding can be identified in 70–85% of patients, and a high-risk lesion can be identified and treated in up to 25%.

4. Nuclear bleeding scans and angiography—In patients with massive lower gastrointestinal bleeding manifested by continued hemodynamic instability and hematochezia despite resuscitative efforts and in patients in whom colonoscopic hemostasis was unsuccessful, urgent radiographic imaging is warranted. In most settings, multidetector CT angiography is preferred to technetium-labeled red blood cell scanning to detect active arterial bleeding and to help localize bleeding to the small intestine, right colon, or left colon. If scintigraphy or CT angiography demonstrates active bleeding, urgent angiography is performed in an attempt to further localize the bleeding site and make embolization therapy possible. In patients with massive lower gastrointestinal bleeding and continued hemodynamic instability, urgent angiography may be performed without first attempting scintigraphy or CT angiography.

► Treatment

Initial stabilization, blood replacement, and triage are managed in the same manner as described above in Acute Upper Gastrointestinal Bleeding. In patients with ongoing bleeding, consideration should be given to discontinuation of antiplatelet agents and anticoagulants. Compared to persons who do not take long-term low-dose aspirin, the incidence of recurrent lower gastrointestinal bleeding

within 5 years was higher in those who resumed low-dose aspirin postdischarge (18.9% vs 6.9%); however, these patients had a lower risk of serious cardiovascular events (22.8% vs 36.5%) and death (8.2% vs 26.7%).

A. Therapeutic Colonoscopy

High-risk lesions (eg, angiectasia or diverticulum, rectal ulcer with active bleeding, or a visible vessel) may be treated endoscopically with epinephrine injection, cautery (bipolar or heater probe), application of metallic endoclips or bands, or application of a hemostatic powder (TC-325). Radiation proctitis is effectively treated with applications of cautery therapy to the rectal telangiectasias, preferably with an argon plasma coagulator or radiofrequency wave ablation.

B. Intra-arterial Embolization

When a bleeding lesion is identified, angiography with selective embolization achieves immediate hemostasis in more than 95% of patients. Major complications occur in 5% (mainly ischemic colitis) and rebleeding occurs in up to 25%.

C. Surgical Treatment

Emergency surgery is rarely required with acute lower gastrointestinal bleeding due to the efficacy of colonoscopic and angiographic therapies.

Surgery may be considered in patients with recurrent diverticular hemorrhage depending on the severity of bleeding and the patient's other comorbid conditions.

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3. Suspected Small Bowel Bleeding

Bleeding from the small intestine can be overt or occult. Overt small bowel bleeding manifests as melena, maroon stools, or bright red blood per rectum. Up to 5–10% of patients admitted to hospitals with clinically overt gastrointestinal bleeding do not have a cause identified on upper endoscopy or colonoscopy and may be suspected to have a small bowel source. In up to one-fourth of cases, however, a source of bleeding has been overlooked in the upper or lower tract on prior endoscopic studies. Occult small bowel bleeding refers to bleeding that is manifested by recurrent positive FOBTs or FITs or recurrent iron deficiency anemia, or both in the absence of visible blood loss. Occult small bowel bleeding is discussed in the next section.

The likely etiology of overt small bowel bleeding depends on the age of the patient. The most common causes of small intestinal bleeding in patients younger than 40 years are neoplasms (stromal tumors, lymphomas, adenocarcinomas, carcinoids), Crohn disease, celiac disease, and Meckel diverticulum. These disorders also occur in patients over age 40; however, angioectasias and NSAID-induced ulcers are far more common.

► Evaluation of Suspected Overt Small Bowel Bleeding

The evaluation of suspected overt small bowel bleeding depends on the age and overall health status of the patient, associated symptoms, and severity of the bleeding. Before pursuing evaluation of the small intestine, upper endoscopy and colonoscopy are often repeated to ascertain that a lesion in these regions has not been overlooked. Repeat upper endoscopy should be performed with a longer instrument (usually a colonoscope) to evaluate the distal duodenum. If these studies are unrevealing and the patient is hemodynamically stable, capsule endoscopy should be performed to evaluate the small intestine. Further management depends on the capsule endoscopic findings, most commonly, angioectasias (25%), ulcers (10–25%), and neoplasms (1–10%). Multiphasic CT enterography may be considered if capsule endoscopy is unrevealing, since it is more sensitive for the detection of small bowel neoplasms and can exclude hepatic or pancreatic sources of bleeding. Laparotomy is warranted if a small bowel tumor is identified by capsule endoscopy or radiographic studies. Most other lesions identified by capsule imaging can be further evaluated with enteroscopes that use overtubes with balloons to advance the scope through most of the small intestine in a forward and retrograde direction (balloon-assisted enteroscopy). Neoplasms can be biopsied or resected, and angioectasias may be cauterized.

For active, hemodynamically significant acute bleeding, multiphasic CT angiography may be useful to identify and localize active small bowel bleeding and guide subsequent urgent angiography with embolization. A nuclear scan for Meckel diverticulum should be obtained in patients under age 30. With the advent of capsule imaging and advanced endoscopic technologies for evaluating and treating bleeding lesions in the small intestine, intraoperative enteroscopy of the small bowel is seldom required.

4. Occult Gastrointestinal Bleeding

Occult gastrointestinal bleeding refers to bleeding that is not apparent to the patient. Chronic gastrointestinal blood loss of less than 100 mL/day may cause no appreciable change in stool appearance. Thus, occult bleeding in an adult is identified by a positive FOBT, FIT, or by iron deficiency anemia in the absence of visible blood loss. FOBT or FIT may be performed in patients with gastrointestinal symptoms or as a screening test for colorectal neoplasia (see Chapter 39). From 2% to 6% of patients in screening programs have a positive FOBT or FIT.

In the United States, 2% of men and 5% of women have iron deficiency anemia (serum ferritin less than

30–45 mcg/L). In premenopausal women, iron deficiency anemia is most commonly attributable to menstrual and pregnancy-associated iron loss; however, a gastrointestinal source of chronic blood loss is present in 10%. Occult blood loss may arise from anywhere in the gastrointestinal tract. Among men and postmenopausal women, a potential gastrointestinal cause of blood loss can be identified in the colon in 15–30% and in the upper gastrointestinal tract in 35–55%; a malignancy is present in the lower gastrointestinal tract in 8.9% and upper tract in 2.0%. Iron deficiency on rare occasions is caused by malabsorption (especially celiac disease) or malnutrition. The most common causes of occult bleeding with iron deficiency are (1) neoplasms; (2) vascular abnormalities (angioectasias); (3) acid-peptic lesions (esophagitis, peptic ulcer disease, erosions in hiatal hernia); (4) infections (nematodes, especially hookworm; tuberculosis); (5) medications (especially NSAIDs or aspirin); and (6) other causes such as inflammatory bowel disease.

► Evaluation of Occult Bleeding

Asymptomatic adults with positive FOBTs or FITs that are performed for routine colorectal cancer screening should undergo colonoscopy (see Chapter 39). All symptomatic adults with positive FOBTs or FITs or iron deficiency anemia should undergo evaluation of the lower and upper gastrointestinal tract with colonoscopy and upper endoscopy, unless the anemia can be definitively ascribed to a nongastrointestinal source (eg, menstruation, blood donation, or recent surgery). Patients with iron deficiency anemia should be evaluated for possible celiac disease with either IgA anti-tissue transglutaminase or duodenal biopsy. After evaluation of the upper and lower gastrointestinal tract with upper endoscopy and colonoscopy, the origin of occult bleeding remains unexplained in 30–50% of patients. In some of these patients, a source for occult bleeding from a small intestine source is suspected.

For patients with iron deficiency anemia who have no significant findings on upper endoscopy or colonoscopy and who are without symptoms of small intestinal disease, a 2020 AGA guideline recommends an initial trial of empiric iron therapy. A sustained rise in ferritin and hemoglobin with 1–2 months of iron therapy may obviate the need for further studies.

Further investigation of the small intestine is recommended in patients who have anemia that responds poorly to empiric iron supplementation, who have signs of ongoing bleeding (fecal occult blood), or who have worrisome symptoms (abdominal pain, weight loss). Capsule endoscopy is recommended as the initial study in most patients to look for vascular ectasias and to exclude a small intestinal neoplasia or inflammatory bowel disease. If a small intestine source is identified, push enteroscopy, balloon-assisted enteroscopy, abdominal CT, angiography, or laparotomy is pursued, as indicated. When possible, antiplatelet agents (aspirin, NSAIDs, clopidogrel) should be discontinued. Patients with occult bleeding without a bleeding source identified after upper endoscopy, colonoscopy, and capsule endoscopy have a low risk of recurrent bleeding and usually can be managed with close observation.

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DISEASES OF THE PERITONEUM

ASSESSMENT OF THE PATIENT WITH ASCITES

Etiology of Ascites

The term “ascites” denotes the pathologic accumulation of fluid in the peritoneal cavity. Healthy men have little or no intraperitoneal fluid, but women normally may have up to 20 mL depending on the phase of the menstrual cycle. The causes of ascites may be classified into two broad pathophysiologic categories: that which is associated with a normal peritoneum and that which occurs due to a diseased peritoneum (Table 15–7). The most common cause of ascites is portal hypertension secondary to chronic liver disease, which accounts for over 80% of patients with ascites. The management of portal hypertensive ascites is discussed in Chapter 16. The most common causes of nonportal hypertensive ascites include infections (tuberculous peritonitis), intra-abdominal malignancy, inflammatory disorders of the peritoneum, and ductal disruptions (chylous, pancreatic, biliary).

Clinical Findings

A. Symptoms and Signs

The history usually is one of increasing abdominal girth, with the presence of abdominal pain depending on the cause. Because most ascites is secondary to chronic liver disease with portal hypertension, patients should be asked about risk factors for liver disease, especially alcohol consumption, transfusions, tattoos, injection drug use, a history of viral hepatitis or jaundice, and birth in an area endemic for hepatitis. A history of cancer or marked weight loss arouses suspicion of malignant ascites. Fevers may suggest infected peritoneal fluid, including bacterial peritonitis (spontaneous or secondary). Patients with chronic liver disease and ascites are at greatest risk for developing spontaneous bacterial peritonitis. In immigrants, immunocompromised hosts, or severely malnourished alcoholics, tuberculous peritonitis should be considered.

Physical examination should emphasize signs of portal hypertension and chronic liver disease. Elevated jugular venous pressure may suggest right-sided heart failure or constrictive pericarditis. A large tender liver is characteristic of acute alcoholic hepatitis or Budd-Chiari syndrome (thrombosis of the hepatic veins). The presence of large abdominal wall veins with cephalad flow also suggests

Table 15–7. Causes of ascites.

Normal Peritoneum
Portal hypertension (SAAG ≥ 1.1 g/dL)
1. Hepatic congestion¹
Heart failure
Constrictive pericarditis
Tricuspid insufficiency
Budd-Chiari syndrome
Veno-occlusive disease
2. Liver disease²
Cirrhosis
Alcoholic hepatitis
Fulminant hepatic failure
Massive hepatic metastases
Hepatic fibrosis
Acute fatty liver of pregnancy
3. Portal vein occlusion
4. Miscellaneous
Myxedema
Hypoalbuminemia (SAAG < 1.1 g/dL)
Nephrotic syndrome
Protein-losing enteropathy
Severe malnutrition with anasarca
Miscellaneous conditions (SAAG < 1.1 g/dL)
Chylous ascites
Pancreatic ascites
Bile ascites
Nephrogenic ascites
Urine ascites
Ovarian disease
Diseased peritoneum (SAAG < 1.1 g/dL)²
Infections
Bacterial peritonitis
Tuberculous peritonitis
Fungal peritonitis
HIV-associated peritonitis
Malignant conditions
Peritoneal carcinomatosis
Primary mesothelioma
Pseudomyxoma peritonei
Massive hepatic metastases
Hepatocellular carcinoma
Other conditions
Familial Mediterranean fever
Vasculitis
Granulomatous peritonitis
Eosinophilic peritonitis

¹Hepatic congestion is usually associated with SAAG ≥ 1.1 g/dL and ascitic fluid total protein > 2.5 g/dL.

²There may be cases of “mixed ascites” in which portal hypertensive ascites is complicated by a secondary process such as infection. In these cases, the SAAG is ≥ 1.1 g/dL.

SAAG, serum-ascites albumin gradient = serum albumin minus ascitic fluid albumin.

portal hypertension; inferiorly directed flow implies hepatic vein obstruction. Signs of chronic liver disease include palmar erythema, cutaneous spider angiomas, gynecomastia, and muscle wasting. Asterixis secondary to hepatic encephalopathy may be present. Anasarca results

from cardiac failure or nephrotic syndrome with hypoalbuminemia. Finally, firm lymph nodes in the left supraclavicular region or umbilicus may suggest intra-abdominal malignancy.

The physical examination is relatively insensitive for detecting ascitic fluid. In general, patients must have at least 1500 mL of fluid to be detected reliably by this method. Even the experienced clinician may find it difficult to distinguish between obesity and small-volume ascites. Abdominal ultrasound establishes the presence of fluid.

B. Laboratory Testing

1. Abdominal paracentesis—Abdominal paracentesis is performed as part of the diagnostic evaluation in all patients with new onset of ascites to help determine the cause. It also is recommended for patients admitted to the hospital with cirrhosis and ascites (in whom the prevalence of bacterial peritonitis is 10–20%) and when patients with known ascites deteriorate clinically (development of fever, abdominal pain, rapid worsening of kidney function, or worsened hepatic encephalopathy) to exclude bacterial peritonitis.

A. INSPECTION—Cloudy fluid suggests infection. Milky fluid is seen with chylous ascites due to high triglyceride levels. Bloody fluid is most commonly attributable to a traumatic paracentesis, but up to 20% of cases of malignant ascites are bloody.

B. ROUTINE STUDIES

(1) Cell count—A white blood cell count with differential is the most important test. Normal ascitic fluid contains less than 500 leukocytes/mcL ($0.5 \times 10^9/L$) and less than 250 polymorphonuclear neutrophils (PMNs)/mcL. Any inflammatory condition can cause an elevated ascitic white blood cell count. A PMN count of greater than 250/mcL ($0.25 \times 10^9/L$) (neutrocytic ascites) with a PMN percentage of more than 75% of all white cells is highly suggestive of bacterial peritonitis, either spontaneous primary peritonitis or secondary peritonitis (ie, caused by an intra-abdominal source of infection, such as a perforated viscus or appendicitis). An elevated white count with a predominance of lymphocytes arouses suspicion of tuberculosis or peritoneal carcinomatosis.

(2) Albumin and total protein—The serum-ascites albumin gradient (SAAG) is the best single test for the classification of ascites into portal hypertensive and nonportal hypertensive causes (Table 15–7). Calculated by subtracting the ascitic fluid albumin from the serum albumin, the gradient correlates directly with the portal pressure. An SAAG of 1.1 g/dL or more suggests underlying portal hypertension, while gradients less than 1.1 g/dL implicate nonportal hypertensive causes.

The accuracy of the SAAG exceeds 95% in classifying ascites. It should be recognized, however, that approximately 4% of patients have “mixed ascites,” ie, underlying cirrhosis with portal hypertension complicated by a second cause for ascites formation (such as malignancy or tuberculosis). Thus, a high SAAG is indicative of portal hypertension but does not exclude concomitant malignancy.

The ascitic fluid total protein provides some additional clues to the cause. An elevated SAAG and a high protein level (greater than 2.5 g/dL) are seen in most cases of hepatic congestion secondary to cardiac disease or Budd-Chiari syndrome. However, an increased ascitic fluid protein is also found in up to 20% of cases of uncomplicated cirrhosis. Two-thirds of patients with malignant ascites have a total protein level more than 2.5 g/dL.

(3) Culture and Gram stain—The best technique consists of the inoculation of aerobic and anaerobic blood culture bottles with 5–10 mL of ascitic fluid at the patient's bedside, which increases the sensitivity for detecting bacterial peritonitis to over 85% in patients with neutrocytic ascites (greater than 250 PMNs/mcL [$0.25 \times 10^9/L$]), compared with approximately 50% sensitivity by conventional agar plate or broth cultures.

C. OPTIONAL STUDIES—Other laboratory tests are of utility in some specific clinical situations. Glucose and lactate dehydrogenase (LD) may be helpful in distinguishing spontaneous from secondary bacterial peritonitis. An elevated amylase may suggest pancreatic ascites or a perforation of the gastrointestinal tract with leakage of pancreatic secretions into the ascitic fluid. Perforation of the biliary tree is suspected with an ascitic bilirubin concentration that is greater than the serum bilirubin. An elevated ascitic creatinine suggests leakage of urine from the bladder or ureters. Ascitic fluid cytologic examination is ordered if peritoneal carcinomatosis is suspected. Adenosine deaminase may be useful for the diagnosis of tuberculous peritonitis.

C. Imaging

Abdominal ultrasound is useful in confirming the presence of ascites and in the guidance of paracentesis. Both ultrasound and CT imaging are useful in distinguishing between causes of portal and nonportal hypertensive ascites. Doppler ultrasound and CT can detect Budd-Chiari syndrome. In patients with nonportal hypertensive ascites, these studies are useful in detecting lymphadenopathy and masses of the mesentery and of solid organs such as the liver, ovaries, and pancreas. Furthermore, they permit directed percutaneous needle biopsies of these lesions. Ultrasound and CT are poor procedures for the detection of peritoneal carcinomatosis; the role of positron emission tomography (PET) imaging is unclear.

D. Laparoscopy

Laparoscopy is an important test in the evaluation of some patients with nonportal hypertensive ascites (low SAAG) or mixed ascites. It permits direct visualization and biopsy of the peritoneum, liver, and some intra-abdominal lymph nodes. Cases of suspected peritoneal tuberculosis or suspected malignancy with nondiagnostic CT imaging and ascitic fluid cytology are best evaluated by this method.

SPONTANEOUS BACTERIAL PERITONITIS



ESSENTIALS OF DIAGNOSIS

- ▶ A history of chronic liver disease and ascites.
- ▶ Fever and abdominal pain.
- ▶ Peritoneal signs uncommonly encountered on examination.
- ▶ Ascitic fluid neutrophil count > 250 white blood cells/mcL ($0.25 \times 10^9/L$).

► General Considerations

“Spontaneous” bacterial infection of ascitic fluid occurs in the absence of an apparent intra-abdominal source of infection. It is seen with few exceptions in patients with ascites caused by chronic liver disease. Translocation of enteric bacteria across the gut wall or mesenteric lymphatics leads to seeding of the ascitic fluid, as may bacteremia from other sites. Approximately 20–30% of cirrhotic patients with ascites develop spontaneous peritonitis; however, the incidence is greater than 40% in patients with ascitic fluid total protein less than 1 g/dL, probably due to decreased ascitic fluid opsonic activity.

Virtually all cases of spontaneous bacterial peritonitis are caused by a monomicrobial infection. The most common pathogens are enteric gram-negative bacteria (*E coli*, *Klebsiella pneumoniae*) or gram-positive bacteria (*Streptococcus pneumoniae*, viridans streptococci, *Enterococcus* species). Anaerobic bacteria are not associated with spontaneous bacterial peritonitis.

► Clinical Findings

A. Symptoms and Signs

Eighty to 90 percent of patients with spontaneous bacterial peritonitis are symptomatic; in many cases the presentation is subtle. Spontaneous bacterial peritonitis may be present in 10–20% of patients hospitalized with chronic liver disease, sometimes in the absence of any suggestive symptoms or signs.

The most common symptoms are fever and abdominal pain, present in two-thirds of patients. Spontaneous bacterial peritonitis may also present with a change in mental status due to exacerbation or precipitation of hepatic encephalopathy, or sudden worsening of kidney function. Physical examination typically demonstrates signs of chronic liver disease with ascites. Abdominal tenderness is present in less than 50% of patients, and its presence suggests other processes.

B. Laboratory Findings

The most important diagnostic test is abdominal paracentesis. Ascitic fluid should be sent for cell count with differential, and blood culture bottles should be inoculated at the bedside; Gram stain and reagent strips are insensitive.

In the proper clinical setting, an ascitic fluid PMN count of greater than 250 cells/mcL (neutrocytic ascites) is presumptive evidence of bacterial peritonitis. The percentage of PMNs is greater than 50–70% of the ascitic fluid white blood cells and commonly approximates 100%. Patients with neutrocytic ascites are presumed to be infected and should be started—regardless of symptoms—on antibiotics. Although 10–30% of patients with neutrocytic ascites have negative ascitic bacterial cultures (“culture-negative neutrocytic ascites”), it is presumed that these patients have bacterial peritonitis and should be treated empirically. Occasionally, a positive blood culture identifies the organism when ascitic fluid is sterile.

► Differential Diagnosis

Spontaneous bacterial peritonitis must be distinguished from secondary bacterial peritonitis, in which ascitic fluid has become secondarily infected by an intra-abdominal infection. Even in the presence of perforation, clinical symptoms and signs of peritonitis may be lacking owing to the separation of the visceral and parietal peritoneum by the ascitic fluid. Causes of secondary bacterial peritonitis include appendicitis, diverticulitis, perforated peptic ulcer, and perforated gallbladder. Secondary bacterial infection accounts for 3% of cases of infected ascitic fluid.

Ascitic fluid total protein, LD, and glucose are useful in distinguishing spontaneous bacterial peritonitis from secondary infection. Up to two-thirds of patients with secondary bacterial peritonitis have at least two of the following: decreased glucose level (less than 50 mg/dL), an elevated LD level (greater than serum), and total protein greater than 1 g/dL. Ascitic neutrophil counts greater than 10,000/mcL ($10 \times 10^9/L$) also are suspicious; however, most patients with secondary peritonitis have neutrophil counts within the range of spontaneous peritonitis. The presence of multiple organisms on ascitic fluid Gram stain or culture is diagnostic of secondary peritonitis.

If secondary bacterial peritonitis is suspected, abdominal CT imaging of the upper and lower gastrointestinal tracts should be obtained to look for evidence of an intra-abdominal source of infection. If these studies are negative and secondary peritonitis still is suspected, repeat paracentesis should be performed after 48 hours of antibiotic therapy to confirm that the PMN count is decreasing. Secondary bacterial peritonitis should be suspected in patients in whom the PMN count is not below the pretreatment value at 48 hours.

Neutrocytic ascites may also be seen in some patients with peritoneal carcinomatosis, pancreatic ascites, or tuberculous ascites. In these circumstances, however, PMNs account for less than 50% of the ascitic white blood cells.

► Prevention

Up to 70% of patients who survive an episode of spontaneous bacterial peritonitis will have another episode within 1 year. Oral once-daily prophylactic therapy—with ciprofloxacin, 500 mg, trimethoprim-sulfamethoxazole, one double-strength tablet, or norfloxacin, 400 mg (no longer available in the United States)—has been shown to reduce

the rate of recurrent infections to less than 20%. Prophylaxis should be considered also in patients who have not had prior bacterial peritonitis but are at increased risk for infection due to low-protein ascites (total ascitic protein less than 1.5 g/dL) with impaired kidney function (serum creatinine 1.2 g/dL or higher) or decompensated cirrhosis (Child-Pugh class C). When used in appropriately selected high-risk patients, prophylactic antibiotics are associated with a lower risk spontaneous bacterial peritonitis, hepatorenal syndrome, and mortality.

Treatment

Empiric therapy for spontaneous bacterial peritonitis should be initiated with a third-generation cephalosporin (such as cefotaxime, 2 g intravenously every 8–12 hours, or ceftriaxone, 1–2 g intravenously every 24 hours) or a combination beta-lactam/beta-lactamase agent (such as ampicillin/sulbactam, 2 g/1 g intravenously every 6 hours). Because of a high risk of nephrotoxicity in patients with chronic liver disease, aminoglycosides should not be used. Although the optimal duration of therapy is unknown, an empiric course of 5–10 days is recommended, or treatment until the ascites fluid PMN count decreases to less than 250 cells/mcL. For most infections, 5 days is sufficient; however, infections caused by more serious, virulent pathogens (*S aureus*, *viridans streptococci*, *Pseudomonas*, or *Enterobacteriaceae*) warrant 10 days of treatment. Patients without significant clinical improvement after 5 days should undergo repeat paracentesis to assess treatment efficacy. If the ascitic neutrophil count has not decreased by 25%, antibiotic coverage should be adjusted (guided by culture and sensitivity results, if available) and secondary causes of peritonitis excluded. If the ascitic PMN count has decreased but remains more than 250 cells/mcL, antibiotics should be continued for an additional 2–3 days before paracentesis is repeated. Patients with suspected secondary bacterial peritonitis should be given broad-spectrum coverage for enteric aerobic and anaerobic flora with a third-generation cephalosporin and metronidazole, pending identification and definitive (usually surgical) treatment of the cause.

Kidney injury develops in up to 40% of patients and is a major cause of death. Intravenous albumin increases effective arterial circulating volume and renal perfusion, decreasing both kidney injury and mortality. Intravenous albumin, 1.5 g/kg on day 1 and 1 g/kg on day 3, should be administered to patients at high risk for hepatorenal failure (ie, patients with baseline creatinine greater than 1 mg/dL, blood urea nitrogen [BUN] greater than 30 mg/dL, or bilirubin greater than 4 mg/dL). Nonselective beta-blockers increase the risk of hepatorenal syndrome in patients with bacterial peritonitis. They should be discontinued permanently due to their adverse impact on cardiac output and renal perfusion in advanced cirrhosis, both of which are associated with decreased long-term survival.

Prognosis

The mortality rate of spontaneous bacterial peritonitis is 25%. However, if the disease is recognized and treated early, the mortality rate is less than 10%. Since the majority of patients

have underlying severe liver disease, many may die of liver failure, hepatorenal syndrome, or bleeding complications of portal hypertension. The most effective treatment for recurrent spontaneous bacterial peritonitis is liver transplantation.

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MALIGNANT ASCITES

Two-thirds of cases of malignant ascites are caused by peritoneal carcinomatosis. The most common tumors causing carcinomatosis are primary adenocarcinomas of the ovary, uterus, pancreas, stomach, colon, lung, or breast. The remaining one-third is due to lymphatic obstruction or portal hypertension due to hepatocellular carcinoma or diffuse hepatic metastases. Patients present with nonspecific abdominal discomfort and weight loss associated with increased abdominal girth. Nausea or vomiting may be caused by partial or complete intestinal obstruction. Abdominal CT may be useful to demonstrate the primary malignancy or hepatic metastases but seldom confirms the diagnosis of peritoneal carcinomatosis. In patients with carcinomatosis, paracentesis demonstrates a low serum ascites-albumin gradient (less than 1.1 mg/dL), an increased total protein (greater than 2.5 g/dL), and an elevated white cell count (often both neutrophils and mononuclear cells) but with a lymphocyte predominance. Cytology is positive in over 95%, but laparoscopy may be required in patients with negative cytology to confirm the diagnosis and to exclude tuberculous peritonitis, with which it may be confused. Malignant ascites attributable to portal hypertension usually is associated with an increased serum ascites-albumin gradient (greater than 1.1 g/dL), a variable total protein, and negative ascitic cytology. Ascites caused by peritoneal carcinomatosis does not respond to diuretics.

Patients may be treated with periodic large-volume paracentesis for symptomatic relief. Indwelling catheters can be left in place for patients approaching the end of life who require periodic paracentesis for symptomatic relief. Intraperitoneal chemotherapy is sometimes used to shrink the tumor, but the overall prognosis is extremely poor, with only 10% survival at 6 months. Ovarian cancers represent an exception to this rule. With newer treatments consisting of surgical debulking and intraperitoneal chemotherapy, long-term survival from ovarian cancer is possible.

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FAMILIAL MEDITERRANEAN FEVER

This is a rare autosomal recessive disorder of unknown pathogenesis that almost exclusively affects people of Mediterranean ancestry, especially Sephardic Jews, Armenians, Turks, and Arabs. Patients lack a protease in serosal fluids that normally inactivates interleukin-8 and the chemotactic complement factor 5A. Symptoms present in most patients before the age of 20 years. It is characterized by episodic bouts of acute peritonitis that may be associated with serositis involving the joints and pleura. Peritoneal attacks are marked by the sudden onset of fever, severe abdominal pain, and abdominal tenderness with guarding or rebound tenderness. If left untreated, attacks resolve within 24–48 hours. Because symptoms resemble those of surgical peritonitis, patients may undergo unnecessary exploratory laparotomy. Colchicine, 0.6 mg orally two or three times daily, has been shown to decrease the frequency and severity of attacks.

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MESOTHELIOMA

(See Chapter 39.)

DISEASES OF THE ESOPHAGUS

(See Chapter 39 for Esophageal Cancer.)

Symptoms

Heartburn, dysphagia, and odynophagia almost always indicate a primary esophageal disorder.

A. Heartburn

Heartburn (pyrosis) is the feeling of substernal burning, often radiating to the neck. Most commonly caused by the reflux of acidic (or, rarely, alkaline) material into the esophagus, heartburn is highly suggestive of GERD.

B. Dysphagia

Dysphagia is defined as difficulty swallowing food or liquid due to the sensation of it sticking in the throat or chest, with a discomfort, or a choking sensation. In a 2020 survey of US adults, 15% of adults reported recent dysphagia that required compensatory maneuvers (avoiding certain foods or cutting into smaller pieces; eating more slowly; drinking liquids). Up to one-half of these adults previously had sought evaluation for their symptoms. Difficulties in swallowing may arise from problems in transferring the food bolus from the oropharynx to the upper esophagus (oropharyngeal dysphagia) or from impaired transport of the bolus through the body of the esophagus (esophageal dysphagia). The history usually suggests the correct diagnosis.

Table 15–8. Causes of oropharyngeal dysphagia.

Neurologic disorders

Brainstem cerebrovascular accident, mass lesion
 Amyotrophic lateral sclerosis, multiple sclerosis, pseudobulbar palsy, post-polio syndrome, Guillain-Barré syndrome
 Parkinson disease, Huntington disease, dementia
 Tardive dyskinesia

Muscular and rheumatologic disorders

Myopathies, polymyositis
 Oculopharyngeal dystrophy
 Sjögren syndrome

Metabolic disorders

Thyrototoxicosis, amyloidosis, Cushing disease, Wilson disease
 Medication side effects: anticholinergics, phenothiazines

Infectious diseases

Polio, diphtheria, botulism, Lyme disease, syphilis, mucositis (*Candida*, herpes)

Structural disorders

Zenker diverticulum
 Cervical osteophytes, cricopharyngeal bar, proximal esophageal webs
 Oropharyngeal tumors
 Postsurgical or radiation changes
 Pill-induced injury

Motility disorders

Upper esophageal sphincter dysfunction

1. Oropharyngeal dysphagia—The oropharyngeal phase of swallowing is a complex process requiring elevation of the tongue, closure of the nasopharynx, relaxation of the upper esophageal sphincter, closure of the airway, and pharyngeal peristalsis. A variety of mechanical and neuromuscular conditions can disrupt this process (Table 15–8). Problems with the oral phase of swallowing cause drooling or spillage of food from the mouth, inability to chew or initiate swallowing, or dry mouth. Pharyngeal dysphagia is characterized by an immediate sense of the bolus catching in the neck, the need to swallow repeatedly to clear food from the pharynx, or coughing or choking during meals. There may be associated dysphonia, dysarthria, or other neurologic symptoms.

2. Esophageal dysphagia—Esophageal dysphagia may be caused by **mechanical obstructions** of the esophagus or by **motility disorders** (Table 15–9). Patients with **mechanical obstruction** experience dysphagia, primarily for solids. This is recurrent, predictable, and, if the lesion progresses, will worsen as the lumen narrows. Patients with **motility disorders** have dysphagia for both solids and liquids. It is episodic, unpredictable, and can be progressive.

C. Odynophagia

Odynophagia is sharp substernal pain on swallowing that may limit oral intake. It usually reflects severe erosive disease. It is most commonly associated with infectious esophagitis due to *Candida*, herpesviruses, or CMV, especially in immunocompromised patients. It may also be caused by corrosive injury due to caustic ingestions and by pill-induced ulcers.

Table 15–9. Causes of esophageal dysphagia.

Cause	Clues
Mechanical obstruction	Solid foods worse than liquids
Schatzki ring	Intermittent dysphagia; not progressive
Peptic stricture	Chronic heartburn; progressive dysphagia
Esophageal cancer	Progressive dysphagia; age over 50 years
Eosinophilic esophagitis	Young adults; small-caliber lumen, proximal stricture, corrugated rings, or white papules
Motility disorder	Solid and liquid foods
Achalasia	Progressive dysphagia
Diffuse esophageal spasm	Intermittent; not progressive; may have chest pain
Systemic sclerosis (scleroderma)	Chronic heartburn; Raynaud phenomenon
Ineffective esophageal motility	Intermittent; not progressive; commonly associated with GERD

► Diagnostic Studies

A. Upper Endoscopy

Endoscopy is the study of choice for evaluating persistent heartburn, dysphagia, odynophagia, and structural abnormalities detected on barium esophagography. In addition to direct visualization, it allows biopsy of mucosal abnormalities and of normal mucosa (to evaluate for eosinophilic esophagitis) as well as dilation of strictures.

B. Videosophagography

Oropharyngeal dysphagia is best evaluated with rapid-sequence videosophagography.

C. Barium Esophagography

Patients with esophageal dysphagia often are evaluated first with a radiographic barium study to differentiate between mechanical lesions and motility disorders, providing important information about the latter in particular. In patients with esophageal dysphagia and a suspected motility disorder, barium esophagoscopy should be obtained first. In patients in whom there is a high suspicion of a mechanical lesion, many clinicians will proceed first to endoscopic evaluation because it better identifies mucosal lesions (eg, erosions) and permits mucosal biopsy and dilation. However, barium study is more sensitive for detecting subtle esophageal narrowing due to rings, achalasia, and proximal esophageal lesions.

D. Esophageal Manometry

Esophageal motility may be assessed using manometric techniques. High-resolution manometry with multiple, closely spaced sensors has replaced conventional

manometry in most centers. Manometry is indicated (1) to determine the location of the LES to allow precise placement of a conventional electrode pH probe; (2) to establish the etiology of dysphagia in patients in whom a mechanical obstruction cannot be found, especially if a diagnosis of achalasia is suspected by endoscopy or barium study; and (3) for the preoperative assessment of patients being considered for antireflux surgery to exclude an alternative diagnosis (eg, achalasia) or possibly to assess peristaltic function in the esophageal body.

E. Esophageal pH Recording and Impedance Testing

The pH within the esophageal lumen may be monitored continuously for 24–48 hours. There are two kinds of systems in use: catheter-based and wireless. Traditional systems use a long transnasal catheter that is connected directly to the recording device. With wireless systems, a capsule is attached directly to the esophageal mucosa under endoscopic visualization and data are transmitted by radio-telemetry to the recording device. The recording provides information about the amount of esophageal acid reflux and the temporal correlations between symptoms and reflux.

Esophageal pH monitoring devices provide information about the amount of esophageal acid reflux but not nonacid reflux. Techniques using combined pH and multi-channel intraluminal impedance allow assessment of acid and nonacid liquid reflux. They may be useful in evaluation of patients with atypical reflux symptoms or persistent symptoms despite therapy with proton pump inhibitors to diagnose hypersensitivity, functional symptoms, and symptoms caused by nonacid reflux.

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GASTROESOPHAGEAL REFLUX DISEASE

ESSENTIALS OF DIAGNOSIS

- ▶ Heartburn; may be exacerbated by meals, bending, or recumbency.
- ▶ Typical uncomplicated cases do not require diagnostic studies.
- ▶ Endoscopy demonstrates abnormalities in one-third of patients.

► General Considerations

GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms or complications. In a 2020 survey of US adults, 31% reported

GERD symptoms within the prior week. The two most common symptoms are heartburn and regurgitation. However, other symptoms of GERD include dyspepsia, dysphagia, belching, chest pain, cough, and hoarseness. Although most patients have mild disease, esophageal mucosal damage (reflux esophagitis) develops in up to one-third and more serious complications develop in a few others. Several factors may contribute to GERD.

A. Dysfunction of the Gastroesophageal Junction

The antireflux barrier at the gastroesophageal junction depends on LES pressure, the intra-abdominal location of the sphincter (resulting in a “flap valve” caused by angulation of the esophageal-gastric junction), and the extrinsic compression of the sphincter by the crural diaphragm. In most patients with GERD, baseline LES pressures are normal (10–35 mm Hg). Most reflux episodes occur during transient relaxations of the LES that are triggered by gastric distention by a vagovagal reflex. A subset of patients with GERD have an incompetent (less than 10 mm Hg) LES that results in increased acid reflux, especially when supine or when intra-abdominal pressures are increased by lifting or bending. A hypotensive sphincter is present in up to 50% of patients with severe erosive GERD.

Hiatal hernias are found in one-fourth of patients with nonerosive GERD, three-fourths of patients with severe erosive esophagitis, and over 90% of patients with Barrett esophagus. They are caused by movement of the LES above the diaphragm, resulting in dysfunction of the gastroesophageal junction reflux barrier. Hiatal hernias are common and may cause no symptoms; however, in patients with gastroesophageal reflux, they are associated with higher amounts of acid reflux and delayed esophageal acid clearance, leading to more severe esophagitis and Barrett esophagus. Increased reflux episodes occur during normal swallowing-induced relaxation, transient LES relaxations, and straining due to reflux of acid from the hiatal hernia sac into the esophagus.

Truncal obesity may contribute to GERD, presumably due to an increased intra-abdominal pressure, which contributes to dysfunction of the gastroesophageal junction and increased likelihood of hiatal hernia.

B. Irritant Effects of Refluxate

Esophageal mucosal damage is related to the potency of the refluxate and the amount of time it is in contact with the mucosa. Acidic gastric fluid (pH less than 4.0) is extremely caustic to the esophageal mucosa and is the major injurious agent in the majority of cases. In some patients, reflux of bile or alkaline pancreatic secretions may be contributory.

C. Abnormal Esophageal Clearance

Acid refluxate normally is cleared and neutralized by esophageal peristalsis and salivary bicarbonate. Patients with severe GERD may have diminished clearance due to hypotensive peristaltic contractions (less than 30 mm Hg) or intermittent failed peristalsis after swallowing. Certain medical conditions such as systemic sclerosis (scleroderma) are associated with diminished peristalsis. Sjögren syndrome,

anticholinergic medications, and oral radiation therapy may exacerbate GERD due to impaired salivation.

D. Delayed Gastric Emptying

Impaired gastric emptying due to gastroparesis or partial gastric outlet obstruction potentiates GERD.

► Clinical Findings

A. Symptoms and Signs

The typical symptom is heartburn. This most often occurs 30–60 minutes after meals and upon reclining. Patients often report relief from taking antacids or baking soda. When this symptom is dominant, the diagnosis is established with a high degree of reliability. Many patients, however, have less specific dyspeptic symptoms with or without heartburn. Overall, a clinical diagnosis of gastroesophageal reflux has a sensitivity and specificity of only 65%. Severity is not correlated with the degree of tissue damage. In fact, some patients with severe esophagitis are only mildly symptomatic. Patients may complain of regurgitation—the spontaneous reflux of sour or bitter gastric contents into the mouth. Dysphagia occurs in one-third of patients and may be due to erosive esophagitis, abnormal esophageal peristalsis, or the development of an esophageal stricture.

“Atypical” or “extraesophageal” manifestations of gastroesophageal disease may occur, including asthma, chronic cough, chronic laryngitis, sore throat, noncardiac chest pain, and sleep disturbances. In the absence of heartburn or regurgitation, atypical symptoms are unlikely to be related to gastroesophageal reflux.

Physical examination and laboratory data are normal in uncomplicated disease.

B. Special Examinations

Initial diagnostic studies are not warranted for patients with typical GERD symptoms suggesting uncomplicated reflux disease. Patients with typical symptoms of heartburn and regurgitation should be treated empirically with a twice-daily H₂-receptor antagonist or a once-daily proton pump inhibitor for 4–8 weeks. Further investigation is required in patients with symptoms that persist despite empiric acid inhibitory therapy to identify complications of reflux disease and to diagnose other conditions, particularly in patients with “alarm features” (troublesome dysphagia, odynophagia, weight loss, iron deficiency anemia).

1. Upper endoscopy—Upper endoscopy is excellent for documenting the type and extent of tissue damage in gastroesophageal reflux; for detecting other gastroesophageal lesions that may mimic GERD; and for detecting GERD complications, including esophageal stricture, Barrett metaplasia, and esophageal adenocarcinoma. In the absence of prior antisecretory therapy, up to one-third of patients with GERD have visible mucosal damage (known as reflux esophagitis), characterized by single or multiple erosions or ulcers in the distal esophagus at the squamocolumnar junction. In patients treated with a proton pump inhibitor prior to endoscopy, preexisting reflux esophagitis

may be partially or completely healed. The Los Angeles (LA) classification grades reflux esophagitis on a scale of A (one or more isolated mucosal breaks 5 mm or less that do not extend between the tops of two mucosal folds) to D (one or more mucosal breaks that involve at least 75% of the esophageal circumference).

2. Barium esophagography—This study should not be performed to diagnose GERD. In patients with severe dysphagia, it is sometimes obtained prior to endoscopy to identify a stricture.

3. Esophageal pH or combined esophageal pH-impedance testing—Esophageal pH monitoring measures the amount of esophageal acid reflux, whereas combined pH-impedance testing measures both acidic and nonacidic reflux. Both tests may also be useful to establish whether there is a temporal relationship between reflux events and symptoms. They are the most accurate studies for documenting gastroesophageal reflux but are unnecessary in most patients who have typical symptoms and satisfactory response to empiric antisecretory therapy. They are indicated in patients with typical symptoms who have unsatisfactory response to empiric therapy, patients with atypical or extraesophageal symptoms, and patients who are being considered for antireflux surgery.

Differential Diagnosis

Symptoms of GERD may be similar to those of other diseases such as angina pectoris, eosinophilic esophagitis, esophageal motility disorders, dyspepsia, peptic ulcer, or functional disorders. Reflux erosive esophagitis may be confused with pill-induced damage, eosinophilic esophagitis, or infections (CMV, herpes, *Candida*).

Complications

A. Barrett Esophagus

This is a condition in which the squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium containing goblet and columnar cells (specialized intestinal metaplasia). Present in 1.5% of the general population and 7–10% of patients with chronic reflux, Barrett esophagus is believed to arise from chronic reflux-induced injury to the esophageal squamous epithelium; however, it is also increased in patients with truncal obesity independent of GERD. Barrett esophagus is suspected at endoscopy from the presence of orange, gastric type epithelium that extends upward more than 1 cm from the gastroesophageal junction into the distal tubular esophagus in a tongue-like or circumferential fashion. Biopsies obtained at endoscopy confirm the diagnosis. Three types of columnar epithelium may be identified: gastric cardiac, gastric fundic, and specialized intestinal metaplasia. There is agreement that the latter carries an increased risk of dysplasia; however, some authorities believe that gastric cardiac mucosa also raises risk.

Barrett esophagus does not provoke specific symptoms but gastroesophageal reflux does. Most patients have a long history of reflux symptoms, such as heartburn and regurgitation. Barrett esophagus should be treated with long-term

proton pump inhibitors once or twice daily to control reflux symptoms. Although these medications do not appear to cause regression of Barrett esophagus, they may reduce the risk of cancer. Paradoxically, one-third of patients report minimal or no symptoms of GERD, suggesting decreased acid sensitivity of Barrett epithelium. Indeed, over 90% of individuals with Barrett esophagus in the general population do not seek medical attention.

The most serious complication of Barrett esophagus is esophageal adenocarcinoma. It is believed that most adenocarcinomas of the esophagus and many such tumors of the gastric cardia arise from dysplastic epithelium in Barrett esophagus. The incidence of adenocarcinoma in patients with Barrett esophagus is estimated at 0.2–0.5% per year. Although this still is an 11-fold increased risk compared with patients without Barrett esophagus, adenocarcinoma of the esophagus remains a relatively uncommon malignancy in the United States (9000 cases/year). Given the large number of adults with chronic GERD relative to the small number in whom adenocarcinoma develops and the costs and risks of upper endoscopy, a 2019 clinical guideline recommended against endoscopic screening for Barrett esophagus in adults with GERD except in those with one or more risk factors for adenocarcinoma (aged older than 50 years, truncal obesity, current or prior history of smoking, or male gender) or in adults with a family history of Barrett esophagus or esophageal adenocarcinoma.

In patients known to have nondysplastic Barrett esophagus, surveillance endoscopy every 3–5 years is recommended to look for low- or high-grade dysplasia or adenocarcinoma. In patients with nondysplastic Barrett esophagus, the risk of progression to high-grade dysplasia or cancer is related to the length of Barrett epithelium. This risk is 0.29%/year for those with columnar epithelium lengths of 1–3 cm (short-segment) and 0.91%/year in those with lengths greater than 3 cm (long-segment). During endoscopy, biopsies are obtained from nodular or irregular mucosa (which have an increased risk of high-grade dysplasia or cancer) as well as randomly from the esophagus every 1–2 cm. The finding of dysplasia should be confirmed by a second, expert pathologist. The detection of dysplasia is increased with use of the WATS (wide-area trans-epithelial sampling) technique in which a brush is deployed through the endoscope to obtain deep epithelial samples that are analyzed by a central laboratory computer.

Endoscopic therapy now is the standard of care for patients who have Barrett esophagus with dysplasia (low-grade, high-grade) or well-differentiated mucosal adenocarcinoma (Tis or T1a). Therapy should be performed by endoscopists with expertise in advanced resection and ablation techniques. All nodules should be removed with mucosal snare resection or dissection techniques to assess for the presence and depth of cancer. Of the patients who have cancer confined to the mucosa, less than 2% have recurrence of cancer or high-grade dysplasia after snare resection. Following resection, ablation of any remaining Barrett mucosa—including flat (nonnodular) high-grade dysplasia—is performed with radiofrequency wave electrocautery or cryotherapy. Current guidelines also

recommend that patients with flat *low-grade* dysplasia (confirmed by a second expert pathologist) also be considered for ablation, reserving annual endoscopic surveillance to patients with increased comorbidities and reduced life-expectancy. The efficacy of endoscopic ablation therapies in patients with Barrett dysplasia is supported by several studies. When high-dose proton pump inhibitors are administered to normalize intraesophageal pH, radiofrequency wave ablation electrocautery eradication of Barrett columnar epithelium is followed by complete healing with normal squamous epithelium in greater than 78% of patients and elimination of dysplasia in 91%.

Endoscopic ablation techniques have a risk of complications (bleeding, perforation, strictures). Therefore, endoscopic eradication therapy currently is not recommended for patients with nondysplastic Barrett esophagus for whom the risk of developing esophageal cancer is low and treatment does not appear to be cost-effective.

B. Peptic Stricture

Stricture formation occurs in about 5% of patients with esophagitis. It is manifested by the gradual development of solid food dysphagia progressive over months to years. Most strictures are located at the gastroesophageal junction. Endoscopy with biopsy is mandatory in all cases to differentiate peptic stricture from stricture by esophageal carcinoma. Active erosive esophagitis is often present. Up to 90% of symptomatic patients are effectively treated with dilation with graduated polyvinyl catheters passed over a wire placed at the time of endoscopy or fluoroscopically, or balloons passed fluoroscopically or through an endoscope. Dilation is continued over one to several sessions. A luminal diameter of 15–18 mm is usually sufficient to relieve dysphagia. Long-term therapy with a proton pump inhibitor is required to decrease the likelihood of stricture recurrence.

Treatment

A. Medical Treatment

The goal of treatment is to provide symptomatic relief, to heal esophagitis (if present), and to prevent complications. In the majority of patients with uncomplicated disease, empiric treatment is initiated based on a compatible history without the need for further confirmatory studies. Patients not responding and those with suspected complications undergo further evaluation with upper endoscopy or esophageal manometry and pH recording.

1. Mild, intermittent symptoms—Patients with mild or intermittent symptoms that do not impact adversely on quality of life may benefit from lifestyle modifications with medical interventions taken as needed. Patients may find that eating smaller meals and elimination of acidic foods (citrus, tomatoes, coffee, spicy foods), foods that precipitate reflux (fatty foods, chocolate, peppermint, alcohol), and cigarettes may reduce symptoms. Weight loss should be recommended for patients who are overweight or have had recent weight gain. All patients should be advised to avoid lying down within 3 hours after meals (the period of greatest reflux). Patients with nocturnal symptoms should

also elevate the head of the bed on 6-inch blocks or a foam wedge to reduce reflux and enhance esophageal clearance.

Patients with infrequent heartburn (less than once weekly) may be treated on demand with antacids or oral H₂-receptor antagonists. Antacids provide rapid relief of heartburn; however, their duration of action is less than 2 hours. Many are available over the counter. Those containing magnesium should not be used for patients with kidney disease, and patients with acute or chronic kidney disease should be cautioned appropriately.

The oral H₂-receptor antagonists come in a variety of strengths: cimetidine 200 mg; famotidine 10 mg and 20 mg; and nizatidine 75 mg and 150 mg. Most of these drug strengths are now available over the counter without need for a prescription. When taken for active heartburn, these agents have a delay in onset of at least 30 minutes. However, once these agents take effect, they provide heartburn relief for up to 8 hours. When taken before meals known to provoke heartburn, these agents reduce the symptom.

2. Troublesome symptoms—

A. INITIAL THERAPY—Patients with troublesome reflux symptoms and patients with known complications of GERD (erosive esophagitis, Barrett esophagus, stricture) should be treated with a once-daily oral proton pump inhibitor (omeprazole or rabeprazole, 20 mg; omeprazole, 40 mg with sodium bicarbonate; lansoprazole, 30 mg; dexlansoprazole, 60 mg; esomeprazole or pantoprazole, 40 mg) taken 30 minutes before breakfast for 4–8 weeks. Because there appears to be little difference between these agents in efficacy or side effect profiles, the choice of agent is determined by cost. Oral omeprazole, 20 mg, and lansoprazole, 15 mg, are available as over-the-counter formulations. Once-daily proton pump inhibitors achieve adequate control of heartburn in 70–80% of patients, complete heartburn resolution in over 50%, and healing of erosive esophagitis (when present) in 75–85%. In contrast, proton pump inhibitors are less effective in reducing bothersome regurgitation. Because of their superior efficacy and ease of use, proton pump inhibitors are preferred to H₂-receptor antagonists for the initial treatment of acute and chronic GERD.

B. LONG-TERM THERAPY—In those who achieve good symptomatic relief with a course of empiric once-daily proton pump inhibitor, therapy may be discontinued after 8–12 weeks. Most patients (over 80%) will experience relapse of GERD symptoms, usually within 3 months. Patients whose symptoms relapse may be treated with either continuous proton pump inhibitor therapy, intermittent 2- to 4-week courses, or “on demand” therapy (ie, drug taken until symptoms abate) depending on symptom frequency and patient preference. Alternatively, twice-daily H₂-receptor antagonists may be used to control symptoms in patients without erosive esophagitis. Patients who require twice-daily proton pump inhibitor therapy for initial symptom control and patients with complications of GERD, including severe erosive esophagitis, Barrett esophagus, or peptic stricture, should be maintained on long-term therapy with a once- or twice-daily proton pump inhibitor titrated to the lowest effective dose to achieve satisfactory symptom control.

Proton pump inhibitors are considered to be extremely safe. Although a number of safety concerns have been raised in retrospective observational studies, it is difficult to determine whether the modest associations identified are due to a causal relationship. Long-term use of proton pump inhibitors likely does have a small increased risk of infectious gastroenteritis (including *C difficile*), small intestinal bacterial overgrowth, and micronutrient deficiencies (iron, vitamin B₁₂, magnesium). A large prospective study of over 17,000 patients taking proton pump inhibitors for a median of 3 years did not find an increased risk of other previously reported adverse events, including pneumonia, bone fractures, kidney disease (due to interstitial nephritis), dementia, or myocardial infarction. Long-term proton pump inhibitor therapy should be prescribed to patients with appropriate indications and at the lowest effective dose.

3. Unresponsive disease—Up to one-third of patients report inadequate relief of heartburn or regurgitation with once-daily proton pump inhibitor therapy. Approximately 25% respond to an increase in proton pump inhibitor therapy to twice daily (30–45 minutes before breakfast and dinner). Patients unresponsive to twice-daily therapy should undergo endoscopy for detection of severe, inadequately treated reflux esophagitis and for other gastroesophageal conditions (including eosinophilic esophagitis and achalasia) that may mimic GERD. Truly refractory esophagitis may be caused by medical noncompliance, resistance to proton pump inhibitors, gastrinoma with gastric acid hypersecretion (Zollinger-Ellison syndrome), or pill-induced esophagitis. Patients without endoscopically visible esophagitis should undergo ambulatory pH monitoring to determine whether the symptoms are correlated with reflux episodes. Combined esophageal pH monitoring with impedance monitoring is preferred over pH testing alone because of its ability to detect both acid and nonacid reflux events. The study generally is performed on twice-daily proton pump inhibitor therapy to determine the number of reflux episodes (acid and nonacid) and symptom association with reflux episodes. Refractory GERD is diagnosed in patients with confirmed reflux (increased acid reflux or significant correlation of symptoms with acid or nonacid reflux episodes) despite proton pump inhibitor therapy. These patients may be candidates for surgical or endoscopic therapy. Approximately 30% of patients with unresponsive symptoms do not have increased reflux or a significant symptom correlation with reflux episodes and are diagnosed with “functional heartburn,” a functional disorder. Treatment with a low-dose tricyclic antidepressant (eg, imipramine or nortriptyline 25 mg orally at bedtime) may be beneficial.

4. Extraesophageal reflux manifestations—Establishing a causal relationship between gastroesophageal reflux and extraesophageal symptoms (eg, asthma, hoarseness, cough, sleep disturbances) is difficult. Gastroesophageal reflux seldom is the sole cause of extraesophageal disorders but may be a contributory factor. Although ambulatory esophageal pH testing can document the presence of increased acid esophageal reflux, it does not prove a causative connection. Current guidelines recommend that a trial of a twice-daily proton pump inhibitor be administered for

2–3 months in patients with suspected extraesophageal GERD syndromes who also have typical GERD symptoms. Improvement of extraesophageal symptoms suggests but does not prove that acid reflux is the causative factor. Esophageal impedance-pH testing may be performed in patients whose extraesophageal symptoms persist after 3 months of proton pump inhibitor therapy and may be considered before proton pump inhibitor therapy in patients without typical GERD symptoms in whom other causes of extraesophageal symptoms have been excluded.

B. Surgical Treatment

Surgical fundoplication affords good to excellent relief of symptoms and healing of esophagitis in over 85% of properly selected patients and can be performed laparoscopically with low complication rates in most instances. Although patient satisfaction is high, typical reflux symptoms recur in 10–30% of patients. Furthermore, new symptoms of dysphagia, bloating, increased flatulence, dyspepsia, or diarrhea develop in over 30% of patients. In a 2019 randomized controlled trial of patients with refractory heartburn and confirmed reflux (acid or nonacid) despite twice-daily proton pump inhibitor therapy, fundoplication resulted in 67% adequate symptom relief at 1 year compared with 12–28% with continued medical therapy.

A minimally invasive magnetic artificial sphincter is FDA approved for the treatment of GERD in patients with hiatal hernias less than 3 cm in size. The device is made up of a flexible, elastic string of titanium beads (wrapped around a magnetic core) that is placed laparoscopically below the diaphragm at the gastroesophageal junction. The magnets are designed to open with pressures generated during swallowing but remain closed during gastroesophageal reflux events, which generate lower pressure than swallowing. In prospective clinical trials with up to 5 years of follow up, magnetic sphincter augmentation has demonstrated GERD symptom relief equivalent to laparoscopic fundoplication but far fewer side effects (long-term dysphagia 4–10%, bloating 8%, diarrhea 2%, nausea/vomiting 2%). In 2020, results were reported comparing magnetic sphincter augmentation with twice-daily proton pump inhibitor therapy in patients with GERD and moderate to severe regurgitation. After 1 year, sphincter augmentation led to significant improvement of regurgitation in 96% of patients and of GERD symptoms in 81% of patients compared with 19% and 8% of patients, respectively, treated with twice-daily proton pump inhibitors. Given the excellent safety and efficacy data demonstrated with this device to date, it should be considered as an alternative to fundoplication surgery for patients with GERD, especially those with troublesome regurgitation and hiatal hernias less than 3 cm in size.

Surgical treatment is not recommended for patients who are well controlled with medical therapies but should be considered for those with severe reflux disease who are unwilling to accept lifelong medical therapy due to its expense, inconvenience, or theoretical risks as well as for patients with proven refractory GERD symptoms or bothersome regurgitation despite proton pump inhibitor therapy. Gastric bypass (rather than fundoplication) should be considered for obese patients with GERD.

Several endoscopic procedures have been developed to treat GERD; however, none have found wide acceptance, largely due to limited long-term efficacy.

► When to Refer

- Patients with typical GERD whose symptoms do not resolve with empiric management with a twice-daily proton pump inhibitor.
- Patients with suspected extraesophageal GERD symptoms that do not resolve with 3 months of twice-daily proton pump inhibitor therapy.
- Patients with significant dysphagia or other alarm symptoms for upper endoscopy.
- Patients with Barrett esophagus for endoscopic surveillance.
- Patients who have Barrett esophagus with dysplasia or early mucosal cancer.
- Surgical therapy is considered.

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Desai M et al. Management of peptic strictures. *Am J Gastroenterol*. 2020;115:967. [PMID: 32618639]

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Standards of Practice Committee; Wani S et al. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. *Gastrointest Endosc*. 2018;87:907. [PMID: 29397943]

Yadlapati R et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: recommendations from an expert panel. *Am J Gastroenterol*. 2018;113:980. [PMID: 29686276]

INFECTIOUS ESOPHAGITIS



- Immunosuppressed patient.
- Odynophagia, dysphagia, and chest pain.
- Endoscopy with biopsy establishes diagnosis.

► General Considerations

Infectious esophagitis occurs most commonly in immunosuppressed patients. Patients with AIDS, solid organ transplants, leukemia, lymphoma, and those receiving immunosuppressive drugs are at particular risk for opportunistic infections. *Candida albicans*, herpes simplex, and CMV are the most common pathogens. *Candida* infection may occur also in patients who have uncontrolled diabetes and those being treated with systemic corticosteroids, radiation therapy, or systemic antibiotic therapy. Herpes simplex can affect normal hosts, in which case the infection is generally self-limited.

► Clinical Findings

A. Symptoms and Signs

The most common symptoms are odynophagia and dysphagia. Substernal chest pain occurs in some patients. Patients with candidal esophagitis are sometimes asymptomatic. Oral thrush is present in only 75% of patients with candidal esophagitis and 25–50% of patients with viral esophagitis and is therefore an unreliable indicator of the cause of esophageal infection. Patients with esophageal CMV infection may have infection at other sites such as the colon and retina. Oral ulcers (herpes labialis) are often associated with herpes simplex esophagitis.

B. Special Examinations

Treatment may be empiric. For diagnostic certainty, endoscopy with biopsy and brushings (for microbiologic and histopathologic analysis) is preferred because of its high diagnostic accuracy. The endoscopic signs of candidal esophagitis are diffuse, linear, yellow-white plaques adherent to the mucosa. CMV esophagitis is characterized by one to several large, shallow, superficial ulcerations. Herpes esophagitis results in multiple small, deep ulcerations.

► Treatment

A. Candidal Esophagitis

Systemic therapy is required for esophageal candidiasis. An empiric trial of antifungal therapy is often administered without performing diagnostic endoscopy. Initial therapy is generally with fluconazole, 400 mg on day 1, then 200–400 mg/day orally for 14–21 days. Patients not responding to empiric therapy within 3–5 days should undergo endoscopy with brushings, biopsy, and culture to distinguish resistant fungal infection from other infections (eg, CMV, herpes). Esophageal candidiasis not responding to fluconazole therapy may be treated with itraconazole suspension (not capsules), 200 mg/day orally, or voriconazole, 200 mg orally twice daily. Refractory infection may be treated intravenously with caspofungin, 50 mg daily.

B. Cytomegalovirus Esophagitis

In patients with HIV infection, immune restoration with antiretroviral therapy is the most effective means of controlling CMV disease. Initial therapy is with ganciclovir,

5 mg/kg intravenously every 12 hours for 3–6 weeks. Neutropenia is a frequent dose-limiting side effect. Once resolution of symptoms occurs, it may be possible to complete the course of therapy with oral valganciclovir, 900 mg once daily. Patients who either do not respond to or cannot tolerate ganciclovir are treated acutely with foscarnet, 90 mg/kg intravenously every 12 hours for 3–6 weeks. The principal toxicities are acute kidney injury, hypocalcemia, and hypomagnesemia.

C. Herpetic Esophagitis

Immunocompetent patients may be treated symptomatically and generally do not require specific antiviral therapy. Immunosuppressed patients may be treated with oral acyclovir, 400 mg orally five times daily, or 250 mg/m² intravenously every 8–12 hours, usually for 14–21 days. Oral famciclovir, 500 mg orally three times daily, or valacyclovir, 1 g twice daily, are also effective but more expensive than generic acyclovir. Nonresponders require therapy with foscarnet, 40 mg/kg intravenously every 8 hours for 21 days.

► Prognosis

Most patients with infectious esophagitis can be effectively treated with complete symptom resolution. Depending on the patient's underlying immunodeficiency, relapse of symptoms off therapy can raise difficulties. Long-term suppressive therapy is sometimes required.

Hoversten P et al. Risk factors, endoscopic features, and clinical outcomes of cytomegalovirus esophagitis based on a 10-year analysis at a single center. *Clin Gastroenterol.* 2020;18:736. [PMID: 31077832]

Narasimhalu T et al. Educational case: infectious esophagitis. *Acad Pathol.* 2020;7:2374289520903438. [PMID: 32083170]

PILL-INDUCED ESOPHAGITIS

A number of different medications may injure the esophagus, presumably through direct, prolonged mucosal contact or mechanisms that disrupt mucosal integrity. The most commonly implicated are the NSAIDs, potassium chloride pills, quinidine, zalcitabine, zidovudine, alendronate and risedronate, emepronium bromide, iron, vitamin C, and antibiotics (doxycycline, tetracycline, clindamycin, trimethoprim-sulfamethoxazole). Because injury is most likely to occur if pills are swallowed without water or while supine, hospitalized or bed-bound patients are at greater risk. Symptoms include severe retrosternal chest pain, odynophagia, and dysphagia, often beginning several hours after taking a pill. These may occur suddenly and persist for days. Some patients (especially older patients) have relatively little pain, presenting with dysphagia. Endoscopy may reveal one to several discrete ulcers that may be shallow or deep. Chronic injury may result in severe esophagitis with stricture, hemorrhage, or perforation. Healing occurs rapidly when the offending agent is eliminated. To prevent pill-induced damage, patients should take pills with 4 oz of water and remain upright for 30 minutes after ingestion. Known offending agents should not be given to patients with esophageal dysmotility, dysphagia, or strictures.

Syed M. Pill-induced oesophagitis. *Postgrad Med J.* 2020. [Epub ahead of print] [PMID: 32423921]

BENIGN ESOPHAGEAL LESIONS

1. Mallory-Weiss Syndrome (Mucosal Laceration of Gastroesophageal Junction)



ESSENTIALS OF DIAGNOSIS

- ▶ Hematemesis; usually self-limited.
- ▶ Prior history of vomiting, retching in 50%.
- ▶ Endoscopy establishes diagnosis.

► General Considerations

Mallory-Weiss syndrome is characterized by a nonpenetrating mucosal tear at the gastroesophageal junction that is hypothesized to arise from events that suddenly raise transabdominal pressure, such as lifting, retching, or vomiting. Alcoholism is a strong predisposing factor. Mallory-Weiss tears are responsible for approximately 5% of cases of upper gastrointestinal bleeding.

► Clinical Findings

A. Symptoms and Signs

Patients usually present with hematemesis with or without melena. A history of retching, vomiting, or straining is obtained in about 50% of cases.

B. Special Examinations

As with other causes of upper gastrointestinal hemorrhage, upper endoscopy should be performed after the patient has been appropriately resuscitated. The diagnosis is established by identification of a 0.5- to 4-cm linear mucosal tear usually located either at the gastroesophageal junction or, more commonly, just below the junction in the gastric mucosa.

► Differential Diagnosis

At endoscopy, other potential causes of upper gastrointestinal hemorrhage are found in over 35% of patients with Mallory-Weiss tears, including peptic ulcer disease, erosive gastritis, arteriovenous malformations, and esophageal varices. Patients with underlying portal hypertension are at higher risk for continued or recurrent bleeding.

► Treatment

Patients are initially treated as needed with fluid resuscitation and blood transfusions. Most patients stop bleeding spontaneously and require no therapy. Endoscopic hemostatic therapy is employed in patients who have continuing active bleeding. Injection with epinephrine (1:10,000), cauterization with a bipolar or heater probe coagulation device, or mechanical compression of the artery by application of an endoclip or band is effective in 90–95% of cases.

Angiographic arterial embolization or operative intervention is required in patients who fail endoscopic therapy.

He L et al. The prediction value of scoring systems in Mallory-Weiss syndrome patients. *Medicine (Baltimore)*. 2019;98:e15751. [PMID: 31145291]

2. Eosinophilic Esophagitis

► General Considerations

Eosinophilia of the esophagus may be caused by eosinophilic esophagitis and GERD (and, rarely, celiac disease, Crohn disease, and pemphigus).

Eosinophilic esophagitis is a disorder in which food or environmental antigens are thought to stimulate an inflammatory response. Initially recognized in children, it is increasingly identified in young or middle-aged adults (estimated prevalence 43/100,000). A history of allergies or atopic conditions (asthma, eczema, hay fever) is present in over half of patients.

► Clinical Findings

Most adults have a long history of dysphagia for solid-foods or an episode of food impaction. Heartburn or chest pain may be present. Children may have abdominal pain, vomiting, or failure to thrive. On laboratory tests, a few have eosinophilia or elevated IgE levels. Barium swallow studies may demonstrate a small-caliber esophagus; focal or long, tapered strictures; or multiple concentric rings. However, endoscopy with esophageal biopsy and histologic evaluation is required to establish the diagnosis. Endoscopic appearances include edema, concentric rings ("trachealization"), exudates (white plaques), furrows (vertical lines), and strictures (EREFS); however, the esophagus is grossly normal in up to 5% of patients. Multiple biopsies (4–8) from the proximal and distal esophagus should be obtained to demonstrate multiple (greater than 15/high-powered field) eosinophils in the mucosa. Consideration should be given to the disorders that may cause increased esophageal eosinophils, including hypereosinophilic syndrome, eosinophilic gastroenteritis, achalasia, connective tissue disorders, drug hypersensitivity, and Crohn disease. Skin testing for food allergies may be helpful to identify causative factors.

► Treatment

The goals of therapy are improvement of symptoms, reduction of inflammation, and prevention and treatment of esophageal strictures. Treatment options include proton pump inhibitors, topical corticosteroids, food elimination diets, and esophageal dilation. First-line therapy for most adults is a proton pump inhibitor orally twice daily for 2 months followed by repeat endoscopy and mucosal biopsy. Up to one-third of symptomatic patients with increased esophageal eosinophils have clinical and histologic improvement with proton pump inhibitor treatment. It is hypothesized that esophageal acid exposure may contribute to antigen-mediated eosinophilic inflammation.

Proton pump inhibitor therapy should be discontinued in patients with persistent symptoms and inflammation.

In patients with continued symptoms, optimal treatment is uncertain. Referral to an allergist for evaluation of coexisting atopic disorders and for testing for food and environmental allergens may be considered, but studies suggest limited predictive value in adults. Empiric elimination of suspected dietary allergens leads to clinical, endoscopic and histologic improvement in 50–70% of adults. The most common allergenic foods are dairy, eggs, wheat, and soy followed by peanuts and shellfish. With progressive reintroduction of each food group, the trigger food group may be identified in up to 85% of patients. Topical corticosteroids lead to symptom resolution in 70% of adults. Either budesonide in sucralose suspension, 1 mg, or powdered fluticasone, 880 mcg (from foil-lined inhaler diskus), is administered twice daily for 6–8 weeks with similar efficacy. Symptomatic relapse is common after discontinuation of therapy and may require maintenance therapy at reduced doses of 0.25 mg twice daily. Graduated dilation of strictures should be conducted in patients with dysphagia and strictures or narrow-caliber esophagus but should be performed cautiously because there is an increased risk of perforation and postprocedural chest pain.

Hirano I et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the management of eosinophilic esophagitis. *Gastroenterology*. 2020;158:1776. [PMID: 32359562]

Kim JP et al. Clinical outcomes of adults with eosinophilic esophagitis with severe stricture. *Gastrointest Endosc*. 2020;92:44. [PMID: 31954704]

Rank MA et al. Technical review on the management of eosinophilic esophagitis: a report of the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters. *Gastroenterology*. 2020;158:1789. [PMID: 32359563]

3. Esophageal Webs & Rings

Esophageal webs are thin, diaphragm-like membranes of squamous mucosa that typically occur in the mid or upper esophagus and may be multiple. They may be congenital but also occur with eosinophilic esophagitis, graft-versus-host disease, pemphigoid, epidermolysis bullosa, pemphigus vulgaris, and, rarely, in association with iron deficiency anemia (Plummer-Vinson syndrome). Esophageal "Schatzki" rings are smooth, circumferential, thin (less than 4 mm in thickness) mucosal structures located in the distal esophagus at the squamocolumnar junction. Their pathogenesis is controversial. They are associated in nearly all cases with a hiatal hernia, and reflux symptoms are common, suggesting that acid gastroesophageal reflux may be contributory in many cases. Most webs and rings are over 20 mm in diameter and are asymptomatic. Solid food dysphagia most often occurs with rings less than 13 mm in diameter. Characteristically, dysphagia is intermittent and not progressive. Large poorly chewed food boluses such as beefsteak are most likely to cause symptoms. Obstructing boluses may pass by drinking extra liquids or after regurgitation. In some cases, an impacted bolus must be extracted endoscopically. Esophageal webs and rings are best visualized using a barium esophagogram with full esophageal distention. Endoscopy is less sensitive than barium esophagography.

The majority of symptomatic patients with a single ring or web can be effectively treated with the passage of bougie or endoscopic balloon dilators to disrupt the lesion or endoscopic electrosurgical incision of the ring. A minimum lumen diameter of 15–18 mm achieves symptom remission in most patients. A single dilation may suffice, but repeat dilations are required in many patients. Patients who have heartburn or who require repeated dilation should receive long-term acid suppressive therapy with a proton pump inhibitor.

Vermeulen BD et al. Risk factors and clinical outcomes of endoscopic dilation in benign esophageal strictures: a long-term follow-up study. *Gastrointest Endosc*. 2020;91:1058. [PMID: 31917167]

4. Zenker Diverticulum

Zenker diverticulum is a protrusion of pharyngeal mucosa that develops at the pharyngoesophageal junction between the inferior pharyngeal constrictor and the cricopharyngeus. The cause is believed to be loss of elasticity of the upper esophageal sphincter, resulting in restricted opening during swallowing. Symptoms of dysphagia and regurgitation tend to develop insidiously over years in older, predominantly male patients. Initial symptoms include vague oropharyngeal dysphagia with coughing or throat discomfort. As the diverticulum enlarges and retains food, patients may note halitosis, spontaneous regurgitation of undigested food, nocturnal choking, gurgling in the throat, or a protrusion in the neck. Complications include aspiration pneumonia, bronchiectasis, and lung abscess. The diagnosis is best established by a videosophagography.

Symptomatic patients require upper esophageal myotomy. Minimally invasive intraluminal approaches have been developed in which the septum between the esophagus and diverticulum is incised using a rigid or flexible endoscope or a diverticuloscope. Significant improvement occurs in over 90% of patients. Small asymptomatic diverticula may be observed.

Brewer Gutierrez OI et al. Zenker's diverticulum per-oral endoscopic myotomy techniques: changing paradigms. *Gastroenterology*. 2019;156:2134. [PMID: 30851303]

Pang M et al. Comparison of flexible endoscopic cricopharyngeal myectomy and myotomy approaches for Zenker diverticulum repair. *Gastrointest Endosc*. 2019;89:880. [PMID: 30342027]

5. Esophageal Varices



ESSENTIALS OF DIAGNOSIS

- Develop secondary to portal hypertension.
- Found in 50% of patients with cirrhosis.
- One-third of patients with varices develop upper gastrointestinal bleeding.
- Diagnosis established by upper endoscopy.

► General Considerations

Esophageal varices are dilated submucosal veins that develop in patients with underlying portal hypertension and that may result in serious upper gastrointestinal bleeding. The causes of portal hypertension are discussed in Chapter 16. Under normal circumstances, there is a 2–6 mm Hg pressure gradient between the portal vein and the inferior vena cava. When the gradient exceeds 10–12 mm Hg, significant portal hypertension exists. Esophageal varices are the most common cause of important gastrointestinal bleeding due to portal hypertension, though gastric varices and, rarely, intestinal varices may also bleed. Bleeding from esophageal varices most commonly occurs in the distal 5 cm of the esophagus.

The most common cause of portal hypertension is cirrhosis. Approximately 50% of patients with cirrhosis have esophageal varices. Bleeding from varices occurs in 30% of patients with esophageal varices. In the absence of any treatment, variceal bleeding spontaneously stops in about 50% of patients. Patients surviving this bleeding episode have a 60% chance of recurrent variceal bleeding, usually within the first 6 weeks. With current therapies, the in-hospital mortality rate associated with bleeding esophageal varices is 15%.

A number of factors have been identified that may portend an increased risk of bleeding from esophageal varices. The most important are (1) the size of the varices; (2) the presence at endoscopy of red wale markings (longitudinal dilated venules on the varix surface); (3) the severity of liver disease (as assessed by Child scoring); and (4) active alcohol abuse—patients with cirrhosis who continue to drink have an extremely high risk of variceal bleeding.

► Clinical Findings

A. Symptoms and Signs

Patients with bleeding esophageal varices present with symptoms and signs of acute gastrointestinal hemorrhage. (See Acute Upper Gastrointestinal Bleeding, above.) In some cases, there may be preceding retching or dyspepsia attributable to alcoholic gastritis or withdrawal. Varices per se do not cause symptoms of dyspepsia, dysphagia, or retching. Variceal bleeding usually is severe, resulting in hypovolemia manifested by postural vital signs or shock. But 20% of patients with chronic liver disease in whom bleeding develops have a nonvariceal source of bleeding.

B. Laboratory Findings

These are identical to those listed above in the section on Acute Upper Gastrointestinal Bleeding.

► Initial Management

A. Acute Resuscitation

The initial management of patients with acute upper gastrointestinal bleeding is also discussed in the section on Acute Upper Gastrointestinal Bleeding. Variceal hemorrhage is life-threatening; rapid assessment and resuscitation with

fluids or blood products are essential. Overtransfusion should be avoided because it leads to increased central and portal venous pressures, increasing the risk of rebleeding. Most patients with bleeding esophageal varices have advanced liver disease with coagulopathy due to thrombocytopenia; deficiencies of liver-derived clotting factors I (fibrinogen), II, VII, IX, and X; and accelerated intravascular fibrinolysis. The INR does not provide an accurate reflection of coagulopathy in advanced liver disease. Fresh frozen plasma should not be administered routinely in stable patients with an elevated INR because it has no proven benefit but does have potential harms, including increased portal pressures and risk of portal vein or deep venous thrombosis. In patients with decompensated cirrhosis and active severe upper gastrointestinal bleeding, platelet transfusion is recommended for platelet counts below 50,000/mcL ($50 \times 10^9/L$) and fresh frozen plasma may be considered for INRs greater than 1.8. Recombinant factor VIIa has not demonstrated efficacy in controlled studies and is not recommended. The role of prothrombin complex concentrates requires further study. Patients with advanced liver disease are at high risk for poor outcome regardless of the bleeding source and should be in an ICU.

B. Pharmacologic Therapy

1. Antibiotic prophylaxis—Cirrhotic patients admitted with upper gastrointestinal bleeding have a greater than 50% chance of developing a severe bacterial infection during hospitalization—such as bacterial peritonitis, pneumonia, or urinary tract infection. Most infections are caused by gram-negative organisms of gut origin. Prophylactic administration of intravenous third-generation cephalosporins (eg, ceftriaxone, 1 g/day) for 5–7 days reduces the risk of serious infection to 10–20% as well as hospital mortality, especially in patients with Child-Pugh class C cirrhosis.

2. Vasoactive drugs—Octreotide and somatostatin infusions reduce portal pressures in ways that are poorly understood. Octreotide (50 mcg intravenous bolus followed by 50 mcg/h) or somatostatin (250 mcg/h)—not available in the United States—reduces splanchnic and hepatic blood flow and portal pressures in cirrhotic patients. Both agents appear to provide acute control of variceal bleeding in up to 80% of patients although neither has been shown to reduce mortality. Combined treatment with octreotide or somatostatin infusion and endoscopic therapy (band ligation or sclerotherapy) is superior to either modality alone in controlling acute bleeding and early rebleeding, and it may improve survival. In patients with advanced liver disease and upper gastrointestinal hemorrhage, it is reasonable to initiate therapy with octreotide or somatostatin on admission and continue for 3–5 days if varices are confirmed by endoscopy. If bleeding is determined by endoscopy not to be secondary to portal hypertension, the infusion can be discontinued.

Terlipressin, 1–2 mg intravenously every 4 hours (not available in the United States), is a synthetic vasopressin analog that causes a significant and sustained reduction in portal and variceal pressures while preserving renal perfusion. Where available, terlipressin may be preferred to

somatostatin or octreotide. Terlipressin is contraindicated in patients with significant coronary, cerebral, or peripheral vascular disease.

3. Vitamin K—In cirrhotic patients with an abnormal prothrombin time, vitamin K (10 mg intravenously) should be administered.

4. Lactulose—Encephalopathy may complicate an episode of gastrointestinal bleeding in patients with severe liver disease. In patients with encephalopathy, lactulose should be administered in a dosage of 30 mL orally every 1–2 hours until evacuation occurs then reduced to 15–45 mL/h every 8–12 hours as needed to promote two or three bowel movements daily. (See Chapter 16.)

C. Emergent Endoscopy

Emergent endoscopy is performed after the patient's hemodynamic status has been appropriately stabilized (usually within 12–24 hours). In patients with active bleeding, endotracheal intubation is commonly performed to protect against aspiration during endoscopy. An endoscopic examination is performed to exclude other or associated causes of upper gastrointestinal bleeding such as Mallory-Weiss tears, peptic ulcer disease, and portal hypertensive gastropathy. In many patients, variceal bleeding has stopped spontaneously by the time of endoscopy, and the diagnosis of variceal bleeding is made presumptively. Immediate endoscopic treatment of the varices generally is performed with banding. In clinical practice, sclerotherapy is now seldom used. These techniques arrest active bleeding in 80–90% of patients and reduce the chance of in-hospital recurrent bleeding to about 20%.

If banding is chosen, repeat sessions are scheduled at intervals of 2–4 weeks until the varices are obliterated or reduced to a small size. Banding achieves lower rates of rebleeding, complications, and death than sclerotherapy and should be considered the endoscopic treatment of choice. For patients with platelet counts less than 50,000/mcL ($50 \times 10^9/L$), consideration should be given to preprocedure administration of avatrombopag, an oral thromboopoietin receptor agonist approved by the FDA in 2018. In phase 3 clinical trials at a dose of 40–60 mg/day for 5 consecutive days beginning 10–13 days prior to endoscopy, 68% of patients with baseline platelet counts less than 40,000/mcL ($40 \times 10^9/L$) and 88% with baseline counts 40,000–50,000/mcL achieved platelet counts greater than 50,000/mcL ($50 \times 10^9/L$) and avoided periprocedural platelet transfusions.

D. Balloon Tube Tamponade

In patients with massive variceal gastrointestinal bleeding, mechanical tamponade with specially designed nasogastric tubes containing large gastric and esophageal balloons (Minnesota or Sengstaken-Blakemore tubes) may provide initial control of hemorrhage in 60–90% of patients. Balloon tamponade is used as a temporizing measure only in patients with bleeding that cannot be controlled with pharmacologic or endoscopic techniques until more definitive decompressive therapy (eg, TIPS) can be provided.

E. Portal Decompressive Procedures

In the 10–20% of patients with variceal bleeding that cannot be controlled with pharmacologic or endoscopic therapy, emergency portal decompression may be considered.

1. Transvenous intrahepatic portosystemic shunts (TIPS)

Over a wire that is passed through a catheter inserted in the jugular vein, an expandable wire mesh stent (8–12 mm in diameter) is passed through the liver parenchyma, creating a portosystemic shunt from the portal vein to the hepatic vein. TIPS can control acute hemorrhage in over 90% of patients actively bleeding from gastric or esophageal varices. However, when TIPS is performed in the actively bleeding patient, the mortality approaches 40%, especially in patients requiring ventilatory support or blood pressure support and patients with renal insufficiency, bilirubin greater than 3 mg/dL, or encephalopathy. Therefore, TIPS should be considered in the 10–20% of patients with acute variceal bleeding that cannot be controlled with pharmacologic and endoscopic therapy, but it may not be warranted in patients with a particularly poor prognosis.

2. Emergency portosystemic shunt surgery

Emergency portosystemic shunt surgery is associated with a 40–60% mortality rate. At centers where TIPS is available, emergency portosystemic shunts are no longer performed.

► Prevention of Rebleeding

Once the initial bleeding episode has been controlled, therapy is warranted to reduce the high risk (60%) of rebleeding.

A. Combination Beta-Blockers and Variceal Band Ligation

Nonselective beta-adrenergic blockers (propranolol, nadolol) reduce the risk of rebleeding from esophageal varices to about 40%. Likewise, long-term treatment with band ligation reduces the incidence of rebleeding to about 30%. In most patients, two to six treatment sessions (performed at 2- to 4-week intervals) are needed to eradicate the varices.

Meta-analyses of randomized controlled trials suggest that a *combination* of band ligation plus beta-blockers is superior to either variceal band ligation alone (RR 0.68) or beta-blockers alone (RR 0.71). Therefore, combination therapy is recommended for patients without contraindications to beta-blockers. Recommended starting doses of beta-blockers are propranolol (20 mg orally twice daily), long-acting propranolol (60 mg orally once daily), or nadolol (20–40 mg orally once daily), with gradual increases in the dosage every 1–2 weeks until the heart rate falls by 25% or reaches 55–60 beats/min, provided the systolic blood pressure remains above 90 mm Hg and the patient has no side effects. The average dosage of long-acting propranolol is 120 mg once daily and for nadolol, 80 mg once daily. One-third of patients with cirrhosis are intolerant of beta-blockers, experiencing fatigue or hypotension. Drug administration at bedtime may reduce the frequency and severity of side effects.

B. Transvenous Intrahepatic Portosystemic Shunt

TIPS has resulted in a significant reduction in recurrent bleeding compared with endoscopic sclerotherapy or band

ligation—either alone or in combination with beta-blocker therapy. At 1 year, rebleeding rates in patients treated with TIPS versus various endoscopic therapies average 20% and 40%, respectively. However, TIPS was also associated with a higher incidence of encephalopathy (35% vs 15%) and did not result in a decrease in mortality. Another limitation of TIPS is that stenosis and thrombosis of the stents occur in the majority of patients over time with a consequent risk of rebleeding. Therefore, periodic monitoring with Doppler ultrasonography or hepatic venography is required. Stent patency usually can be maintained by balloon angioplasty or additional stent placement. Given these problems, TIPS should be reserved for patients who have recurrent (two or more) episodes of variceal bleeding that have failed endoscopic or pharmacologic therapies. TIPS is also useful in patients with recurrent bleeding from gastric varices or portal hypertensive gastropathy (for which endoscopic therapies cannot be used). TIPS is likewise considered in patients who are noncompliant with other therapies or who live in remote locations (without access to emergency care).

C. Surgical Portosystemic Shunts

Shunt surgery has a significantly lower rate of rebleeding compared with endoscopic therapy but also a higher incidence of encephalopathy. With the advent and widespread adoption of TIPS, surgical shunts are seldom performed.

D. Liver Transplantation

Candidacy for orthotopic liver transplantation should be assessed in all patients with chronic liver disease and bleeding due to portal hypertension. Transplant candidates should be treated with band ligation or TIPS to control bleeding pretransplant.

► Prevention of First Episodes of Variceal Bleeding

Among patients with varices that have not previously bled, bleeding occurs in 12% of patients each year, with a lifetime risk of 30%. Because of the high mortality rate associated with variceal hemorrhage, prevention of the initial bleeding episode is desirable. Therefore, it is recommended that patients with chronic liver disease with compensated cirrhosis or suspected cirrhosis should undergo diagnostic endoscopy or capsule endoscopy to determine whether varices are present. Transient elastography (FibroScan) is a noninvasive method for assessing liver stiffness and fibrosis that may be used to stratify patients at high risk for varices (who may benefit from endoscopy) versus those at low risk (in whom endoscopy is not needed). Varices are present in 40% of patients with Child-Pugh class A cirrhosis and in 85% with Child-Pugh class C cirrhosis. In patients without varices on screening endoscopy, a repeat endoscopy is recommended in 3 years, since varices develop in 8% of patients per year. Patients with varices have a higher risk of bleeding if they have varices larger than 5 mm, varices with red wale markings, or Child-Pugh class B or C cirrhosis. The risk of bleeding in patients with varices smaller than 5 mm is 5% per year and with large varices is

15–20% per year. Patients with small varices without red wale marks and compensated (Child-Pugh class A) cirrhosis have a low risk of bleeding; hence, prophylaxis is unnecessary, but endoscopy should be repeated in 1–2 years to reassess size.

Nonselective beta-adrenergic blockers are recommended to reduce the risk of first variceal hemorrhage in patients with medium/large varices and patients with small varices who either have variceal red wale marks or advanced cirrhosis (Child-Pugh class B or C). (See Combination Beta-Blockers and Variceal Band Ligation, above.) Band ligation is not recommended for small varices due to technical difficulties in band application. Prophylactic band ligation may be preferred over beta-blockers for patients at higher risk for bleeding, especially patients with medium/large varices with red wale markings or with advanced cirrhosis (Child-Pugh class B or C) as well as patients with contraindications to or intolerance of beta-blockers.

► When to Refer

- All patients with upper gastrointestinal bleeding and suspected varices should be evaluated by a physician skilled in therapeutic endoscopy.
- Patients being considered for TIPS procedures or liver transplantation.
- Patients with cirrhosis for endoscopic evaluation for varices.

► When to Admit

All patients with acute upper gastrointestinal bleeding and suspected cirrhosis should be admitted to an ICU.

Baiges A et al. Pharmacologic prevention of variceal bleeding and rebleeding. *Hepatol Int*. 2018;12:68. [PMID: 29210030]
 Ibrahim M et al. New developments in managing variceal bleeding. *Gastroenterology*. 2018;154:1964. [PMID: 29481777]
 Jakab SS et al. Screening and surveillance of varices in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2019;17:26. [PMID: 29551741]

O'Leary JG et al. AGA Clinical Practice Update: coagulation in cirrhosis. *Gastroenterology*. 2019;157:34. [PMID: 30986390]
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ESOPHAGEAL MOTILITY DISORDERS

1. Achalasia



ESSENTIALS OF DIAGNOSIS

- ▶ Gradual, progressive dysphagia for solids and liquids.
- ▶ Regurgitation of undigested food.
- ▶ Barium esophagogram with “bird’s beak” distal esophagus.
- ▶ Esophageal manometry confirms diagnosis.

► General Considerations

Achalasia is an idiopathic motility disorder characterized by loss of peristalsis in the distal two-thirds (smooth muscle) of the esophagus and impaired relaxation of the LES. There appears to be denervation of the esophagus resulting primarily from loss of nitric oxide-producing inhibitory neurons in the myenteric plexus. The cause of the neuronal degeneration is unknown.

► Clinical Findings

A. Symptoms and Signs

There is a steady increase in the incidence of achalasia with age; however, it can be seen in individuals as young as 25 years. Patients complain of the gradual onset of dysphagia for solid foods and, in the majority, of liquids also. Symptoms at presentation may have persisted for months to years. Substernal discomfort or fullness may be noted after eating. Many patients eat more slowly and adopt specific maneuvers such as lifting the neck or throwing the shoulders back to enhance esophageal emptying. Regurgitation of undigested food is common and may occur during meals or up to several hours later. Nocturnal regurgitation can provoke coughing or aspiration. Up to 50% of patients report substernal chest pain that is unrelated to meals or exercise and may last up to hours. Weight loss is common. Physical examination is unhelpful.

B. Imaging

Chest radiographs may show an air-fluid level in the enlarged, fluid-filled esophagus. Barium esophagography discloses characteristic findings, including esophageal dilation, loss of esophageal peristalsis, poor esophageal emptying, and a smooth, symmetric “bird’s beak” tapering of the distal esophagus. Five minutes after ingestion of 8 oz of barium, a column height of more than 2 cm has a sensitivity and specificity of greater than 85% in differentiating achalasia from other causes of dysphagia. Without treatment, the esophagus may become markedly dilated (“sigmoid esophagus”).

C. Special Examinations

After esophagography, endoscopy is always performed to evaluate the distal esophagus and gastroesophageal junction to exclude a distal stricture or a submucosal infiltrating carcinoma. The diagnosis is confirmed by high-resolution esophageal manometry demonstrating absence of normal peristalsis and impaired esophagogastric junction relaxation after swallowing. An integrated post-swallow relaxation pressure greater than 15 mm Hg has a diagnostic sensitivity of 97%. Three achalasia subtypes are recognized based on esophageal contractility and pressure patterns: types I and II (nonspastic) and type III (characterized by distal high-amplitude spastic contractions).

► Differential Diagnosis

Chagas disease is associated with esophageal dysfunction that is indistinguishable from idiopathic achalasia and should be considered in patients from endemic regions (Central and South America); it is becoming more common

in the southern United States. Primary or metastatic tumors can invade the gastroesophageal junction, resulting in a picture resembling that of achalasia, called “pseudoachalasia.” Endoscopic ultrasonography and chest CT may be required to examine the distal esophagus in suspicious cases.

► Treatment

Several effective treatment options are available, all of which promote improved esophageal emptying by lowering distal esophageal pressure either through endoscopic injection with botulinum or disruption of the LES by pneumatic balloon dilation or cardiosophageal myotomy (surgical or endoscopic).

A. Botulinum Toxin Injection

Endoscopically guided injection of botulinum toxin directly into the LES results in a marked reduction in LES pressure with initial improvement in symptoms in 65–85% of patients. However, symptom relapse occurs in over 50% of patients within 6–9 months and in all patients within 2 years. Because it is inferior to pneumatic dilation therapy and surgery in producing sustained symptomatic relief, this therapy is most appropriate for patients with comorbidities who are poor candidates for more invasive procedures.

B. Pneumatic Dilation

Over 80% of patients derive good to excellent relief of dysphagia after one to three sessions of pneumatic dilation of the LES. Dilation is less effective in patients who are younger than age 45, have the type III variant, or have a dilated esophagus. Perforations occur in less than 3% of dilations but infrequently require operative repair. Patients who do not respond to initial treatment with pneumatic dilation should be referred for cardiomyotomy (Heller or POEM). Conversely, pneumatic dilation is the preferred initial treatment option for patients with inadequate symptom relief after cardiomyotomy.

C. Surgical Heller Cardiomyotomy

A modified Heller cardiomyotomy of the LES and cardia (usually performed with a laparoscopic approach) results in symptomatic improvement in approximately 90% of patients. Because gastroesophageal reflux develops in up to 20% of patients after myotomy, most surgeons also perform an antireflux procedure (fundoplication), and most patients are prescribed a once-daily proton pump inhibitor. Symptoms recur in greater than 5–15% of cases within 10 years but usually respond to pneumatic dilation. A 2017 systematic review of five randomized comparative cardiomyotomy trials detected a higher clinical success rate after 1 year with laparoscopic myotomy than Heller myotomy (RR 1.14) but no significant differences after 2–5 years.

D. Per Oral Endoscopic Myotomy (POEM)

POEM is a less invasive endoscopic procedure in which an endoscope is inserted into the patient’s mouth and passed into the upper esophagus. After a small incision is made in

the esophageal mucosa, the endoscope dissects through the submucosal space to the lower esophageal sphincter, where the circular muscle fibers of the cardia and distal esophagus are incised. Because a fundoplication is not performed, long-term antisecretory therapy for gastroesophageal reflux with a proton pump inhibitor is required in most patients. POEM may be the preferred treatment modality for type III achalasia (where a longer myotomy of the distal esophagus is indicated). In a 2019 randomized controlled trial of 133 patients with achalasia, satisfactory symptom improvement was significantly higher at 2 years in patients treated with POEM (92%) than in those treated with pneumatic dilation(s) (76%). However, gastroesophageal reflux symptoms, esophagitis, and proton pump inhibitor use were significantly greater in patients treated with POEM than pneumatic dilation. Another 2019 randomized controlled trial of 221 patients with achalasia showed that satisfactory symptom improvement was equivalent both in patients treated with POEM (83%) and in those treated with surgical myotomy (81.7%) 2 years after treatment. Serious adverse events occurred in 2.7% of patients treated with POEM and 7.3% with surgical myotomy, but postoperative reflux esophagitis was higher with POEM (44%) than with surgical myotomy (29%).

In summary, optimal treatment of achalasia depends on the patient’s age, achalasia subtype, provider’s expertise, and patient’s preferences or concerns regarding surgery or posttreatment gastroesophageal reflux. Pneumatic dilation, Heller cardiomyotomy, and POEM provide comparable short- and long-term symptomatic improvement in achalasia types I or II. For type III (spastic) achalasia, POEM with a long distal myotomy may be preferred to Heller cardiomyotomy where expertise is available.

► Management of Refractory Achalasia

Complete esophagectomy or percutaneous gastrostomy is required in the 1% of patients in whom massive dilation of the esophagus (megaesophagus) develops despite dilation or myotomy. In megaesophagus, dysphagia, food retention, and regurgitation may decrease nutrition and quality of life and increase risk of aspiration.

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Khashab M et al. ASGE guideline on the management of achalasia. *Gastrointest Endosc*. 2020;91:213. [PMID: 31839408]

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2. Other Primary Esophageal Motility Disorders

► Clinical Findings

A. Symptoms and Signs

Abnormalities in esophageal motility may cause dysphagia or chest pain. Dysphagia for liquids as well as solids tends to be intermittent and nonprogressive. Periods of normal swallowing may alternate with periods of dysphagia, which

usually is mild though bothersome—rarely severe enough to result in significant alterations in lifestyle or weight loss. Dysphagia may be provoked by stress, large boluses of food, or hot or cold liquids. Some patients may experience anterior chest pain that may be confused with angina pectoris but usually is nonexertional. The pain generally is unrelated to eating. (See Chest Pain of Undetermined Origin, below.)

B. Diagnostic Tests

The evaluation of suspected esophageal motility disorders includes barium esophagography, upper endoscopy, and, in some cases, esophageal manometry. Barium esophagography is useful to exclude mechanical obstruction and to evaluate esophageal motility. The presence of simultaneous contractions (spasm), disordered peristalsis, or failed peristalsis supports a diagnosis of esophageal dysmotility. Upper endoscopy also is performed to exclude a mechanical obstruction (as a cause of dysphagia) and to look for evidence of erosive reflux esophagitis (a common cause of chest pain) or eosinophilic esophagitis (confirmed by esophageal biopsy). Manometry is not routinely used for mild to moderate symptoms because the findings seldom influence further medical management, but it may be useful in patients with persistent, disabling dysphagia to exclude achalasia and to look for other disorders of esophageal motility. These include diffuse esophageal spasm, hypercontractile (“jackhammer”) esophagus, esophagogastric junction outflow obstruction, and findings of ineffective esophageal peristalsis (failed or weak esophageal peristalsis). The further evaluation of noncardiac chest pain is discussed below.

Treatment

For patients with mild symptoms of dysphagia, therapy is directed at symptom reduction and reassurance. Patients should be instructed to eat more slowly and take smaller bites of food. In some cases, a warm liquid at the start of a meal may facilitate swallowing. Because unrecognized gastroesophageal reflux may cause dysphagia, a trial of a proton pump inhibitor (esomeprazole 40 mg, lansoprazole 30 mg) orally twice daily should be administered for 4–8 weeks. Treatment of patients with severe dysphagia is empiric. Suspected spastic disorders may be treated with (1) smooth muscle relaxants (isosorbide [10–20 mg four times daily] or nitroglycerin [0.4 mg sublingually as needed]); (2) calcium channel blockers (nifedipine [10 mg] or diltiazem [60–90 mg] 30–45 minutes before meals); (3) phosphodiesterase type 5 inhibitors (eg, sildenafil); (4) botulinum toxin injection into the lower esophagus; or (5) POEM. Esophageal dilation provides symptomatic relief in some cases.

Kahrilas PJ et al. Advances in management of esophageal motility disorders. *Clin Gastroenterol Hepatol*. 2018;16:1692. [PMID: 29702296]

Khalaf M et al. Distal esophageal spasm: a review. *Am J Med*. 2018;131:1034. [PMID: 29605413]

Mittal R et al. Esophageal motility disorders and gastroesophageal reflux disease. *N Engl J Med*. 2020;383:1961. [PMID: 33176086]

CHEST PAIN OF UNDETERMINED ORIGIN

One-third of patients with chest pain undergo negative cardiac evaluation. Patients with recurrent noncardiac chest pain thus pose a difficult clinical problem. Because coronary artery disease is common and can present atypically, it must be excluded prior to evaluation for other causes.

Causes of noncardiac chest pain may include the following.

A. Chest Wall and Thoracic Spine Disease

These are easily diagnosed by history and physical examination.

B. Gastroesophageal Reflux

Up to 50% of patients have increased amounts of gastroesophageal acid reflux or a correlation between acid reflux episodes and chest pain demonstrated on esophageal pH testing. An empiric 4-week trial of acid-suppressive therapy with a high-dose proton pump inhibitor is recommended (eg, omeprazole or rabeprazole, 40 mg orally twice daily; lansoprazole, 30–60 mg orally twice daily; or esomeprazole or pantoprazole, 40 mg orally twice daily), especially in patients with reflux symptoms. In patients with persistent symptoms, ambulatory esophageal pH or impedance and pH study may be useful to exclude definitively a relationship between acid and nonacid reflux episodes and chest pain events.

C. Esophageal Dysmotility

Esophageal motility abnormalities such as diffuse esophageal spasm or hypercontractile swallow (“jackhammer esophagus”) are uncommon causes of noncardiac chest pain. In patients with chest pain and dysphagia, a barium swallow radiograph should be obtained to look for evidence of achalasia or diffuse esophageal spasm. Esophageal manometry is not routinely performed because of low specificity and the unlikelihood of finding a clinically significant disorder, but it may be recommended in patients with frequent symptoms.

D. Heightened Visceral Sensitivity

Some patients with noncardiac chest pain report pain in response to a variety of minor noxious stimuli such as physiologically normal amounts of acid reflux, inflation of balloons within the esophageal lumen, injection of intravenous edrophonium (a cholinergic stimulus), or intracardiac catheter manipulation. Low doses of oral antidepressants such as trazodone 50 mg or imipramine 10–50 mg reduce chest pain symptoms and are thought to reduce visceral afferent awareness. In a 2010 controlled crossover trial, over 50% of patients treated with venlafaxine, 75 mg once daily at bedtime, achieved symptomatic improvement compared with only 4% treated with placebo.

E. Psychological Disorders

A significant number of patients have underlying depression, anxiety, and panic disorder. Patients reporting

dyspnea, sweating, tachycardia, suffocation, or fear of dying should be evaluated for panic disorder.

Albers D et al. Peroral endoscopic myotomy (POEM) is effective in treatment of noncardiac chest pain caused by hypercontractile esophageal motility disorders: results of the POEM-HYPE-Study. *Z Gastroenterol*. 2018;56:1337. [PMID: 30296811]

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Wertli MM et al. Non-cardiac chest pain patients in the emergency department: do physicians have a plan how to diagnose and treat them? A retrospective study. *PLoS One*. 2019;14:e0211615. [PMID: 30707725]

DISEASES OF THE STOMACH & DUODENUM

(See Chapter 39 for Gastric Cancers.)

GASTRITIS & GASTROPATHY

The term “gastropathy” should be used to denote conditions in which there is epithelial or endothelial damage without inflammation, and “gastritis” should be used to denote conditions in which there is histologic evidence of inflammation. In clinical practice, the term “gastritis” is commonly applied to three categories: (1) erosive and hemorrhagic “gastritis” (gastropathy); (2) nonerosive, non-specific (histologic) gastritis; and (3) specific types of gastritis, characterized by distinctive histologic and endoscopic features diagnostic of specific disorders.

1. Erosive & Hemorrhagic “Gastritis” (Gastropathy)



ESSENTIALS OF DIAGNOSIS

- ▶ Most commonly seen in alcoholic or critically ill patients, or patients taking NSAIDs.
- ▶ Often asymptomatic; may cause epigastric pain, nausea, and vomiting.
- ▶ May cause hematemesis; usually insignificant bleeding.

► General Considerations

The most common causes of erosive gastropathy are medications (especially NSAIDs), alcohol, stress due to severe medical or surgical illness, and portal hypertension (“portal gastropathy”). Major risk factors for stress gastritis include mechanical ventilation, coagulopathy, trauma, burns, shock, sepsis, central nervous system injury, liver failure, kidney disease, and multiorgan failure. The use of enteral nutrition reduces the risk of stress-related bleeding. Uncommon causes of erosive gastropathy include ischemia, caustic ingestion, and radiation. Erosive and hemorrhagic gastropathy typically are diagnosed at endoscopy,

often being performed because of dyspepsia or upper gastrointestinal bleeding. Endoscopic findings include subepithelial hemorrhages, petechiae, and erosions. These lesions are superficial, vary in size and number, and may be focal or diffuse. There usually is no significant inflammation on histologic examination.

► Clinical Findings

A. Symptoms and Signs

Erosive gastropathy is usually asymptomatic. Symptoms, when they occur, include anorexia, epigastric pain, nausea, and vomiting. There is poor correlation between symptoms and the number or severity of endoscopic abnormalities. The most common clinical manifestation of erosive gastritis is upper gastrointestinal bleeding, which presents as hematemesis, “coffee grounds” emesis, or bloody aspirate in a patient receiving nasogastric suction, or as melena. Because erosive gastritis is superficial, hemodynamically significant bleeding is rare.

B. Laboratory Findings

The laboratory findings are nonspecific. The hematocrit is low if significant bleeding has occurred; iron deficiency may be found.

C. Special Examinations

Upper endoscopy is the most sensitive method of diagnosis. Although bleeding from gastritis is usually insignificant, it cannot be distinguished on clinical grounds from more serious lesions such as peptic ulcers or esophageal varices. Hence, endoscopy is generally performed within 24 hours in patients with upper gastrointestinal bleeding to identify the source. An upper gastrointestinal series is sometimes obtained in lieu of endoscopy in patients with hemodynamically insignificant upper gastrointestinal bleeds to exclude serious (eg, mass) lesions but is insensitive for the detection of gastritis.

► Differential Diagnosis

Epigastric pain may be due to peptic ulcer, gastroesophageal reflux, gastric cancer, biliary tract disease, food poisoning, viral gastroenteritis, and functional dyspepsia. With severe pain, one should consider a perforated or penetrating ulcer, pancreatic disease, esophageal rupture, ruptured aortic aneurysm, gastric volvulus, gastrointestinal ischemia, and myocardial ischemia. Causes of upper gastrointestinal bleeding include peptic ulcer disease, esophageal varices, Mallory-Weiss tear, and angioectasias.

► Specific Causes & Treatment

A. Stress Gastritis

1. Prophylaxis—Stress-related mucosal erosions and subepithelial hemorrhages may develop within 72 hours in critically ill patients. Clinically overt bleeding occurs in 6% of ICU patients, but clinically important bleeding in less than 1.5%. Bleeding is associated with a higher mortality rate but is seldom the cause of death. Two of the most

important risk factors for bleeding are coagulopathy (platelets less than 50,000/mcL [$50 \times 10^9/L$] or INR greater than 1.5) and respiratory failure with the need for mechanical ventilation for over 48 hours. When these two risk factors are absent, the risk of significant bleeding is only 0.1%. Other risk factors include traumatic brain injury, severe burns, sepsis, shock, liver disease, and prior history of peptic ulcer disease and gastrointestinal bleeding. Early enteral tube feeding may decrease the risk of significant bleeding.

Prophylaxis should be routinely administered to critically ill patients with risk factors for significant bleeding upon admission. Prophylactic suppression of gastric acid with H₂-receptor antagonists (intravenous) or proton pump inhibitors (oral or intravenous) have both been shown to reduce the incidence of clinically overt and significant bleeding. A 2018 Cochrane meta-analysis of 57 randomized controlled trials suggested that proton pump inhibitors were more effective than H₂-receptor antagonists in reducing clinically significant bleeding (OR 0.38) but may increase the risk of pneumonia (OR 1.27). A 2020 randomized clinical trial of 26,828 patients in 50 intensive care units requiring mechanical ventilation reported a lower incidence of clinically significant bleeding in patients given prophylactic proton pump inhibitors (1.3%) than in those given H₂-antagonists (1.8%) but a nonsignificant higher mortality (HR, 1.05; 95% CI, 1.00–1.10).

The optimal, cost-effective prophylactic regimen remains uncertain, hence clinical practices vary. For patients with nasoenteric tubes, immediate-release omeprazole (40 mg at 1 and 6 hours on day 1; then 40 mg once daily beginning on day 2) may be preferred because of lower cost and ease of administration. For patients requiring intravenous administration, continuous intravenous infusions of H₂-receptor antagonists provide adequate control of intragastric pH in most patients in the following doses over 24 hours: cimetidine (900–1200 mg) or famotidine (20 mg). Alternatively, intravenous proton pump inhibitors, although more expensive, may be preferred due to superior efficacy. The optimal dosing of intravenous proton pump inhibitors is uncertain; however, in clinical trials pantoprazole doses ranging from 40 mg to 80 mg and administered every 8–24 hours appear equally effective.

2. Treatment—Once bleeding occurs, patients should receive continuous infusions of a proton pump inhibitor (esomeprazole or pantoprazole, 80 mg intravenous bolus, followed by 8 mg/h continuous infusion) as well as sucralfate suspension, 1 g orally every 4 to 6 hours. Endoscopy should be performed in patients with clinically significant bleeding to look for treatable causes, especially stress-related peptic ulcers with active bleeding or visible vessels. When bleeding arises from diffuse gastritis, endoscopic hemostasis techniques are not helpful.

B. NSAID Gastritis

Of patients receiving NSAIDs in clinical trials, 25–50% have gastritis and 10–20% have ulcers at endoscopy; however, symptoms of significant dyspepsia develop in about 5%. NSAIDs that are more selective for the cyclooxygenase (COX)-2 enzyme (“coxibs”), such as celecoxib, etodolac,

and meloxicam, decrease the incidence of endoscopically visible ulcers by approximately 75% and significant ulcer complications by up to 50% compared with nonselective NSAIDs (nsNSAIDs). COX-2 selective NSAIDs are associated with increased risk of cardiovascular complications and therefore should be used with caution in patients with cardiovascular risk factors (see Peptic Ulcer Disease – NSAID-Induced Ulcers).

Dyspepsia is increased 1.5- to 2-fold with both nsNSAID and coxib use. However, dyspeptic symptoms correlate poorly with mucosal abnormalities (erosions or ulcers) or the development of adverse clinical events (ulcer bleeding or perforation). Given the frequency of dyspeptic symptoms in patients taking NSAIDs, it is neither feasible nor desirable to investigate all such cases. Patients with alarm symptoms or signs, such as severe pain, weight loss, vomiting, gastrointestinal bleeding, or anemia, should undergo diagnostic upper endoscopy. For other patients, symptoms may improve with discontinuation of the agent, reduction to the lowest effective dose, or administration with meals. Proton pump inhibitors have demonstrated efficacy in controlled trials for the treatment of NSAID-related dyspepsia and superiority to H₂-receptor antagonists for healing of NSAID-related ulcers even in the setting of continued NSAID use. Therefore, an empiric 2- to 4-week trial of an oral proton pump inhibitor (omeprazole, rabeprazole, or esomeprazole, 20–40 mg/day; lansoprazole or dexlansoprazole, 30 mg/day; pantoprazole, 40 mg/day) is recommended for patients with NSAID-related dyspepsia, especially those in whom continued NSAID treatment is required. If symptoms do not improve, diagnostic upper endoscopy should be conducted.

C. Alcoholic Gastritis

Excessive alcohol consumption may lead to dyspepsia, nausea, emesis, and minor hematemesis—a condition sometimes labeled “alcoholic gastritis.” However, it is not proven that alcohol alone actually causes significant erosive gastritis. Therapy with H₂-receptor antagonists, proton pump inhibitors, or sucralfate for 2–4 weeks often is empirically prescribed.

D. Portal Hypertensive Gastropathy

Portal hypertension commonly results in gastric mucosal and submucosal congestion of capillaries and venules, which is correlated with the severity of the portal hypertension and underlying liver disease. Usually asymptomatic, it may cause chronic gastrointestinal bleeding in 10% of patients and, less commonly, clinically significant bleeding with hematemesis. Treatment with propranolol or nadolol reduces the incidence of recurrent acute bleeding by lowering portal pressures. Patients who fail propranolol therapy may be successfully treated with portal decompressive procedures (see section above on treatment of esophageal varices).

Ahazzani W et al. Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials. *Intensive Care Med.* 2018;44:1. [PMID: 29199388]

PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group; Young PJ et al. Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: the PEP-TIC randomized clinical trial. JAMA. 2020;323:616. [PMID: 31950977]

Wang Y et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: a systematic review and network meta-analysis. BMJ. 2020;368:16744. [PMID: 31907166]

2. Nonerosive, Nonspecific Gastritis & Intestinal Metaplasia

Nonerosive gastritis is characterized by histologic inflammation. The main types of nonerosive gastritis are those due to *H pylori* infection, those associated with pernicious anemia, and eosinophilic gastritis, and possibly other genetic and environmental factors (see Specific Types of Gastritis below). The diagnosis of nonerosive gastritis is based on histologic assessment of mucosal biopsies. Endoscopic findings are normal in many cases and do not reliably predict the presence of histologic inflammation. While clinically silent in most patients, ongoing inflammation and glandular destruction may lead to patchy or diffuse atrophy of the normal cardia, fundic or antral mucosa with subsequent development of gastric intestinal metaplasia, diagnosed histologically by the presence of goblet cells and Paneth cells. Gastric intestinal metaplasia is believed to be an important precursor to the development of gastric cancer. The prevalence of gastric metaplasia varies dramatically worldwide, ranging from 3% to 5% in the United States and Northern European countries to over 20% in East Asia and South America. In the United States, the prevalence is higher among Hispanics, Blacks, and Native Americans. The estimated risk of developing gastric cancer with intestinal metaplasia is 1.6% within 10 years. Population-based screening for intestinal metaplasia and early gastric cancer is not endorsed by professional guidelines in regions with low gastric cancer incidence but is practiced in high-incidence regions.

In patients undergoing endoscopy for other indications in whom gastric biopsies are obtained, gastric intestinal metaplasia may be identified incidentally. Testing for *H pylori* is recommended, and if present, followed by eradication, which is associated with a 32% reduction in risk of gastric cancer. Routine surveillance in patients with gastric dysplasia for cancer is not recommended by professional guidelines but may be considered in higher risk individuals (eg, family history of gastric cancer).

Altayor O et al. AGA technical review on gastric intestinal metaplasia—epidemiology and risk factors. Gastroenterology. 2020;158:732. [PMID: 31816301]

Gawron AJ et al. AGA technical review on gastric intestinal metaplasia—natural history and clinical outcomes. Gastroenterology. 2020;158:705. [PMID: 31816300]

Shah SC et al. Surveillance of gastric intestinal metaplasia. Am J Gastroenterol. 2020;115:641. [PMID: 32058339]

A. *Helicobacter pylori* Gastritis

H pylori is a spiral gram-negative rod that resides beneath the gastric mucous layer adjacent to gastric epithelial cells. Although not invasive, it causes gastric mucosal inflammation with PMNs and lymphocytes.

In developed countries, the prevalence of *H pylori* is rapidly declining. In the United States, the prevalence rises from less than 10% in non-immigrants under age 30 years to over 50% in those over age 60 years. The prevalence is higher in non-Whites and immigrants from developing countries and is correlated inversely with socioeconomic status. Transmission is from person to person, mainly during infancy and childhood; however, the mode of transmission is unknown.

Acute infection with *H pylori* may cause a transient clinical illness characterized by nausea and abdominal pain that may last for several days and is associated with acute histologic gastritis with PMNs. After these symptoms resolve, the majority progress to chronic infection with chronic, diffuse mucosal inflammation (gastritis) characterized by PMNs and lymphocytes. Most persons are asymptomatic and suffer no sequelae. Many patients have inflammation that predominates in the gastric antrum but spares the gastric body (where acid is secreted). People with this phenotype tend to have increased gastrin; increased acid production; and increased risk of developing peptic ulcers, especially duodenal ulcers. Over time, inflammation may become more diffuse, involving the gastric body. In some patients, this may lead to destruction of acid-secreting glands with resultant mucosal atrophy, decreased acid secretion, and intestinal metaplasia. This phenotype is associated with an increased risk of gastric ulcers and gastric cancer. Chronic *H pylori* gastritis leads to the development of duodenal or gastric ulcers in up to 10%, gastric cancer in 0.1–3%, and low-grade B cell gastric lymphoma (mucosa-associated lymphoid tissue lymphoma; MALToma) in less than 0.01%. *H pylori* is estimated to account for 80–89% of non-cardia gastric cancers.

Eradication of *H pylori* may be achieved with antibiotics in over 85% of patients and leads to resolution of the chronic gastritis (see section on Peptic Ulcer Disease). Testing for *H pylori* is indicated for patients with either active or a past history of documented peptic ulcer disease, gastric metaplasia (see above), gastric MALToma, and a personal or family history of gastric carcinoma. Testing and empiric treatment are cost-effective in young patients (less than 60 years of age) with uncomplicated dyspepsia prior to further medical evaluation. Testing for and treating *H pylori* in patients with functional dyspepsia is generally recommended (see Dyspepsia, above). In addition, to reduce the risk of ulcer-related bleeding, testing for (and, if positive, treating) *H pylori* infection is recommended in patients taking low-dose aspirin or NSAIDs long-term. Some groups recommend population-based screening of all asymptomatic persons in regions in which there is a high prevalence of *H pylori* and gastric cancer (such as Japan, Korea, and China) to reduce the incidence of gastric cancer. Population-based screening of asymptomatic individuals is not recommended in western countries, in which the incidence of gastric cancer is low, but

should be considered in immigrants from high-prevalence regions.

1. Noninvasive testing for *H pylori*—Although serologic tests are easily obtained and widely available, clinical guidelines no longer endorse their use for testing for *H pylori* infection because they are less accurate than other noninvasive tests that measure active infection. Laboratory-based quantitative serologic ELISA tests have an overall accuracy of only 80%. In comparison, the fecal antigen immunoassay and [¹³C] urea breath test have excellent sensitivity and specificity (greater than 90–95%). Although more expensive and cumbersome to perform, these tests of active infection are more cost-effective in most clinical settings because they reduce unnecessary treatment for patients without active infection.

Recent proton pump inhibitors or antibiotics significantly reduce the sensitivity of urea breath tests and fecal antigen assays (but not serologic tests). Prior to testing, proton pump inhibitors should be discontinued for 14 days and antibiotics for at least 28 days.

2. Endoscopic testing for *H pylori*—When upper endoscopy is performed in patients with symptoms suggestive of upper gastrointestinal disease (dyspepsia, dysphagia, vomiting, weight loss, gastrointestinal bleeding), gastric biopsy specimens can be obtained for histology and detection of *H pylori* with a sensitivity and specificity of greater than 95%.

Crowe SE. *Helicobacter pylori* infection. N Engl J Med. 2019;380:1158. [PMID: 3089353]

Gupta S et al. AGA Clinical Practice Guidelines on management of gastric intestinal metaplasia. Gastroenterology. 2020;158:693. [PMID: 31816298]

Sonnenberg A et al. Low prevalence of *Helicobacter pylori*-positive peptic ulcers in private outpatient endoscopy centers in the United States. Am J Gastroenterol. 2020;115:244. [PMID: 31972622]

B. Pernicious Anemia Gastritis

Pernicious anemia gastritis is a rare autoimmune disorder involving the fundic glands with resultant achlorhydria, decreased intrinsic factor secretion, and vitamin B₁₂ malabsorption. Of patients with B₁₂ deficiency, a small number have pernicious anemia. Most patients have malabsorption secondary to chronic *H pylori* infection that results in atrophic gastritis, small intestine bacterial overgrowth, or dietary insufficiency. Fundic histology in pernicious anemia is characterized by severe gland atrophy and intestinal metaplasia caused by autoimmune destruction of the gastric fundic mucosa. Anti-intrinsic factor antibodies are present in 70% of patients. Achlorhydria leads to pronounced hypergastrinemia (greater than 1000 pg/mL) due to loss of acid inhibition of gastrin G cells. Hypergastrinemia may induce hyperplasia of gastric enterochromaffin-like cells that may lead to the development of small, multicentric carcinoid tumors in 5% of patients. Metastatic spread is uncommon in lesions smaller than 2 cm. The risk of gastric adenocarcinoma is increased threefold, with a prevalence of 1–3%. Endoscopy with biopsy is indicated in patients with pernicious anemia at the time of diagnosis. Endoscopic surveillance for dysplasia or cancer is not

recommended. Pernicious anemia is discussed in detail in Chapter 13.

Annibale E et al. A current clinical overview of atrophic gastritis. Expert Rev Gastroenterol Hepatol. 2020;14:93. [PMID: 31951768]

Massironi S et al. The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective. Autoimmun Rev. 2019;18:215. [PMID: 30639639]

3. Specific Types of Gastritis

► Infections

Acute bacterial infection of the gastric submucosa and muscularis with a variety of aerobic or anaerobic organisms produces a rare, rapidly progressive, life-threatening condition known as phlegmonous or necrotizing gastritis, which requires broad-spectrum antibiotic therapy and, in many cases, emergency gastric resection. Viral infection with CMV is seen in patients with AIDS and after bone marrow or solid organ transplantation. Endoscopic findings include thickened gastric folds and ulcerations. Fungal infection with mucormycosis and *Candida* may occur in immunocompromised and diabetic patients. Larvae of *Anisakis marina* ingested in raw fish or sushi may become embedded in the gastric mucosa, producing severe abdominal pain. Pain persists for several days until the larvae die. Endoscopic removal of the larvae provides rapid symptomatic relief.

PEPTIC ULCER DISEASE



ESSENTIALS OF DIAGNOSIS

- History of dyspepsia present in 80–90% of patients with variable relationship to meals.
- Ulcer symptoms characterized by rhythmicity and periodicity.
- Ulcer complications present without antecedent symptoms in 10–20% of patients.
- Most NSAID-induced ulcers are asymptomatic.
- Upper endoscopy with gastric biopsy for *H pylori* is the diagnostic procedure of choice in most patients.
- Gastric ulcer biopsy or documentation of complete healing necessary to exclude gastric malignancy.

► General Considerations

Peptic ulcer is a break in the gastric or duodenal mucosa that arises when the normal mucosal defensive factors are impaired or are overwhelmed by aggressive luminal factors such as acid and pepsin. In the United States, there are about 500,000 new cases per year of peptic ulcer and 4 million ulcer recurrences; the lifetime prevalence of ulcers in the adult population is approximately 10%. Ulcers occur either

in the duodenum, where over 95% are in the bulb or pyloric channel, or in the stomach, where benign ulcers are located most commonly in the antrum (60%) or at the junction of the antrum and body on the lesser curvature (25%).

Although ulcers can occur in any age group, duodenal ulcers most commonly occur in patients between the ages of 30 and 55 years, whereas gastric ulcers are more common in patients between the ages of 55 and 70 years. The incidence of duodenal ulcer disease has been declining dramatically for the past 30 years (due to the eradication of *H pylori*), but the incidence of gastric ulcers has not been declining (due to the widespread use of NSAIDs and low-dose aspirin).

Etiology

There are two major causes of peptic ulcer disease: NSAIDs and chronic *H pylori* infection. Evidence of *H pylori* infection or NSAID ingestion should be sought in all patients with peptic ulcer. Alcohol, dietary factors, and stress do not appear to cause ulcer disease. Less than 5–10% of ulcers are caused by other conditions, including acid hypersecretory states (such as Zollinger-Ellison syndrome or systemic mastocytosis), CMV (especially in transplant recipients), Crohn disease, lymphoma, medications (eg, alendronate), or chronic medical illness (cirrhosis or chronic kidney disease), or are idiopathic. NSAID-induced and *H pylori*-associated ulcers will be presented in this section; Zollinger-Ellison syndrome will be discussed subsequently.

A. *H pylori*-Associated Ulcers

H pylori infection with associated gastritis appears to be a necessary cofactor for the majority of duodenal and gastric ulcers not associated with NSAIDs. Ulcer disease will develop in an estimated 10% of infected patients. The prevalence of *H pylori* infection in duodenal ulcer patients is 70–90%. The association with gastric ulcers is lower, but *H pylori* is found in most patients in whom NSAIDs cannot be implicated.

The natural history of *H pylori*-associated peptic ulcer disease is well defined. In the absence of specific antibiotic treatment to eradicate the organism, 85% of patients will have an endoscopically visible recurrence within 1 year. Half of these will be symptomatic. After successful eradication of *H pylori* with antibiotics, ulcer recurrence rates are reduced dramatically to 5–20% at 1 year. Most of these ulcer recurrences are due to NSAID use or, rarely, reinfection with *H pylori*.

B. NSAID-Induced Ulcers

There is a 10–20% prevalence of gastric ulcers and a 2–5% prevalence of duodenal ulcers in long-term NSAID users. Approximately 2–5%/year of long-term NSAID users will have an ulcer that causes clinically significant dyspepsia or a serious complication. The incidence of serious gastrointestinal complications (hospitalization, bleeding, perforation) is 0.2–1.9%/year. Meta-analyses of clinical trials detected an increased risk of upper gastrointestinal bleeding in patients taking low-dose aspirin (1 of 1000), coxibs (2 of

1000), and nsNSAIDs (4–6 of 1000). The risk of NSAID complications is greater within the first 3 months of therapy and in patients who are older than 60 years; who have a prior history of ulcer disease; or who take NSAIDs in combination with aspirin, corticosteroids, or anticoagulants.

Traditional nsNSAIDs inhibit prostaglandins through reversible inhibition of both COX-1 and COX-2 enzymes. Aspirin causes irreversible inhibition of COX-1 and COX-2 as well as of platelet aggregation. Coxibs (or selective NSAIDs) preferentially inhibit COX-2—the principal enzyme involved in prostaglandin production at sites of inflammation—while providing relative sparing of COX-1, the principal enzyme involved with mucosal cytoprotection in the stomach and duodenum. Celecoxib is the only coxib currently available in the United States, although other older NSAIDs (etodolac, meloxicam) may have similar COX-2/COX-1 selectivity.

Coxibs decrease the incidence of endoscopically visible ulcers by approximately 75% compared with nsNSAIDs. Of greater clinical importance, the risk of significant clinical events (obstruction, perforation, bleeding) is reduced by up to 50% in patients taking coxibs versus nsNSAIDs. However, a twofold increase in the incidence in cardiovascular complications (myocardial infarction, cerebrovascular infarction, and death) has been detected in patients taking coxibs compared with placebo, prompting the voluntary withdrawal of two highly selective coxibs (rofecoxib and valdecoxib) from the market by the manufacturers. A review by an FDA panel suggested that all NSAIDs (other than aspirin and, possibly, naproxen) may be associated with an increased risk of cardiovascular complications, but concluded that celecoxib, which has less COX-2 selectivity than rofecoxib and valdecoxib, does not have higher risk than other nsNSAIDs when used in currently recommended doses (200 mg/day). In 2016, a large, randomized, noninferiority trial comparing ibuprofen, naproxen, and celecoxib in arthritis patients with increased cardiovascular risk found no difference in cardiovascular safety between the three drugs over 3 years. However, celecoxib was associated with significantly fewer serious gastrointestinal events than both naproxen (hazard ratio 0.71) and ibuprofen (hazard ratio 0.65).

Use of even low-dose aspirin (81–325 mg/day) leads to a twofold increased risk of gastrointestinal bleeding complications. In population studies, gastrointestinal bleeding occurs in 1.2% of patients each year. Patients with a prior history of peptic ulcers or gastrointestinal bleeding have a markedly increased risk of complications on low-dose aspirin. It should be noted that low-dose aspirin in combination with NSAIDs or coxibs increases the risk of ulcer complications by up to tenfold compared with NSAIDs or low-dose aspirin alone. Dual antiplatelet therapy with aspirin and a thienopyridine (eg, clopidogrel) incurs a twofold to threefold increased risk of bleeding compared with aspirin alone.

H pylori infection increases the risk of ulcer disease and complications over threefold in patients taking NSAIDs or low-dose aspirin. It is hypothesized that NSAID initiation may potentiate or aggravate ulcer disease in susceptible infected individuals.

► Clinical Findings

A. Symptoms and Signs

Epigastric pain (dyspepsia), the hallmark of peptic ulcer disease, is present in 80–90% of patients. However, this complaint is not sensitive or specific enough to serve as a reliable diagnostic criterion for peptic ulcer disease. The clinical history cannot accurately distinguish duodenal from gastric ulcers. Less than 25% of patients with dyspepsia have ulcer disease at endoscopy. Twenty percent of patients with ulcer complications such as bleeding have no antecedent symptoms (“silent ulcers”). Nearly 60% of patients with NSAID-related ulcer complications do not have prior symptoms.

Pain is typically well localized to the epigastrium and not severe. It is described as gnawing, dull, aching, or “hunger-like.” Approximately 50% of patients report relief of pain with food or antacids (especially those with duodenal ulcers) and a recurrence of pain 2–4 hours later. However, many patients deny any relationship to meals or report worsening of pain. Two-thirds of duodenal ulcers and one-third of gastric ulcers cause nocturnal pain that awakens the patient. A change from a patient’s typical rhythmic discomfort to constant or radiating pain may reflect ulcer penetration or perforation. Most patients have symptomatic periods lasting up to several weeks with intervals of months to years in which they are pain free (periodicity).

Nausea and anorexia may occur with gastric ulcers. Significant vomiting and weight loss are unusual with uncomplicated ulcer disease and suggest gastric outlet obstruction or gastric malignancy.

The physical examination is often normal in uncomplicated peptic ulcer disease. Mild, localized epigastric tenderness to deep palpation may be present. FOBT or FIT is positive in one-third of patients.

B. Laboratory Findings

Laboratory tests are normal in uncomplicated peptic ulcer disease but are ordered to exclude ulcer complications or confounding disease entities. Anemia may occur with acute blood loss from a bleeding ulcer or less commonly from chronic blood loss. Leukocytosis suggests ulcer penetration or perforation. An elevated serum amylase in a patient with severe epigastric pain suggests ulcer penetration into the pancreas. A fasting serum gastrin level to screen for Zollinger-Ellison syndrome is obtained in some patients.

C. Endoscopy

Upper endoscopy is the procedure of choice for the diagnosis of duodenal and gastric ulcers. Duodenal ulcers are virtually never malignant and do not require biopsy. Three to 5 percent of benign-appearing gastric ulcers prove to be malignant. Hence, biopsies of the ulcer margin are almost always performed. Provided that the gastric ulcer appears benign to the endoscopist and adequate biopsy specimens reveal no evidence of cancer, dysplasia, or atypia, the patient may be monitored without further endoscopy. If these conditions are not fulfilled, follow-up endoscopy should be performed 12 weeks after the start of therapy to

document complete healing; nonhealing ulcers are suspicious for malignancy.

D. Imaging

Abdominal CT imaging is obtained in patients with suspected complications of peptic ulcer disease (perforation, penetration, or obstruction). Barium upper gastrointestinal series is no longer recommended.

E. Testing for *H pylori*

In patients in whom an ulcer is diagnosed by endoscopy, gastric mucosal biopsies should be obtained for histologic evaluation. Noninvasive assessment for *H pylori* with fecal antigen assay or urea breath testing may be done in patients with a history of peptic ulcer disease to diagnose active infection or in patients following its treatment to confirm successful eradication. Both tests have a sensitivity and specificity of 92–95%. Proton pump inhibitors may cause false-negative urea breath tests and fecal antigen tests and should be withheld for at least 14 days before testing. Because of its lower sensitivity (85%) and specificity (79%), serologic testing should not be performed unless fecal antigen testing or urea breath testing is unavailable.

► Differential Diagnosis

Peptic ulcer disease must be distinguished from other causes of epigastric distress (dyspepsia). Over 50% of patients with dyspepsia have no obvious organic explanation for their symptoms and are classified as having functional dyspepsia (see sections above on Dyspepsia and Functional Dyspepsia). Atypical gastroesophageal reflux may be manifested by epigastric symptoms. Biliary tract disease is characterized by discrete, intermittent episodes of pain that should not be confused with other causes of dyspepsia. Severe epigastric pain is atypical for peptic ulcer disease unless complicated by a perforation or penetration. Other causes include acute pancreatitis, acute cholecystitis or choledocholithiasis, esophageal rupture, gastric volvulus, gastric or intestinal ischemia, and ruptured aortic aneurysm.

► Pharmacologic Agents

The pharmacology and use of several agents that enhance the healing of peptic ulcers are briefly discussed here. They may be divided into three categories: (1) acid-antisecretory agents, (2) mucosal protective agents, and (3) agents that promote healing through eradication of *H pylori*.

A. Acid-Antisecretory Agents

1. Proton pump inhibitors—Proton pump inhibitors covalently bind the acid-secreting enzyme H⁺-K⁺-ATPase, or “proton pump,” permanently inactivating it.

There are six oral proton pump inhibitors currently available: omeprazole, rabeprazole, esomeprazole, lansoprazole, dexlansoprazole, and pantoprazole. Despite minor differences in their pharmacology, they are equally efficacious in the treatment of peptic ulcer disease. Treatment with oral proton pump inhibitors results in over 90% healing of duodenal ulcers after 4 weeks and 90% of gastric

ulcers after 8 weeks when given once daily (30 minutes before breakfast) at the following recommended doses: omeprazole, 20–40 mg; esomeprazole, 40 mg; rabeprazole, 20 mg; lansoprazole, 30 mg; dexlansoprazole, 30–60 mg; and pantoprazole, 40 mg. Compared with H₂-receptor antagonists, proton pump inhibitors provide faster pain relief and more rapid ulcer healing.

The proton pump inhibitors are remarkably safe for short-term therapy. (For potential long-term risks, see Gastroesophageal Reflux Disease.) Long-term use may lead to increased risk of enteric infections (including *C difficile*) and micronutrient deficiencies (vitamin B₁₂, iron, magnesium, and possibly calcium). Observational studies report an association with a number of adverse events, including interstitial nephritis, pneumonia, bone fracture, myocardial infarction and dementia, but these have not been confirmed in large prospective studies. Nonetheless, long-term proton pump inhibitor therapy should be prescribed only for patients with appropriate indications. Serum gastrin levels rise significantly in 3% of patients receiving long-term therapy but return to normal limits within 2 weeks after discontinuation.

2. H₂-receptor antagonists—Although H₂-receptor antagonists are effective in the treatment of peptic ulcer disease, proton pump inhibitors are now the preferred agents because of their ease of use and superior efficacy. Three H₂-receptor antagonists are available: cimetidine, famotidine, and nizatidine. For uncomplicated peptic ulcers, H₂-receptor antagonists may be administered once daily at bedtime as follows: nizatidine 300 mg, famotidine 40 mg, and cimetidine 800 mg. Duodenal and gastric ulcer healing rates of 85–90% are obtained within 6 weeks and 8 weeks, respectively. NOTE: Ranitidine has now been withdrawn from the US market by the FDA after an ongoing investigation showed that, when stored at higher-than-normal temperatures, it could contain an increased and unsafe quantity of N-nitrosodimethylamine (NDMA), a probable human carcinogen.

B. Agents Enhancing Mucosal Defenses

Bismuth sucralfate, misoprostol, and antacids all have been shown to promote ulcer healing through the enhancement of mucosal defensive mechanisms. Given the greater efficacy and safety of antisecretory agents and better compliance of patients, these agents are no longer used as first-line therapy for active ulcers in most clinical settings.

C. *H pylori* Eradication Therapy

Eradication of *H pylori* has proved difficult. Combination regimens that use two or three antibiotics with a proton pump inhibitor or bismuth are required to achieve adequate rates of eradication and to reduce the number of failures due to antibiotic resistance. In the United States, up to 50% of strains are resistant to metronidazole and 10–20% are resistant to clarithromycin. Recommended regimens are listed in Table 15–10. Ideally, the optimal regimen would be determined by antibiotic susceptibility testing. However, this requires endoscopic biopsy, and few laboratories are equipped for *H pylori* cultures. Thus, in most clinical settings, therapy is chosen empirically. Until recently, in the

United States a 14-day course of so-called triple therapy with a proton pump inhibitor, clarithromycin, and either amoxicillin (or metronidazole, if penicillin allergic) was recommended as first-line therapy. However, a 2016 updated guideline from the Toronto Consensus group and 2017 guideline from the American College of Gastroenterology recommended that triple therapy no longer be used (due to increasing clarithromycin resistance) except in areas with known low-level clarithromycin resistance (less than 15%). In most settings, empiric treatment with a 14-day bismuth-based or a nonbismuth-based regimen of so-called quadruple therapy is now recommended as first-line therapy. Both achieve a greater than 85% eradication rate. The bismuth-based quadruple therapy regimen consists of bismuth, tetracycline, a proton pump inhibitor, and metronidazole or tinidazole (Table 15–10). It is effective even for metronidazole-resistant strains. Nonbismuth-based quadruple therapy consists of a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin; it is effective even for clarithromycin-resistant strains.

► Medical Treatment

Patients should be encouraged to eat balanced meals at regular intervals. There is no justification for bland or restrictive diets. Moderate alcohol intake is not harmful. Smoking retards the rate of ulcer healing and increases the frequency of recurrences and should be prohibited.

A. Treatment of *H pylori*-Associated Ulcers

1. Treatment of active ulcer—The goals of treatment of active *H pylori*-associated ulcers are to relieve dyspeptic symptoms, to promote ulcer healing, and to eradicate *H pylori* infection. Uncomplicated *H pylori*-associated ulcers should be treated for 14 days with one of the proton pump inhibitor-based *H pylori* eradication regimens listed in Table 15–10. At that point, no further antisecretory therapy is needed, provided the ulcer was small (less than 1 cm) and dyspeptic symptoms have resolved. For patients with large or complicated ulcers, an antisecretory agent should be continued for an additional 2–4 weeks (duodenal ulcer) or 4–6 weeks (gastric ulcer) after completion of the antibiotic regimen to ensure complete ulcer healing. A once-daily oral proton pump inhibitor (as listed in Table 15–10) is recommended. Confirmation of *H pylori* eradication is recommended for all patients more than 4 weeks after completion of antibiotic therapy and more than 2 weeks after discontinuation of the proton pump inhibitor either with noninvasive tests (urea breath test, fecal antigen test) or endoscopy with biopsy for histology.

2. Therapy to prevent recurrence—Successful eradication reduces ulcer recurrences to less than 20% after 1–2 years. The most common cause of recurrence after antibiotic therapy is failure to achieve successful eradication. Once cure has been achieved, reinfection rates are less than 0.5% per year. Although *H pylori* eradication has reduced the need for long-term maintenance antisecretory therapy to prevent ulcer recurrences, there remains a subset of patients who require long-term therapy with a proton pump inhibitor once daily. This subset includes patients

Table 15–10. Treatment options for peptic ulcer disease.**Active *Helicobacter pylori*-associated ulcer**

1. Treat with anti-*H pylori* regimen for 14 days. Treatment options:

Standard Bismuth Quadruple Therapy

- Proton pump inhibitor orally twice daily^{1,2}
- Bismuth subsalicylate 262 mg two tablets orally four times daily or bismuth subcitrate 120–400 mg orally four times daily
- Tetracycline 500 mg orally four times daily
- Metronidazole 500 mg three times daily

OR

- Proton pump inhibitor orally twice daily¹
- Bismuth subcitrate potassium 140 mg/metronidazole 125 mg/tetracycline 125 mg (Pylera) three capsules orally four times daily for 10 days³

Standard Nonbismuth Quadruple Therapy

- Proton pump inhibitor orally twice daily
- Amoxicillin 1000 mg orally twice daily
- Metronidazole 500 mg orally twice daily
- Clarithromycin 500 mg orally twice daily

Standard Triple Therapy (No longer recommended except in locales where clarithromycin resistance is < 15%)

- Proton pump inhibitor orally twice daily
- Clarithromycin 500 mg orally twice daily
- Amoxicillin 1 g orally twice daily (or, if penicillin allergic, metronidazole 500 mg orally twice daily)

Levofloxacin Triple Therapy (Recommended after failed previous treatment in a patient with clarithromycin and tetracycline allergy)

- Proton pump inhibitor orally twice daily
- Levofloxacin 500 mg orally twice daily
- Amoxicillin 1 g orally twice daily

2. After completion of course of *H pylori* eradication therapy, continue treatment with proton pump inhibitor¹ once daily for 4–6 weeks if ulcer is large (> 1 cm) or complicated.

3. Confirm successful eradication of *H pylori* with urea breath test, fecal antigen test, or endoscopy with biopsy at least 4 weeks after completion of antibiotic treatment and 2 weeks after completion of proton pump inhibitor treatment.

Active ulcer not attributable to *H pylori*

Consider other causes: NSAIDs, Zollinger-Ellison syndrome, gastric malignancy. Treatment options:

- Proton pump inhibitors¹:

Uncomplicated duodenal ulcer: treat for 4 weeks
Uncomplicated gastric ulcer: treat for 8 weeks

- H₂-receptor antagonists:

Uncomplicated duodenal ulcer: cimetidine 800 mg, nizatidine 300 mg, famotidine 40 mg, orally once daily at bedtime for 6 weeks
Uncomplicated gastric ulcer: cimetidine 400 mg, nizatidine 150 mg, famotidine 20 mg, orally twice daily for 8 weeks
Complicated ulcers: proton pump inhibitors¹ are the preferred drugs

Prevention of ulcer relapse

1. NSAID-induced ulcer: prophylactic therapy for high-risk patients (prior ulcer disease or ulcer complications, use of corticosteroids or anticoagulants, age > 60 years, serious comorbid illnesses). Treatment options:
 - Proton pump inhibitor once daily
 - Celecoxib (contraindicated in patients with increased risk of cardiovascular disease)
 - Misoprostol 200 mcg orally 4 times daily
2. Long-term “maintenance” therapy indicated in patients with recurrent ulcers who either are *H pylori*-negative or who have failed attempts at eradication therapy: once-daily oral proton pump inhibitor¹

¹Oral proton pump inhibitors: omeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, dexlansoprazole 30–60 mg, pantoprazole 40 mg, esomeprazole 40 mg. Proton pump inhibitors are administered 30 minutes before meals.

²Preferred regimen in regions with high clarithromycin resistance or in patients who have previously received a macrolide antibiotic or are penicillin allergic. Effective against metronidazole-resistant organisms.

³Pylera is an FDA-approved formulation containing bismuth subcitrate 140 mg/tetracycline 125 mg/metronidazole 125 mg per capsule. NSAIDs, nonsteroidal anti-inflammatory drugs.

with *H pylori*-positive ulcers who have not responded to repeated attempts at eradication therapy, patients with a history of *H pylori*-positive ulcers who have recurrent ulcers despite successful eradication, and patients with idiopathic ulcers (ie, *H pylori*-negative and not taking NSAIDs). In all patients with recurrent ulcers, NSAID usage (unintentional or surreptitious) and hypersecretory states (including gastrinoma) should be excluded.

B. Treatment of NSAID-Induced Ulcers

1. Treatment of active ulcers—In patients with NSAID-induced ulcers, the offending agent should be discontinued whenever possible. Both gastric and duodenal ulcers respond rapidly to therapy with H₂-receptor antagonists or proton pump inhibitors (Table 15–10) once NSAIDs are eliminated. All patients with NSAID-associated ulcers should undergo

testing for *H pylori* infection. Antibiotic eradication therapy should be given if *H pylori* tests are positive.

2. Prevention of NSAID-induced ulcers—Clinicians should carefully weigh the benefits of NSAID therapy with the risks of cardiovascular and gastrointestinal complications. Ulcer complications occur in up to 2% of all nsNSAID-treated patients per year, but in up to 10–20% per year of patients with multiple risk factors. These include age over 60 years, history of ulcer disease or complications, concurrent use of antiplatelet therapy (low-dose aspirin or clopidogrel, or both), concurrent therapy with anticoagulants or corticosteroids, and serious underlying medical illness. After considering the patient's risk of cardiovascular and gastrointestinal complications due to NSAID use, the clinician can decide what type of NSAID (nsNSAID vs coxib) is appropriate and what strategies should be used to reduce the risk of such complications. To minimize cardiovascular and gastrointestinal risks, all NSAIDs should be used at the lowest effective dose and for the shortest time necessary.

A. TEST FOR AND TREAT *H PYLORI* INFECTION—All patients with a known history of peptic ulcer disease who are treated with NSAIDs or antiplatelet agents (aspirin, clopidogrel) should be tested for *H pylori* infection and treated, if positive. Although *H pylori* eradication may decrease the risk of NSAID-related complications, co-therapy with a proton pump inhibitor is still required in high-risk patients.

B. PROTON PUMP INHIBITOR—Treatment with an oral proton pump inhibitor given once daily (rabeprazole 20 mg, omeprazole 20–40 mg, lansoprazole 30 mg, dexlansoprazole 30–60 mg, or pantoprazole or esomeprazole 40 mg) is effective in the prevention of NSAID-induced gastric and duodenal ulcers and is approved by the FDA for this indication. Among high-risk patients taking nsNSAIDs or coxibs, the incidence of endoscopically visible gastric and duodenal ulcers after 6 months of therapy in patients treated with esomeprazole 20–40 mg/day was 5%, compared with 17% who were given placebo. Nonetheless, proton pump inhibitors are not fully protective in high-risk patients in preventing NSAID-related complications. In prospective, controlled trials of patients with a prior history of NSAID-related ulcer complications, the incidence of recurrent bleeding was almost 5% after 6 months in patients taking nsNSAIDs and a proton pump inhibitor. In prospective, controlled trials of patients with a prior history of ulcer complications related to low-dose aspirin, the incidence of recurrent ulcer bleeding in patients taking low-dose aspirin alone was approximately 15% per year compared with 0–2% per year in patients taking low-dose aspirin and proton pump inhibitor and 9–14% per year in patients taking clopidogrel. Thus, proton pump inhibitors are highly effective in preventing complications related to low-dose aspirin, even in high-risk patients. Enteric coating of aspirin may reduce direct topical damage to the stomach but does not reduce its other complications.

C. RECOMMENDATIONS TO REDUCE RISK OF ULCER COMPLICATIONS FROM nsNSAIDS AND COXIBS—For patients with a low risk of cardiovascular disease who have no risk factors for gastrointestinal complications, an nsNSAID

alone may be given. For patients with one or two gastrointestinal risk factors, a coxib alone or an nsNSAID should be given with a proton pump inhibitor once daily to reduce the risk of gastrointestinal complications. NSAIDs should be avoided, if possible, in patients with multiple risk factors; if required, however, combination therapy of a coxib or a partially COX-2 selective nsNSAID (etodolac, meloxicam) with a proton pump inhibitor once daily is recommended.

For patients with an increased risk of cardiovascular complications, it is preferable to avoid NSAIDs, if possible. Almost all patients with increased cardiovascular risk also will be taking antiplatelet therapy with low-dose aspirin or clopidogrel, or both. Because combination therapy with an nsNSAID and antiplatelet therapy increases the risks of gastrointestinal complications, these patients should all receive cotherapy with a proton pump inhibitor once daily or misoprostol.

D. RECOMMENDATIONS TO REDUCE RISK OF ULCER COMPLICATIONS WITH USE OF ANTIPLATELET AGENTS

The risk of significant gastrointestinal complications in persons taking low-dose aspirin (81–325 mg/day) or clopidogrel, or both, for cardiovascular prophylaxis is 0.5%/year. Aspirin, 81 mg/day, is recommended in most patients because it has a lower risk of gastrointestinal complications but equivalent cardiovascular protection compared with higher aspirin doses. Complications are increased with combinations of aspirin and clopidogrel or aspirin and anticoagulants. Clopidogrel does not cause gastrointestinal ulcers or erosions. However, its antiplatelet activity may promote bleeding from erosions or ulcers caused by low-dose aspirin or *H pylori*. Patients with dyspepsia or prior ulcer disease should be tested for *H pylori* infection and treated, if positive. Patients younger than 60–70 years who have no other risk factors for gastrointestinal complications may be treated with low-dose aspirin or dual antiplatelet therapy without a proton pump inhibitor. Virtually all other patients who require low-dose aspirin or aspirin plus anticoagulant therapy should receive a proton pump inhibitor once daily.

At the present time, the optimal management of patients who require dual antiplatelet therapy with clopidogrel and aspirin is uncertain. Clopidogrel is a prodrug that is activated by the cytochrome P450 CYP2C19 enzyme. All proton pump inhibitors inhibit CYP2C19 to varying degrees, with omeprazole having the highest and pantoprazole the least level of inhibition. In vitro and in vivo platelet aggregation studies demonstrate that proton pump inhibitors (especially omeprazole) may attenuate the antiplatelet effects of clopidogrel, although the clinical importance of this interaction is uncertain. The FDA has issued a warning that patients should avoid using clopidogrel with omeprazole and esomeprazole. A 2010 expert consensus panel concluded that once daily treatment with an oral proton pump inhibitor (pantoprazole 40 mg; rabeprazole 20 mg; lansoprazole or dexlansoprazole 30 mg) may be recommended for patients who have an increased risk of upper gastrointestinal bleeding (prior history of peptic ulcer disease or gastrointestinal bleeding; concomitant NSAIDs). For patients with a lower risk of gastrointestinal bleeding, the risks and benefits of proton pump inhibitors must be weighed. Pending further recommendations, an acceptable

alternative is to treat with an oral H₂-receptor antagonist (famotidine 20 mg, nizatidine 150 mg) twice daily; however, proton pump inhibitors are more effective in preventing upper gastrointestinal bleeding. Cimetidine is a CYP2C19 inhibitor and should not be used. An alternative strategy is ticagrelor, an antiplatelet agent approved for use with low-dose aspirin in the treatment of acute coronary syndrome. Like clopidogrel, ticagrelor blocks the platelet ADP p2y12 receptor; however, it does not require hepatic activation, it does not interact with the CYP2C19 enzyme, and its efficacy is not diminished by proton pump inhibitors.

C. Refractory Ulcers

Ulcers that are truly refractory to medical therapy are now uncommon. Less than 5% of ulcers are unhealed after 8 weeks of once daily therapy with proton pump inhibitors, and almost all benign ulcers heal with twice-daily therapy. Thus, noncompliance is the most common cause of ulcer nonhealing. NSAID and aspirin use, sometimes surreptitious, are commonly implicated in refractory ulcers and must be stopped. Single or multiple linear gastric ulcers may occur in large hiatal hernias where the stomach slides back and forth through the diaphragmatic hiatus ("Cameron lesions"); this may be a cause of iron deficiency anemia. Other causes of nonhealing ulcers include acid hypersecretion (Zollinger-Ellison syndrome), unrecognized malignancy (adenocarcinoma or lymphoma), medications causing gastrointestinal ulceration (eg, iron or bisphosphonates), Crohn disease, and unusual infections (*H heilmanni*, CMV, mucormycosis). Fasting serum gastrin levels should be obtained to exclude gastrinoma with acid hypersecretion (Zollinger-Ellison syndrome). Repeat ulcer biopsies are mandatory after 2–3 months of therapy in all nonhealed ulcers to look for malignancy or infection. Patients with persistent nonhealing ulcers are referred for surgical therapy after exclusion of NSAID use and persistent *H pylori* infection.

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COMPLICATIONS OF PEPTIC ULCER DISEASE

1. Gastrointestinal Hemorrhage



- ▶ "Coffee grounds" emesis, hematemesis, melena, or hematochezia.
- ▶ Emergent upper endoscopy is diagnostic and therapeutic.

► General Considerations

Approximately 50% of all episodes of upper gastrointestinal bleeding are due to peptic ulcer. Clinically significant bleeding occurs in 10% of ulcer patients. About 80% of patients stop bleeding spontaneously and generally have an uneventful recovery; the remaining 20% have more severe bleeding. The overall mortality rate for ulcer bleeding is 7%, but it is higher in older patients, in patients with comorbid medical problems, and in patients with hospital-associated bleeding. Mortality is also higher in patients who present with persistent hypotension or shock, bright red blood in the vomitus or nasogastric lavage fluid, or severe coagulopathy.

► Clinical Findings

A. Symptoms and Signs

Up to 20% of patients have no antecedent symptoms of pain; this is particularly true of patients receiving NSAIDs. Common presenting signs include melena and hematemesis. Massive upper gastrointestinal bleeding or rapid gastrointestinal transit may result in hematochezia rather than melena; this may be misinterpreted as signifying a lower tract bleeding source. Nasogastric lavage that demonstrates "coffee grounds" or bright red blood confirms an upper tract source. Recovered nasogastric lavage fluid that is negative for blood does not exclude active bleeding from a duodenal ulcer.

B. Laboratory Findings

The hematocrit may fall as a result of bleeding or expansion of the intravascular volume with intravenous fluids. The BUN may rise as a result of absorption of blood nitrogen from the small intestine and prerenal azotemia.

► Treatment

The assessment and initial management of upper gastrointestinal tract bleeding are discussed above. Specific issues pertaining to peptic ulcer bleeding are described below.

A. Medical Therapy

1. Antisecretory agents—Intravenous proton pump inhibitors should be administered for 3 days in patients with ulcers whose endoscopic appearance suggests a high risk of rebleeding after endoscopic therapy. Intravenous proton pump inhibitors have been associated with a reduction in rebleeding, transfusions, need for further endoscopic therapy, and surgery in the subset of patients with high-risk ulcers, ie, an ulcer with active bleeding, visible vessel, or adherent clot. After initial successful endoscopic treatment of ulcer hemorrhage, intravenous esomeprazole, pantoprazole, or omeprazole (80 mg bolus injection, followed by 8 mg/h continuous infusion for 72 hours) reduces the rebleeding rate from approximately 20% to less than 10%; however, intravenous omeprazole is not available in the United States.

High-dose oral proton pump inhibitors (omeprazole 40 mg twice daily) also appear to be effective in reducing

rebleeding but have not been compared with the intravenous regimen. Intravenous H₂-receptor antagonists have not been demonstrated to be of any benefit in the treatment of acute ulcer bleeding.

2. Long-term prevention of rebleeding—Recurrent ulcer bleeding develops within 3 years in one-third of patients if no specific therapy is given. In patients with bleeding ulcers who are *H pylori*-positive, successful eradication effectively prevents recurrent ulcer bleeding in almost all cases. It is therefore recommended that all patients with bleeding ulcers be tested for *H pylori* infection and treated if positive. Four weeks after completion of antibiotic therapy, a urea breath or fecal antigen test for *H pylori* should be administered or endoscopy performed with biopsy and histology for confirmation of successful eradication. In patients in whom *H pylori* persists or the small subset of patients whose ulcers are not associated with NSAIDs or *H pylori*, long-term acid suppression with a once-daily proton pump inhibitor should be prescribed to reduce the likelihood of recurrence of bleeding.

B. Endoscopy

Endoscopy is the preferred diagnostic procedure in almost all cases of upper gastrointestinal bleeding because of its high diagnostic accuracy, its ability to predict the likelihood of recurrent bleeding, and its availability for therapeutic intervention in high-risk lesions. Endoscopy should be performed within 24 hours in most cases. In cases of severe active bleeding, endoscopy is performed as soon as patients have been appropriately resuscitated and are hemodynamically stable.

On the basis of clinical and endoscopic criteria, it is possible to predict which patients are at a higher risk of rebleeding and therefore to make more rational use of hospital resources. Nonbleeding ulcers under 2 cm in size with a base that is clean have a less than 5% chance of rebleeding. Most young (under age 60 years), otherwise healthy patients with clean-based ulcers may be safely discharged from the emergency department or hospital after endoscopy. Ulcers that have a flat red or black spot have a less than 10% chance of significant rebleeding. Patients who are hemodynamically stable with these findings should be admitted to a hospital ward for 24–72 hours and may begin immediate oral feedings and antiulcer (or anti-*H pylori*) medication.

By contrast, the risk of rebleeding or continued bleeding in ulcers with a nonbleeding visible vessel is 50%, and with active bleeding, it is 80–90%. Endoscopic therapy with thermocoagulation (bipolar or heater probes) or application of endoscopic clips (akin to a staple) is the standard of care for such lesions because it reduces the risk of rebleeding, the number of transfusions, and the need for subsequent surgery. The optimal treatment of ulcers with a dense clot that adheres despite vigorous washing is controversial; removal of the clot followed by endoscopic treatment of an underlying vessel may be considered in selected high-risk patients. For actively bleeding ulcers, a combination of epinephrine injection followed by thermocoagulation or clip application commonly is used. These techniques

achieve successful hemostasis of actively bleeding lesions in 90% of patients. After endoscopic therapy followed by an intravenous proton pump inhibitor, significant rebleeding occurs in less than 10% of cases, of which over 70% can be managed successfully with repeat endoscopic treatment. After endoscopic treatment, patients should remain hospitalized for at least 72 hours, when the risk of rebleeding falls to below 3%.

C. Recurrent Bleeding

Less than 5% of patients have persistent or recurrent bleeding that cannot be controlled with endoscopic techniques. The availability of newer, larger over-the-scope clips (“bear claw”) has further reduced the risk of persistent bleeding requiring other more aggressive interventions. In a randomized prospective study of patients with recurrent ulcer bleeding after conventional medical and endoscopic therapy, persistent bleeding occurred in 6% of patients treated with over-the-scope clips versus 42.4% treated with further conventional endoscopic modalities. For patients in whom endoscopic therapy is unsuccessful, percutaneous radiologic embolization or surgery should be considered. Overall surgical mortality for emergency ulcer bleeding is less than 6%. The prognosis is poorer for patients over age 60 years, those with serious underlying medical illnesses or chronic kidney disease, and those who require more than 10 units of blood transfusion.

2. Ulcer Perforation

Perforations develop in less than 5% of ulcer patients, usually from ulcers on the anterior wall of the stomach or duodenum. Perforation results in a chemical peritonitis that causes sudden, severe generalized abdominal pain that prompts most patients to seek immediate attention. Elderly or debilitated patients and those receiving long-term corticosteroid therapy may experience minimal initial symptoms, presenting late with bacterial peritonitis, sepsis, and shock. On physical examination, patients appear ill, with a rigid, quiet abdomen and rebound tenderness. Hypotension develops later after bacterial peritonitis has developed. If hypotension is present early with the onset of pain, other abdominal emergencies should be considered such as a ruptured aortic aneurysm, mesenteric infarction, or acute pancreatitis. Leukocytosis is almost always present. A mildly elevated serum amylase (less than twice normal) is sometimes seen with ulcer perforation. Abdominal CT usually establishes the diagnosis without need for further studies. The absence of free air may lead to a misdiagnosis of pancreatitis, cholecystitis, or appendicitis.

Laparoscopic closure of perforations can be performed in many centers, significantly reducing operative morbidity compared with open laparotomy.

3. Gastric Outlet Obstruction

Gastric outlet obstruction occurs in less than 2% of patients with ulcer disease and is due to edema or cicatricial narrowing of the pylorus or duodenal bulb. With the advent of potent antisecretory therapy with proton pump inhibitors and the eradication of *H pylori*, obstruction now

is less commonly caused by peptic ulcers than by gastric neoplasms or extrinsic duodenal obstruction by intra-abdominal neoplasms. The most common symptoms are early satiety, vomiting, and weight loss. Later, vomiting may develop that typically occurs one to several hours after eating and consists of partially digested food contents. Patients may develop dehydration, metabolic alkalosis, and hypokalemia. On physical examination, a succussion splash may be heard in the epigastrium. In most cases, nasogastric aspiration will result in evacuation of a large amount (greater than 200 mL) of foul-smelling fluid, which establishes the diagnosis. Patients are treated initially with intravenous isotonic saline and KCl to correct fluid and electrolyte disorders, an intravenous proton pump inhibitor, and nasogastric decompression of the stomach. Upper endoscopy is performed after 24–72 hours to define the nature of the obstruction and to exclude gastric neoplasm.

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ZOLLINGER-ELLISON SYNDROME (Gastrinoma)

ESSENTIALS OF DIAGNOSIS

- ▶ Peptic ulcer disease; may be severe and atypical.
- ▶ Gastric acid hypersecretion.
- ▶ Diarrhea common, relieved by nasogastric suction.
- ▶ Most cases are sporadic; 25% occur with multiple endocrine neoplasia type 1 (MEN 1).

General Considerations

Zollinger-Ellison syndrome is caused by gastrin-secreting gut neuroendocrine tumors (gastrinomas), which result in hypergastrinemia and acid hypersecretion. Less than 1% of peptic ulcer disease is caused by gastrinomas. Primary gastrinomas may arise in the pancreas (25%), duodenal wall (45%), or lymph nodes (5–15%), and in

other locations including unknown primary sites (20%). Approximately 80% arise within the “gastrinoma triangle” bounded by the porta hepatis, the neck of the pancreas, and the third portion of the duodenum. Most gastrinomas are solitary or multifocal nodules that are potentially resectable. Approximately 25% of patients have small multicentric gastrinomas associated with MEN 1 that are more difficult to resect. Over two-thirds of gastrinomas are malignant, and one-third have already metastasized to the liver at initial presentation.

Clinical Findings

A. Symptoms and Signs

Over 90% of patients with Zollinger-Ellison syndrome develop peptic ulcers. In most cases, the symptoms are indistinguishable from other causes of peptic ulcer disease, and therefore, the syndrome may go undetected for years. Ulcers usually are solitary and located in the duodenal bulb, but they may be multiple or occur more distally in the duodenum. Isolated gastric ulcers do not occur. Gastroesophageal reflux symptoms occur often. Diarrhea occurs in one-third of patients, in some cases in the absence of peptic symptoms. Gastric acid hypersecretion can cause direct intestinal mucosal injury and pancreatic enzyme inactivation, resulting in diarrhea, steatorrhea, and weight loss; nasogastric aspiration of stomach acid stops the diarrhea. Screening for Zollinger-Ellison syndrome with fasting gastrin levels should be done in patients with ulcers that are refractory to standard therapies, giant ulcers (larger than 2 cm), ulcers located distal to the duodenal bulb, multiple duodenal ulcers, frequent ulcer recurrences, ulcers associated with diarrhea, ulcers occurring after ulcer surgery, and ulcers with complications. Ulcer patients with hypercalcemia or family histories of ulcers (suggesting MEN 1) should also be screened. Finally, patients with peptic ulcers who are *H pylori* negative and who are not taking NSAIDs should be screened.

B. Laboratory Findings

The most sensitive and specific method for identifying Zollinger-Ellison syndrome is demonstration of an increased fasting serum gastrin concentration (greater than 150 pg/mL [150 ng/L]). If possible, levels should be obtained with patients not taking H₂-receptor antagonists for 24 hours or proton pump inhibitors for 6 days; however, withdrawal of the proton pump inhibitor may result in marked gastric hypersecretion with serious consequences and patients should be closely monitored. The median gastrin level is 500–700 pg/mL (500–700 ng/L), and 60% of patients have levels less than 1000 pg/mL (1000 ng/L). Hypochlorhydria with increased gastric pH is a much more common cause of hypergastrinemia than is gastrinoma. Therefore, a measurement of gastric pH (and, where available, a gastric secretory study) is performed in patients with fasting hypergastrinemia. Most patients have a basal acid output of over 15 mEq/h. A gastric pH of greater than 3.0 implies hypochlorhydria and excludes gastrinoma. In a patient with a serum gastrin level of greater than 1000 pg/mL (1000 ng/L) and acid hypersecretion, the diagnosis of

Zollinger-Ellison syndrome is established. With lower gastrin levels (150–1000 pg/mL [150–1000 ng/L]) and acid secretion, a secretin stimulation test may be performed to distinguish Zollinger-Ellison syndrome from other causes of hypergastrinemia. Intravenous secretin (2 units/kg) produces a rise in serum gastrin of over 200 pg/mL (200 ng/L) within 2–30 minutes in 85% of patients with gastrinoma. An elevated serum calcium suggests hyperparathyroidism and MEN 1 syndrome. In all patients with Zollinger-Ellison syndrome, serum parathyroid hormone (PTH), prolactin, luteinizing hormone-follicle-stimulating hormone (LH-FSH), and growth hormone (GH) levels should be obtained to exclude MEN 1.

C. Imaging

Imaging studies are obtained in an attempt to determine whether there is metastatic disease and, if not, to identify the site of the primary tumor. CT and MRI scans are commonly obtained first to look for large hepatic metastases and primary lesions, but they have low sensitivity for small lesions. Gastrinomas express somatostatin receptors that bind radiolabeled octreotide. Somatostatin receptor scintigraphy (SRS) with single photon emission computed tomography (SPECT) allows total body imaging for detection of primary gastrinomas in the pancreas and lymph nodes, primary gastrinomas in unusual locations, and metastatic gastrinomas (liver and bone). The 80% sensitivity for tumor detection of SRS exceeds all other imaging studies combined. If SRS is positive for tumor localization, further imaging studies are not necessary. In patients with negative SRS, endoscopic ultrasonography (EUS) may be useful to detect small gastrinomas in the duodenal wall, pancreas, or peripancreatic lymph nodes. With a combination of SRS and EUS, more than 90% of primary gastrinomas can be localized preoperatively.

Treatment

A. Metastatic Disease

The most important predictor of survival is the presence of hepatic metastases. In patients with multiple hepatic metastases, initial therapy should be directed at controlling hypersecretion. Oral proton pump inhibitors (omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, dexlansoprazole) are given at a dose of 40–120 mg/day, titrated to achieve a basal acid output of less than 10 mEq/h. At this level, there is complete symptomatic relief and ulcer healing. Owing to the slow growth of these tumors, 30% of patients with hepatic metastases have a survival of 10 years.

B. Localized Disease

Cure can be achieved only if the gastrinoma can be resected before hepatic metastatic spread has occurred. Lymph node metastases do not adversely affect prognosis. Laparotomy should be considered in all patients in whom preoperative studies fail to demonstrate hepatic or other distant metastases. A combination of preoperative studies, duodenotomy with careful duodenal inspection, and intraoperative palpation and sonography allows successful localization and resection in the majority of cases. The 15-year survival of patients who do not have liver metastases at initial presentation is over 95%. Surgery usually is not recommended in patients with MEN 1 due to the presence of multifocal tumors and long-term survival in the absence of surgery in most patients.

De Angelis C et al. Diagnosis and management of Zollinger-Ellison syndrome in 2017. *Minerva Endocrinol*. 2018;43:212. [PMID: 28949124]

Norton JA et al. Gastrinomas: medical or surgical treatment. *Endocrinol Metab Clin North Am*. 2018;47:577. [PMID: 30098717]

DISEASES OF THE SMALL INTESTINE

MALABSORPTION

The term “malabsorption” denotes disorders in which there is a disruption of digestion and nutrient absorption. The clinical and laboratory manifestations of malabsorption are summarized in Table 15–11.

1. Celiac Disease



ESSENTIALS OF DIAGNOSIS

- ▶ **Typical symptoms:** weight loss, chronic diarrhea, abdominal distention, growth retardation.
- ▶ **Atypical symptoms:** dermatitis herpetiformis, iron deficiency anemia, osteoporosis.
- ▶ Abnormal serologic test results.
- ▶ Abnormal small bowel biopsy.
- ▶ Clinical improvement on gluten-free diet.

Hypergastrinemia due to gastrinoma must be distinguished from other causes of hypergastrinemia. Atrophic gastritis with decreased acid secretion is detected by gastric secretory analysis. Other conditions associated with hypergastrinemia (eg, gastric outlet obstruction, vagotomy, chronic kidney disease) are associated with a negative secretin stimulation test.

Table 15–11. Clinical manifestations and laboratory findings in malabsorption of various nutrients.

Manifestations	Laboratory Findings	Malabsorbed Nutrients
Steatorrhea (bulky, light-colored stools)	Increased fecal fat; decreased serum cholesterol; decreased serum carotene, vitamin A, vitamin D	Triglycerides, fatty acids, phospholipids, cholesterol. Fat-soluble vitamins: A, D, E, K
Diarrhea (increased fecal water)	Increased stool volume and weight; increased fecal fat; increased stool osmolality gap	Fats, carbohydrates
Weight loss; muscle wasting	Increased fecal fat; decreased carbohydrate (D-xylose) absorption	Fat, protein, carbohydrates
Microcytic anemia	Low serum iron	Iron
Macrocytic anemia	Decreased serum vitamin B ₁₂ or red blood cell folate	Vitamin B ₁₂ or folic acid
Paresthesia; tetany; positive Trousseau and Chvostek signs	Decreased serum calcium or magnesium	Calcium, vitamin D, magnesium
Bone pain; pathologic fractures; skeletal deformities	Osteopenia on radiograph; osteoporosis (adults); osteomalacia (children)	Calcium, vitamin D
Bleeding tendency (ecchymoses, epistaxis)	Prolonged prothrombin time or INR	Vitamin K
Edema	Decreased serum total protein and albumin; increased fecal loss of alpha-1-antitrypsin	Protein
Milk intolerance (cramps, bloating, diarrhea)	Abnormal lactose tolerance test	Lactose

INR, international normalized ratio.

► General Considerations

Celiac disease (also called sprue, celiac sprue, and gluten enteropathy) is a permanent dietary disorder caused by an immunologic response to gluten, a storage protein found in certain grains, that results in diffuse damage to the proximal small intestinal mucosa with malabsorption of nutrients. Although symptoms may manifest between 6 months and 24 months of age after the introduction of weaning foods, most cases present in childhood or adulthood. Population screening with serologic tests suggests that the global prevalence of this disease is 1.4%. In North America, the prevalence of biopsy-confirmed disease is 0.5%. Although the precise pathogenesis is unclear, celiac disease arises in a small subset of genetically susceptible (-DQ2 or -DQ8) individuals when dietary gluten stimulates an inappropriate immunologic response.

► Clinical Findings

The most important step in diagnosing celiac disease is to consider the diagnosis. Because of its protean manifestations, celiac disease is underdiagnosed in the adult population.

A. Symptoms and Signs

The gastrointestinal symptoms and signs of celiac disease depend on the length of small intestine involved and the patient's age when the disease presents. "Classic" symptoms of malabsorption, including diarrhea, steatorrhea, weight loss, abdominal distention, weakness, muscle wasting, or growth retardation, more commonly present in infants (younger than 2 years). Older children and adults are less likely to manifest signs of serious malabsorption. They may

report chronic diarrhea, dyspepsia, or flatulence due to colonic bacterial digestion of malabsorbed nutrients, but the severity of weight loss is variable. Many adults have minimal or no gastrointestinal symptoms but present with extraintestinal "atypical" manifestations, including fatigue, depression, iron deficiency anemia, osteoporosis, short stature, delayed puberty, amenorrhea, or reduced fertility. Approximately 40% of patients with positive serologic tests consistent with disease have no symptoms of disease; the natural history of these patients with "silent" disease is unclear.

Physical examination may be normal in mild cases or may reveal signs of malabsorption such as loss of muscle mass or subcutaneous fat, pallor due to anemia, easy bruising due to vitamin K deficiency, hyperkeratosis due to vitamin A deficiency, bone pain due to osteomalacia, or neurologic signs (peripheral neuropathy, ataxia) due to vitamin B₁₂ or vitamin E deficiency (Table 15–11). Abdominal examination may reveal distention with hyperactive bowel sounds.

Dermatitis herpetiformis is regarded as a cutaneous variant of celiac disease. It is a characteristic skin rash consisting of pruritic papulovesicles over the extensor surfaces of the extremities and over the trunk, scalp, and neck. Dermatitis herpetiformis occurs in less than 10% of patients with celiac disease; however, almost all patients who present with dermatitis herpetiformis have evidence of celiac disease on intestinal mucosal biopsy, though it may not be clinically evident.

B. Laboratory Findings

1. Routine laboratory tests—Depending on the severity of illness and the extent of intestinal involvement, nonspecific laboratory abnormalities may be present that may raise the

suspicion of malabsorption and celiac disease (Table 15–11). Limited proximal involvement may result only in microcytic anemia due to iron deficiency. Up to 3% of adults with iron deficiency not due to gastrointestinal blood loss have undiagnosed celiac disease. Megaloblastic anemia may be due to folate or vitamin B₁₂ deficiency (due to terminal ileal involvement or associated autoimmune gastritis). Low serum calcium or elevated alkaline phosphatase may reflect impaired calcium or vitamin D absorption with osteomalacia or osteoporosis. Dual-energy x-ray densitometry scanning is recommended for all patients with celiac disease to screen for osteoporosis. Elevations of prothrombin time, or decreased vitamin A or D levels reflect impaired fat-soluble vitamin absorption. A low serum albumin may reflect small intestine protein loss or poor nutrition. Other deficiencies may include zinc and vitamin B₆. Mild elevations of aminotransferases are found in up to 40%.

2. Serologic tests—Serologic tests should be performed in all patients in whom there is a suspicion of celiac disease. Patient self-elimination of gluten before serologic testing may result in false-negative test results. The recommended test is the IgA transglutaminase-2 (IgA TG2) antibody, which has a 98% sensitivity and 98% specificity for the diagnosis of celiac disease. Antigliadin antibodies are not recommended because of their lower sensitivity and specificity. An IgA level should be obtained in patients with a negative IgA TG antibody when celiac disease is strongly suspected because up to 3% of patients with celiac disease have IgA deficiency. In patients with IgA deficiency, tests that measure IgG antibodies to tissue transglutaminase (IgG TG) or to deamidated gliadin peptides (anti-DGP) have excellent sensitivity and specificity. Levels of all antibodies become undetectable after 3–24 months of dietary gluten withdrawal and may be used to monitor dietary compliance, especially in patients whose symptoms fail to resolve after institution of a gluten-free diet.

C. Mucosal Biopsy

Endoscopic mucosal biopsy of the proximal duodenum (bulb) and distal duodenum is the standard method for confirmation of the diagnosis in patients with a positive serologic test for celiac disease. At endoscopy, atrophy or scalloping of the duodenal folds may be observed. Histology reveals abnormalities ranging from intraepithelial lymphocytosis alone to extensive infiltration of the lamina propria with lymphocytes and plasma cells, hypertrophy of the intestinal crypts, and blunting or complete loss of intestinal villi. In patients in whom celiac disease is first suspected on intestinal biopsies, celiac serologic tests should be obtained to confirm the diagnosis. Partial or complete reversion of these abnormalities occurs within 3–24 months after a patient is placed on a gluten-free diet, but symptom resolution remains incomplete in 30% of patients. If a patient with a compatible biopsy demonstrates prompt clinical improvement on a gluten-free diet and a decrease in serologic markers, a repeat biopsy is unnecessary.

Differential Diagnosis

Many patients with chronic diarrhea or flatulence are erroneously diagnosed as having IBS. Celiac disease must be

distinguished from other causes of malabsorption, as outlined above. Severe panmalabsorption of multiple nutrients is almost always caused by mucosal disease. The histologic appearance of celiac disease may resemble other mucosal diseases such as tropical sprue, bacterial overgrowth, cow's milk intolerance, viral gastroenteritis, eosinophilic gastroenteritis, and mucosal damage caused by acid hypersecretion associated with gastrinoma. Documentation of clinical response to gluten withdrawal therefore is essential to the diagnosis.

Over the past decade, there has been a growing proportion (now 10%) of the population reporting symptoms after gluten ingestion who do not have serologic or histologic evidence of celiac disease. This has led to increases in gluten-free offerings from the restaurant and food industry. Foods with gluten often contain a number of other FODMAPs. Blinded clinical trials suggest that self-reported wheat sensitivity is not due to gluten intolerance and that the symptom improvement reported by patients with gluten restriction is due to broader FODMAP elimination.

Treatment

Removal of all gluten (wheat, rye, and barley) from the diet is essential to therapy. Although oats appear to be safe for many patients, commercial products may be contaminated with wheat or barley during processing. Because of the pervasive use of gluten products in manufactured foods and additives, in medications, and by restaurants, it is imperative that patients and their families confer with a knowledgeable dietitian to comply satisfactorily with this lifelong diet. Several excellent dietary guides and patient support groups are available. Most patients with celiac disease also have lactose intolerance either temporarily or permanently and should avoid dairy products until the intestinal symptoms have improved on the gluten-free diet. Dietary supplements (folate, iron, zinc, calcium, and vitamins A, B₆, B₁₂, D, and E) should be provided in the initial stages of therapy but usually are not required long-term with a gluten-free diet. Patients with confirmed osteoporosis may require long-term calcium, vitamin D, and bisphosphonate therapy.

Improvement in symptoms should be evident within a few weeks on the gluten-free diet. The most common reason for treatment failure is incomplete removal of gluten. Intentional or unintentional rechallenge with gluten may trigger acute severe diarrhea with dehydration and electrolyte imbalance and may require TPN and intravenous or oral corticosteroids (prednisone 40 mg or budesonide 9 mg) for 2 or more weeks while a gluten-free diet is reinitiated.

Prognosis & Complications

If appropriately diagnosed and treated, patients with celiac disease have an excellent prognosis. Celiac disease may be associated with other autoimmune disorders, including Addison disease, Graves disease, type 1 diabetes mellitus, myasthenia gravis, systemic sclerosis, Sjögren syndrome, atrophic gastritis, and pancreatic insufficiency. In some patients, celiac disease may evolve and become refractory to the gluten-free diet. The most common cause is

intentional or unintentional dietary noncompliance, which may be suggested by positive serologic tests. Celiac disease that is truly refractory to gluten withdrawal occurs in less than 5% and generally carries a poor prognosis. There are two types of refractory disease, which are distinguished by their intraepithelial lymphocyte phenotype. This diagnosis should be considered in patients previously responsive to the gluten-free diet in whom new weight loss, abdominal pain, and malabsorption develop.

- Celiac Disease Foundation, 20350 Ventura Blvd, Suite #240, Woodland Hills, CA 91364. <https://celiac.org>
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- Rubin JE et al. Celiac disease. *Ann Intern Med*. 2020;172:ITC1. [PMID: 31905394]

2. Whipple Disease



ESSENTIALS OF DIAGNOSIS

- ▶ Multisystem disease.
- ▶ Fever, lymphadenopathy, arthralgias.
- ▶ Weight loss, malabsorption, chronic diarrhea.
- ▶ Duodenal biopsy with periodic acid-Schiff (PAS)-positive macrophages with characteristic bacillus.

► General Considerations

Whipple disease is a rare multisystem illness with an estimated prevalence of 1 per 100,000 caused by infection with the bacillus *Tropheryma whipplei*. It may occur at any age but most commonly affects White men in the fourth to sixth decades. The source of infection is unknown, but no cases of human-to-human spread have been documented.

► Clinical Findings

A. Symptoms and Signs

The clinical manifestations are protean; however, the most common are arthralgias, diarrhea, abdominal pain, and weight loss. Arthralgias or a migratory, nondeforming arthritis occurs in 80% and is typically the first symptom experienced. Gastrointestinal symptoms occur in approximately 75% of cases. They include abdominal pain, diarrhea, and some degree of malabsorption with distention, flatulence, and steatorrhea. Weight loss is the most common presenting symptom—seen in almost all patients. Loss of protein due to intestinal or lymphatic involvement may result in protein-losing enteropathy with hypoalbuminemia and edema. In the absence of gastrointestinal symptoms, the diagnosis often is delayed for several years. Intermittent low-grade fever occurs in over 50% of cases.

Physical examination may reveal hypotension (a late finding), low-grade fever, and evidence of malabsorption (see Table 15–11). Lymphadenopathy is present in 50%. Heart murmurs due to valvular involvement may be evident. Peripheral joints may be enlarged or warm, and peripheral edema may be present. Neurologic findings are cited above. Hyperpigmentation on sun-exposed areas is evident in up to 40%.

B. Laboratory Findings

If significant malabsorption is present, patients may have laboratory abnormalities as outlined in Table 15–11. There may be steatorrhea.

C. Histologic Evaluation

The diagnosis of Whipple disease is established in 90% of cases by endoscopic biopsy of the duodenum with histologic evaluation, which demonstrates infiltration of the lamina propria with PAS-positive macrophages that contain gram-positive bacilli (which are not acid-fast) and dilation of the lacteals. The remainder of cases are diagnosed by *T. whipplei*-specific PCR or immunohistochemistry of duodenal biopsies or extraintestinal fluids (cerebrospinal, synovial) or tissue (lymph nodes, synovium, endocardium). The sensitivity of PCR is 97% and the specificity 100%. Because asymptomatic central nervous system infection occurs in 40% of patients, examination of the cerebrospinal fluid by PCR for *T. whipplei* should be performed routinely.

► Differential Diagnosis

Whipple disease should be considered in patients who present with signs of malabsorption, fever of unknown origin, lymphadenopathy, seronegative arthritis, culture-negative endocarditis, or multisystem disease. Small bowel biopsy readily distinguishes Whipple disease from other mucosal malabsorptive disorders, such as celiac disease.

► Treatment

Antibiotic therapy results in a dramatic clinical improvement within several weeks, even in some patients with neurologic involvement. The optimal regimen is unknown. Complete clinical response usually is evident within 1–3 months; however, relapse may occur in up to one-third of patients after discontinuation of treatment. Therefore, prolonged treatment for at least 1 year is required. Drugs that cross the blood-brain barrier are preferred. A randomized controlled trial in 40 patients with 3–10 years' follow-up demonstrated 100% remission with either ceftriaxone 1 g intravenously twice daily or meropenem 1 g intravenously three times daily for 2 weeks, followed by trimethoprim-sulfamethoxazole 160/800 mg twice daily for 12 months. After treatment, repeat duodenal biopsies for histologic analysis and cerebrospinal fluid PCR should be obtained every 6 months for at least 1 year. The absence of PAS-positive material predicts a low likelihood of clinical relapse.

► Prognosis

If untreated, the disease is fatal. Because some neurologic signs may be permanent, the goal of treatment is to prevent

this progression. Patients must be followed closely after treatment for signs of symptom recurrence.

Elchert JA et al. Epidemiology of Whipple's disease in the USA between 2012 and 2017: a population-based national study. *Dig Dis Sci.* 2019;64:1305. [PMID: 30488239]

FERIERES L et al. Whipple's disease; diagnosis and predictive factor of relapse. *Eur J Gastroenterol Hepatol.* 2020;32:325. [PMID: 31764405]

HUJOEL IA et al. *Tropheryma whipplei* infection (Whipple disease) in the USA. *Dig Dis Sci.* 2019;64:213. [PMID: 29572616]

3. Bacterial Overgrowth

ESSENTIALS OF DIAGNOSIS

- ▶ Symptoms of distention, bloating, flatulence, and diarrhea.
- ▶ Advanced cases associated with weight loss, steatorrhea, and deficiencies of iron or vitamins A, D, and B₁₂.
- ▶ Diagnosis suggested by breath tests using glucose or lactulose as substrates.
- ▶ Diagnosis confirmed by jejunal aspiration with quantitative bacterial cultures.

General Considerations

The small intestine normally contains a small number of bacteria. Bacterial overgrowth in the small intestine of whatever cause may result in malabsorption via several mechanisms. Passage of the malabsorbed bile acids and carbohydrates into the colon leads to an osmotic and secretory diarrhea and increased flatulence.

Causes of bacterial overgrowth include (1) gastric achlorhydria (including proton pump inhibitor therapy); (2) anatomic abnormalities of the small intestine with stagnation (afferent limb of Billroth II gastrojejunostomy, resection of ileocecal valve, small intestine diverticula, obstruction, blind loop); (3) small intestine motility disorders (vagotomy, systemic sclerosis, diabetic enteropathy, chronic intestinal pseudo-obstruction); (4) gastrocolic or coloenteric fistula (Crohn disease, malignancy, surgical resection); and (5) miscellaneous disorders. Bacterial overgrowth is an important cause of malabsorption in older patients, perhaps because of decreased gastric acidity or impaired intestinal motility. It may also be present in a subset of patients with IBS.

Clinical Findings

Many patients with bacterial overgrowth are asymptomatic. Symptoms are nonspecific and include bloating, flatulence, abdominal pain, diarrhea, and sometimes steatorrhea with weight loss. Bacterial overgrowth should be considered in any patient with these symptoms, especially if the patient has a predisposing cause (such as prior gastrointestinal surgery). Severe cases may result in clinically significant vitamin and mineral deficiencies, including fat-soluble

vitamins A or D, vitamin B₁₂, and iron (Table 15–11). A specific diagnosis can be established firmly only by an aspirate and culture of distal duodenal secretion that demonstrates over 10³ organisms/mL. However, this is an invasive and laborious test that requires careful collection and culturing techniques and therefore is not available in most clinical settings. Noninvasive breath hydrogen and methane tests with glucose or lactulose as substrates are generally preferred because of their ease of use. Following ingestion of glucose 75 g or lactulose 10 g, a rise in exhaled breath hydrogen of 20 ppm or methane of 10 ppm or more within 90 minutes is suggestive of bacterial overgrowth and has 65% diagnostic agreement with small bowel cultures. A small bowel study (CT or MR enterography, barium radiography) may be obtained to look for mechanical factors predisposing to intestinal stasis.

A 2020 American College of Gastroenterology guideline suggests breath testing when bacterial overgrowth is suspected. However, many clinicians prefer to use an empiric antibiotic trial as a diagnostic and therapeutic strategy.

Treatment

Where possible, the anatomic defect that has potentiated bacterial overgrowth should be corrected. Otherwise, treatment for 7–10 days with oral broad-spectrum antibiotics improves symptoms in up to 90% of patients for weeks to months. Recommended regimens include ciprofloxacin, 500 mg twice daily; norfloxacin, 400 mg twice daily; or amoxicillin clavulanate, 875 mg twice daily; trimethoprim-sulfamethoxazole (one double-strength tablet) twice daily; rifaximin, 400–550 mg three times daily; or a combination of neomycin, 500 mg twice daily, plus metronidazole, 250 mg three times daily.

Within 6 months of completing antibiotic therapy, symptoms recur in over 25% of patients. In patients with more frequent symptomatic relapse, cyclic antibiotic therapy (eg, 1 week out of 4) may be sufficient. Continuous antibiotics should be avoided, if possible, to avoid development of bacterial antibiotic resistance.

PIMENTAL M et al. ACG Clinical Guideline: small intestinal bacterial overgrowth. *Am J Gastroenterol.* 2020;115:165. [PMID: 32023228]

QUIGLEY EM et al. AGA Clinical Practice update on small intestinal bacterial overgrowth: expert review. *Gastroenterology.* 2020;159:1526. [PMID: 32679220]

4. Short Bowel Syndrome

Short bowel syndrome is the malabsorptive condition that arises secondary to removal of significant segments of the small intestine. The most common causes in adults are Crohn disease, mesenteric infarction, radiation enteritis, volvulus, tumor resection, and trauma. The type and degree of malabsorption depend on the length and site of the resection and the degree of adaptation of the remaining bowel.

Terminal Ileal Resection

Resection of the terminal ileum results in malabsorption of bile salts and vitamin B₁₂, which are normally absorbed

in this region. Patients with low serum vitamin B₁₂ levels or resection of over 50 cm of ileum require monthly subcutaneous or intramuscular vitamin B₁₂ injections. In patients with less than 100 cm of ileal resection, bile salt malabsorption stimulates fluid secretion from the colon, resulting in watery diarrhea. This may be treated with administration of bile salt-binding resins one to three times daily with meals (cholestyramine, 2–4 g/day orally, colestipol tablets, 2 g orally, or colesevelam, 625 mg orally). Resection of over 100 cm of ileum leads to a reduction in the bile salt pool that results in steatorrhea and malabsorption of fat-soluble vitamins. Treatment is with a low-fat diet and vitamins supplemented with medium-chain triglycerides, which do not require micellar solubilization. Unabsorbed fatty acids bind with calcium, reducing its absorption and enhancing the absorption of oxalate. Oxalate kidney stones may develop. Calcium supplements should be administered to bind oxalate and increase serum calcium. Cholesterol gallstones due to decreased bile salts are common also. In patients with resection of the ileocolonic valve, bacterial overgrowth may occur in the small intestine, further complicating malabsorption.

► Extensive Small Bowel Resection

Resection of up to 40–50% of the total length of small intestine usually is well tolerated. A more massive resection may result in “short bowel syndrome,” characterized by weight loss and diarrhea due to nutrient, water, and electrolyte malabsorption. If the colon is preserved, 100 cm of proximal jejunum may be sufficient to maintain adequate oral nutrition with a low-fat, high-complex carbohydrate diet, though fluid and electrolyte losses may still be significant. In patients in whom the colon has been removed, at least 200 cm of proximal jejunum is typically required to maintain oral nutrition. Antidiarrheal agents (loperamide, 2–4 mg orally three times daily) slow transit and reduce diarrheal volume. Octreotide reduces intestinal transit time and fluid and electrolyte secretion. Gastric hypersecretion initially complicates intestinal resection and should be treated with proton pump inhibitors.

Patients with less than 100–200 cm of proximal jejunum remaining almost always require parenteral nutrition. Teduglutide (recombinant) is a glucagon-like peptide-2 analogue that stimulates small bowel growth and absorption and is FDA approved for the treatment of short bowel syndrome. In clinical trials, it resulted in a reduced need for parenteral nutrition. Small intestine transplantation has reported 5-year graft survival rates of 40%. Currently, it is performed chiefly in patients in whom serious problems develop due to parenteral nutrition.

Da Roach HM et al. Treating short bowel syndrome with pharmacotherapy. *Expert Opin Pharmacother.* 2020;21:709. [PMID: 32052720]

Sadowski DC et al. Canadian Association of Gastroenterology clinical practice guideline on the management of bile acid diarrhea. *Clin Gastroenterol Hepatol.* 2020;18:24. [PMID: 31526844]

5. Lactase Deficiency



- Diarrhea, bloating, flatulence, and abdominal pain after ingestion of milk-containing products.
- Diagnosis supported by symptomatic improvement on lactose-free diet.
- Diagnosis confirmed by hydrogen breath test.

► General Considerations

Lactase is a brush border enzyme that hydrolyzes the disaccharide lactose into glucose and galactose. The concentration of lactase enzyme levels is high at birth but declines steadily in most people of non-European ancestry during childhood and adolescence and into adulthood. As many as 90% of Asian Americans, 70% of African Americans, 95% of Native Americans, 50% of Mexican Americans, and 60% of Jewish Americans are lactose intolerant compared with less than 25% of White adults. Lactase deficiency may also arise secondary to other gastrointestinal disorders that affect the proximal small intestinal mucosa. These include Crohn disease, celiac disease, viral gastroenteritis, giardiasis, short bowel syndrome, and malnutrition. Malabsorbed lactose is fermented by intestinal bacteria, producing gas and organic acids. The nonmetabolized lactose and organic acids result in an increased stool osmotic load with an obligatory fluid loss.

► Clinical Findings

A. Symptoms and Signs

Patients have great variability in clinical symptoms, depending both on the severity of lactase deficiency and the amount of lactose ingested. Because of the nonspecific nature of these symptoms, there is a tendency for both lactose-intolerant and lactose-tolerant individuals to mistakenly attribute a variety of abdominal symptoms to lactose intolerance. Most patients with lactose intolerance can drink at least one 8-oz serving of milk daily (12 g of lactose) without symptoms, though rare patients have almost complete intolerance. With mild to moderate amounts of lactose malabsorption, patients may experience bloating, abdominal cramps, and flatulence. With higher lactose ingestions, an osmotic diarrhea will result. Isolated lactase deficiency does not result in other signs of malabsorption or weight loss. If these findings are present, other gastrointestinal disorders should be pursued.

B. Laboratory Findings

The most widely available test for the diagnosis of lactase deficiency is the hydrogen breath test. After ingestion of 50 g of lactose, a rise in breath hydrogen of more than 20 ppm within 90 minutes is a positive test, indicative of bacterial carbohydrate metabolism. In clinical practice, many clinicians prescribe an empiric trial of a lactose-free diet for 2 weeks. Resolution of symptoms (bloating, flatulence,

diarrhea) is suggestive of lactase deficiency (though a placebo response cannot be excluded) and may be confirmed, if necessary, with a hydrogen breath test.

► Differential Diagnosis

The symptoms of late-onset lactose intolerance are nonspecific and may mimic several gastrointestinal disorders, such as inflammatory bowel disease, mucosal malabsorptive disorders, IBS, and pancreatic insufficiency. Furthermore, lactase deficiency frequently develops secondary to other gastrointestinal disorders (as listed above).

► Treatment

The goal of treatment in patients with isolated lactase deficiency is achieving patient comfort. Patients usually find their “threshold” of intake at which symptoms will occur. Foods that are high in lactose include milk (12 g/cup), ice cream (9 g/cup), and cottage cheese (8 g/cup). Aged cheeses have a lower lactose content (0.5 g/oz). Unpasteurized yogurt contains bacteria that produce lactase and is generally well tolerated.

By spreading dairy product intake throughout the day in quantities of less than 12 g of lactose (one cup of milk), most patients can take dairy products without symptoms and do not require lactase supplements. Most food markets provide milk that has been pretreated with lactase, rendering it 100% lactose free (Fairlife). Lactase enzyme replacement is commercially available as nonprescription formulations (Lactaid, Lactrase, Dairy Ease). Caplets or drops of lactase may be taken with milk products, improving lactose absorption and eliminating symptoms. The number of caplets ingested depends on the degree of lactose intolerance. Patients who choose to restrict or eliminate milk products should consider calcium supplementation (calcium carbonate 500 mg orally two to three times daily) to meet calcium intake needs and reduce risk of osteoporosis.

Misselwitz B et al. Update on lactose malabsorption and intolerance: pathogenesis, diagnosis and clinical management. Gut. 2019;68:2080. [PMID: 31427404]

Silberman ES et al. JAMA patient page. Lactose intolerance. JAMA. 2019;322:1620. [PMID: 31638683]

INTESTINAL MOTILITY DISORDERS

1. Acute Paralytic Ileus



ESSENTIALS OF DIAGNOSIS

- ▶ Precipitating factors: surgery, peritonitis, electrolyte abnormalities, medications, severe medical illness.
- ▶ Nausea, vomiting, obstipation, distention.
- ▶ Minimal abdominal tenderness; decreased bowel sounds.
- ▶ Plain abdominal radiography with gas and fluid distention in small and large bowel.

► General Considerations

Ileus is a condition in which there is neurogenic failure or loss of peristalsis in the intestine in the absence of any mechanical obstruction. It is commonly seen in hospitalized patients as a result of (1) intra-abdominal processes such as recent gastrointestinal or abdominal surgery or peritoneal irritation (peritonitis, pancreatitis, ruptured viscus, hemorrhage); (2) severe medical illness such as pneumonia, respiratory failure requiring intubation, sepsis or severe infections, uremia, diabetic ketoacidosis, and electrolyte abnormalities (hypokalemia, hypercalcemia, hypomagnesemia, hypophosphatemia); and (3) medications that affect intestinal motility (opioids, anticholinergics, phenothiazines). Following surgery, small intestinal motility usually normalizes first (often within hours), followed by the stomach (24–48 hours), and the colon (48–72 hours). Postoperative ileus is reduced with minimally invasive (eg, laparoscopic) surgery, by the use of patient-controlled or epidural analgesia, and by avoidance of intravenous opioids as well as early ambulation, gum chewing, and initiation of a clear liquid diet.

► Clinical Findings

A. Symptoms and Signs

Patients who are conscious report mild diffuse, continuous abdominal discomfort with nausea and vomiting. Generalized abdominal distention is present with minimal abdominal tenderness but no signs of peritoneal irritation (unless due to the primary disease). Bowel sounds are diminished to absent.

B. Laboratory Findings

The laboratory abnormalities are attributable to the underlying condition. Serum electrolytes (sodium, potassium, magnesium, phosphorus, and calcium), should be obtained to exclude abnormalities as contributing factors.

C. Imaging

Plain film radiography of the abdomen demonstrates distended gas-filled loops of the small and large intestine. Air-fluid levels may be seen. Under some circumstances, it may be difficult to distinguish ileus from partial small bowel obstruction. A CT scan may be useful in such instances to exclude mechanical obstruction, especially in postoperative patients.

► Differential Diagnosis

Ileus must be distinguished from mechanical obstruction of the small bowel or proximal colon. Pain from small bowel mechanical obstruction is usually intermittent, cramping, and associated initially with profuse vomiting. Acute gastroenteritis, acute appendicitis, and acute pancreatitis may all present with ileus.

► Treatment

The primary medical or surgical illness that has precipitated adynamic ileus should be treated. Most cases of ileus

respond to restriction of oral intake with gradual liberalization of diet as bowel function returns. Severe or prolonged ileus requires nasogastric suction and parenteral administration of fluids and electrolytes. Alvimopan is a peripherally acting mu-opioid receptor antagonist with limited absorption or systemic activity that reverses opioid-induced inhibition of intestinal motility.

2. Acute Colonic Pseudo-Obstruction (Ogilvie Syndrome)



ESSENTIALS OF DIAGNOSIS

- ▶ Severe abdominal distention.
- ▶ Arises in postoperative state or with severe medical illness.
- ▶ May be precipitated by electrolyte imbalances, medications.
- ▶ Absent to mild abdominal pain; minimal tenderness.
- ▶ Massive dilation of cecum or right colon.

► General Considerations

Spontaneous massive dilation of the cecum and proximal colon may occur in many different settings in hospitalized patients. Progressive cecal dilation may lead to ischemia and spontaneous perforation with dire consequences. The risk of perforation increases with duration of distention beyond 6 days but correlates poorly with absolute cecal size. Early detection and management are important to reduce morbidity and mortality. Colonic pseudo-obstruction is most commonly detected in postsurgical patients (mean 3–5 days), after trauma, and in medical patients with respiratory failure, metabolic imbalance, malignancy, myocardial infarction, heart failure, pancreatitis, or a recent neurologic event (stroke, subarachnoid hemorrhage, trauma). Liberal use of opioids or anticholinergic agents may precipitate colonic pseudo-obstruction in susceptible patients.

► Clinical Findings

A. Symptoms and Signs

Many patients are on ventilatory support or are unable to report symptoms due to altered mental status. Abdominal distention is frequently noted by the clinician as the first sign, often leading to a plain film radiograph that demonstrates colonic dilation. Some patients are asymptomatic, although most report constant but mild abdominal pain. Nausea and vomiting may be present. Bowel movements may be absent, but up to 40% of patients continue to pass flatus or stool. Abdominal tenderness with some degree of guarding or rebound tenderness may be detected; however, signs of peritonitis are absent unless perforation has occurred. Bowel sounds may be normal or decreased.

B. Laboratory Findings

Laboratory findings reflect the underlying medical or surgical problems. Serum sodium, potassium, magnesium, phosphorus, and calcium should be obtained to exclude abnormalities as contributing factors. Significant fever or leukocytosis raises concern for colonic ischemia or perforation.

C. Imaging

Radiographs demonstrate colonic dilation, usually confined to the cecum and proximal colon. The upper limit of normal for cecal size is 9 cm. A cecal diameter greater than 10–12 cm is associated with an increased risk of colonic perforation. Varying amounts of small intestinal dilation and air-fluid levels due to adynamic ileus may be seen. Generally, a CT scan should be obtained to exclude a distal colonic mechanical obstruction due to malignancy, volvulus, or fecal impaction.

► Differential Diagnosis

Colonic pseudo-obstruction should be distinguished from distal colonic mechanical obstruction (as above) and toxic megacolon, which is acute dilation of the colon due to inflammation (inflammatory bowel disease) or infection (*C difficile*-associated colitis, CMV). Patients with toxic megacolon manifest fever; dehydration; significant abdominal pain; leukocytosis; and diarrhea, which is often bloody.

► Treatment

Conservative treatment is the appropriate first step for patients with no or minimal abdominal tenderness, no fever, no leukocytosis, and a cecal diameter smaller than 12 cm. The underlying illness is treated appropriately. A nasogastric tube and a rectal tube should be placed. Patients should be ambulated or periodically rolled from side to side and to the knee-chest position in an effort to promote expulsion of colonic gas. All drugs that reduce intestinal motility, such as opioids, anticholinergics, and calcium channel blockers, should be discontinued if possible. Enemas may be administered judiciously if large amounts of stool are evident on radiography. Oral laxatives are not helpful and may cause perforation, pain, or electrolyte abnormalities.

Conservative treatment is successful in over 80% of cases within 1–2 days. Patients must be watched for signs of worsening distention or abdominal tenderness. Cecal size should be assessed by abdominal radiographs every 12 hours. Intervention should be considered in patients with any of the following: (1) no improvement or clinical deterioration after 24–48 hours of conservative therapy; (2) cecal dilation greater than 10 cm for a prolonged period (more than 3–4 days); or (3) patients with cecal dilation greater than 12 cm. Neostigmine injection should be given unless contraindicated. A single dose (2 mg intravenously) results in rapid (within 30 minutes) colonic decompression in 75–90% of patients. Cardiac monitoring during neostigmine infusion is indicated for possible bradycardia that may require atropine administration. Colonoscopic

decompression is indicated in patients who fail to respond to neostigmine. Colonic decompression with aspiration of air or placement of a decompression tube is successful in 70% of patients. However, the procedure is technically difficult in an unprepared bowel and has been associated with perforations in the distended colon. Dilatation recurs in up to 50% of patients. In patients in whom colonoscopy is unsuccessful, a tube cecostomy can be created through a small laparotomy or with percutaneous radiologically guided placement.

► Prognosis

In most cases, the prognosis is related to the underlying illness. The risk of perforation or ischemia is increased with cecal diameter more than 12 cm and when distention has been present for more than 6 days. With aggressive therapy, the development of perforation is unusual.

Jeong SJ et al. Endoscopic management of benign colonic obstruction and pseudo-obstruction. Clin Endosc. 2020;53:18. [PMID: 31645090]

Naveed M et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of acute colonic pseudo-obstruction and colonic volvulus. Gastrointest Endosc. 2020;91:228. [PMID: 31791596]

3. Chronic Intestinal Pseudo-Obstruction & Gastroparesis

Gastroparesis and chronic intestinal pseudo-obstruction are chronic conditions characterized by intermittent, waxing and waning symptoms and signs of gastric or intestinal obstruction in the absence of any mechanical lesions to account for the findings. They are caused by a heterogeneous group of endocrine disorders (diabetes mellitus, hypothyroidism, cortisol deficiency), postsurgical conditions (vagotomy, partial gastric resection, fundoplication, gastric bypass, Whipple procedure), neurologic conditions (Parkinson disease, muscular and myotonic dystrophy, autonomic dysfunction, multiple sclerosis, postpolio syndrome, porphyria), rheumatologic syndromes (progressive systemic sclerosis), infections (postviral, Chagas disease), amyloidosis, paraneoplastic syndromes, medications, and eating disorders (anorexia); a cause may not always be identified.

► Clinical Findings

A. Symptoms and Signs

Gastric involvement leads to chronic or intermittent symptoms of gastroparesis with postprandial fullness (early satiety), nausea, and vomiting (1–3 hours after meals). Upper abdominal symptoms correlate poorly with the severity of gastric emptying and may be attributable to impaired proximal gastric accommodation after meals, visceral hypersensitivity to gastric distension, afferent nerve dysfunction, gastric electrical rhythm disturbances, or concomitant small intestinal dysmotility. Patients with predominantly small bowel involvement may have abdominal distention, vomiting, diarrhea, and varying degrees of malnutrition. Abdominal pain is not common and should prompt

investigation for structural causes of obstruction. Bacterial overgrowth in the stagnant intestine may result in malabsorption. Colonic involvement may result in constipation or alternating diarrhea and constipation.

B. Imaging

Plain film radiography may demonstrate dilation of the esophagus, stomach, small intestine, or colon resembling ileus or mechanical obstruction. Mechanical obstruction of the stomach, small intestine, or colon is much more common than gastroparesis or intestinal pseudo-obstruction and must be excluded with endoscopy or CT enterography, especially in patients with prior surgery, recent onset of symptoms, or abdominal pain. In cases of unclear origin, studies based on the clinical picture are obtained to exclude underlying systemic disease. Gastric scintigraphy with a low-fat solid meal remains the preferred method for assessing gastric emptying. Gastric retention of 60% after 2 hours or more than 10% after 4 hours is abnormal. A wireless motility capsule and a nonradioactive or 13-C labeled breath test using blue-green algae (*Spirulina platensis*) also are available. Small bowel manometry is useful for distinguishing visceral from myopathic disorders and for excluding cases of mechanical obstruction that are otherwise difficult to diagnose by endoscopy or radiographic studies.

► Treatment

There is no specific therapy for gastroparesis or pseudo-obstruction. Acute exacerbations are treated with nasogastric suction and intravenous fluids. Long-term treatment is directed at maintaining nutrition. Patients should eat small, frequent meals that are low in fiber, milk, gas-forming foods, and fat. Foods that are well tolerated include tea, ginger ale, soup, white rice, potatoes and sweet potatoes, fish, gluten-free foods, and applesauce. Some patients may require liquid enteral supplements. Agents that reduce gastrointestinal motility (opioids, anticholinergics) should be avoided. In diabetic patients, glucose levels should be maintained below 200 mg/dL, as hyperglycemia may slow gastric emptying even in the absence of diabetic neuropathy, and amylin and GLP-1 analogs (exenatide or pramlintide) should be discontinued. Currently available prokinetic agents have shown limited improvement of gastric emptying or upper gastrointestinal symptoms in patients with gastroparesis. Metoclopramide (5–20 mg orally or 5–10 mg intravenously or subcutaneously four times daily) may enhance gastric emptying but not small bowel dysmotility. Since the use of metoclopramide for more than 3 months is associated with a less than 1% risk of tardive dyskinesia, patients are advised to discontinue the medication if neuromuscular side effects, particularly involuntary movements, develop. Older patients are at greatest risk. In 2019, a small, blinded, crossover trial involving 34 patients with confirmed gastroparesis showed that prucalopride, a serotonin 5-HT₄-receptor agonist (currently FDA approved for treatment of chronic constipation), significantly improved gastric emptying and symptoms after 2 weeks of therapy (2 mg daily orally) compared with placebo. Uncontrolled studies report symptom improvement

with modalities that reduce intrapyloric pressure, including botulinum toxin injection, laparoscopic myotomy, and endoscopic myotomy. Bacterial overgrowth should be treated with intermittent antibiotics. Patients with predominant small bowel distention may require a venting gastrostomy to relieve distress. Some patients may require placement of a jejunostomy for long-term enteral nutrition. Patients unable to maintain adequate enteral nutrition require TPN or small bowel transplantation. Difficult cases should be referred to centers with expertise in this area.

- Navas CM et al. Symptomatic management of gastroparesis. *Gastrointest Endosc Clin N Am.* 2019;29:55. [PMID: 30396528]
- Parsi MA et al. Techniques and devices for the endoscopic treatment of gastroparesis (with video). *Gastrointest Endosc.* 2020;92:483. [PMID: 32684298]
- Shen S et al. Diabetic gastroparesis and nondiabetic gastroparesis. *Gastrointest Endosc Clin N Am.* 2019;29:15. [PMID: 30396524]
- Vijayvargiya P et al. Effects of promotility agents on gastric emptying and symptoms: a systematic review and meta-analysis. *Gastroenterology.* 2019;156:1650. [PMID: 30711628]

APPENDICITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Early: perumbilical pain; later: right lower quadrant pain and tenderness.
- ▶ Anorexia, nausea and vomiting, obstipation.
- ▶ Tenderness or localized rigidity at McBurney point.
- ▶ Low-grade fever and leukocytosis.

► General Considerations

Appendicitis is the most common abdominal surgical emergency, affecting approximately 10% of the population. It occurs most commonly between the ages of 10 and 30 years. It is initiated by obstruction of the appendix by a fecalith, inflammation, foreign body, or neoplasm. Obstruction leads to increased intraluminal pressure, venous congestion, infection, and thrombosis of intramural vessels. If untreated, gangrene and perforation develop within 36 hours.

► Clinical Findings

A. Symptoms and Signs

Appendicitis usually begins with vague, often colicky perumbilical or epigastric pain. Within 12 hours the pain shifts to the right lower quadrant, manifested as a steady ache that is worsened by walking or coughing. Almost all patients have nausea with one or two episodes of vomiting. Protracted vomiting or vomiting that begins before the onset of pain suggests another diagnosis. A sense of constipation is typical, and some patients administer cathartics in an effort to relieve their symptoms—though some report diarrhea.

Low-grade fever (below 38°C) is typical; high fever or rigors suggest another diagnosis or appendiceal perforation.

On physical examination, localized tenderness with guarding in the right lower quadrant can be elicited with gentle palpation with one finger. When asked to cough, patients may be able to precisely localize the painful area, a sign of peritoneal irritation. Light percussion may also elicit pain. Although rebound tenderness is also present, it is unnecessary to elicit this finding if the above signs are present. The psoas sign (pain on passive extension of the right hip) and the obturator sign (pain with passive flexion and internal rotation of the right hip) are indicative of adjacent inflammation and strongly suggestive of appendicitis.

B. Atypical Presentations of Appendicitis

Owing to the variable location of the appendix, there are a number of “atypical” presentations. Because the retrocecal appendix does not touch the anterior abdominal wall, the pain remains less intense and poorly localized; abdominal tenderness is minimal and may be elicited in the right flank. The psoas sign may be positive. With pelvic appendicitis, there is pain in the lower abdomen, often on the left, with an urge to urinate or defecate. Abdominal tenderness is absent, but tenderness is evident on pelvic or rectal examination; the obturator sign may be present. In elderly patients, the diagnosis of appendicitis is often delayed because patients present with minimal, vague symptoms and mild abdominal tenderness.

C. Laboratory Findings

Moderate leukocytosis (10,000–20,000/mcL [10–20 × 10⁹/L]) with neutrophilia is common. Microscopic hematuria and pyuria are present in 25% of patients.

D. Imaging

Both abdominal ultrasound and CT scanning are useful in diagnosing appendicitis as well as excluding other diseases presenting with similar symptoms, including adnexal disease in younger women. However, CT scanning appears to be more accurate (sensitivity 94%, specificity 95%, positive likelihood ratio 13.3, negative likelihood ratio 0.09). Abdominal CT scanning is also useful in cases of suspected appendiceal perforation to diagnose a periappendiceal abscess. In patients in whom there is a clinically high suspicion of appendicitis, some surgeons feel that preoperative diagnostic imaging is unnecessary. However, studies suggest that even in this group, imaging studies suggest an alternative diagnosis in up to 15%.

► Differential Diagnosis

Given its frequency and myriad presentations, appendicitis should be considered in the differential diagnosis of all patients with abdominal pain. A several-hour period of close observation with reassessment usually clarifies the diagnosis. In a 2020 retrospective review of 123,711 adults with appendicitis, the diagnosis was more commonly missed in women, patients with comorbidities, and patients who experienced abdominal pain with constipation.

Absence of classic migration of pain (from epigastrium to right lower abdomen); right lower quadrant pain; fever; or guarding each makes appendicitis less likely. Widespread use of ultrasonography and CT has reduced the number of incorrect diagnoses to less than 2%. Still, in some cases, diagnostic laparotomy or laparoscopy is required.

The most common causes of diagnostic confusion are gastroenteritis and gynecologic disorders. Viral gastroenteritis presents with nausea, vomiting, low-grade fever, and diarrhea and can be difficult to distinguish from appendicitis. The onset of vomiting before pain makes appendicitis less likely. As a rule, the pain of gastroenteritis is more generalized and the tenderness less well localized. Acute salpingitis or tubo-ovarian abscess should be considered in young, sexually active women with fever and bilateral abdominal or pelvic tenderness. A twisted ovarian cyst may also cause sudden severe pain. The sudden onset of lower abdominal pain in the middle of the menstrual cycle suggests mittelschmerz. Sudden severe abdominal pain with diffuse pelvic tenderness and shock suggests a ruptured ectopic pregnancy. A positive pregnancy test and pelvic ultrasonography are diagnostic. Retrocecal or retroileal appendicitis (often associated with pyuria or hematuria) may be confused with ureteral colic or pyelonephritis. Other conditions that may resemble appendicitis are diverticulitis, carcinoid of the appendix, perforated colonic cancer, Crohn ileitis, perforated peptic ulcer, cholecystitis, and mesenteric adenitis. It is virtually impossible to distinguish appendicitis from Meckel diverticulitis, but both require surgical treatment.

▶ Complications

Perforation occurs in 20% of patients and should be suspected in patients with pain persisting for over 36 hours, high fever, diffuse abdominal tenderness or peritoneal findings, a palpable abdominal mass, or marked leukocytosis. Localized perforation results in a contained abscess, usually in the pelvis. A free perforation leads to suppurative peritonitis with toxicity. Septic thrombophlebitis (pylephlebitis) of the portal venous system is rare and suggested by high fever, chills, bacteremia, and jaundice.

▶ Treatment

The treatment of early, uncomplicated appendicitis is surgical appendectomy in most patients. When possible, a laparoscopic approach is preferred to open laparotomy. Prior to surgery, patients should be given broad-spectrum antibiotics with gram-negative and anaerobic coverage to reduce the incidence of postoperative infections. Recommended preoperative intravenous regimens include cefoxitin or cefotetan 1–2 g every 8 hours; ampicillin-sulbactam 3 g every 6 hours; or ertapenem 1 g as a single dose. Up to 80–90% of patients with uncomplicated appendicitis treated with antibiotics alone for 7 days have resolution of symptoms and signs. Therefore, conservative management with antibiotics alone may be considered in patients with a nonperforated appendicitis with surgical contraindications or with a strong preference to avoid surgery; however, appendectomy generally still is recommended in most patients to prevent recurrent appendicitis (20–35% within 1 year).

Emergency appendectomy is required in patients with perforated appendicitis with generalized peritonitis. The optimal treatment of stable patients with perforated appendicitis and a contained abscess is controversial. Surgery in this setting can be difficult. Many recommend percutaneous CT-guided drainage of the abscess with intravenous fluids and antibiotics to allow the inflammation to subside. An interval appendectomy may be performed after 6 weeks to prevent recurrent appendicitis.

▶ Prognosis

The mortality rate from uncomplicated appendicitis is extremely low. Even with perforated appendicitis, the mortality rate in most groups is only 0.2%, though it approaches 15% in older adults.

Majajan P et al. Factors associated with potentially missed diagnosis of appendicitis in the emergency department. *JAMA Netw Open*. 2020;3:e200612. [PMID: 32150270]

Nimmagadda N et al. Complicated appendicitis: immediate operation or trial of nonoperative management? *Am J Surg*. 2019;217:713. [PMID: 30635209]

Poprom N et al. The efficacy of antibiotic treatment versus surgical treatment of uncomplicated acute appendicitis: systematic review and network meta-analysis of randomized controlled trial. *Am J Surg*. 2019;218:192. [PMID: 30340760]

INTESTINAL TUBERCULOSIS

Intestinal tuberculosis is common in underdeveloped countries but rare in the United States except in immigrant groups or in patients with untreated AIDS. It is caused by both *Mycobacterium tuberculosis* and *M bovis*. Active pulmonary disease is present in less than 50% of patients. The most frequent site of involvement is the ileocecal region; however, any region of the gastrointestinal tract may be involved. Patients may be without symptoms or complain of chronic abdominal pain, obstructive symptoms, weight loss, and diarrhea. An abdominal mass may be palpable. Complications include intestinal obstruction, hemorrhage, and fistula formation. The purified protein derivative (PPD) skin test may be negative, especially in patients with weight loss or AIDS. Abdominal CT may show thickening of the cecum and ileocecal valve and massive lymphadenopathy. Colonoscopy may demonstrate an ulcerated mass, multiple ulcers with steep edges and adjacent small sessile polyps, small ulcers or erosions, or small diverticula, most commonly in the ileocecal region. The differential diagnosis includes Crohn disease, carcinoma, lymphoma, and intestinal amebiasis. The diagnosis is established by either endoscopic or surgical biopsy revealing acid-fast bacilli, caseating granuloma, or positive cultures for the organism. Detection of tubercle bacilli in biopsy specimens by PCR is now the most sensitive means of diagnosis.

Treatment with standard antituberculous regimens (Tables 9–14 and 9–15) is effective.

Lu S et al. Clinical diagnosis and endoscopic analysis of 10 cases of intestinal tuberculosis. *Medicine (Baltimore)*. 2020;99: e21175. [PMID: 32664157]

PROTEIN-LOSING ENTEROPATHY

Protein-losing enteropathy comprises a number of conditions that result in excessive loss of serum proteins into the gastrointestinal tract.

Hypoalbuminemia is the sine qua non of protein-losing enteropathy. However, other serum proteins such as alpha-1-antitrypsin also are lost from the gut epithelium. In protein-losing enteropathy caused by lymphatic obstruction, loss of lymphatic fluid commonly results in lymphocytopenia (less than 1000/mcL), hypoglobulinemia, and hypcholesterolemia.

In most cases, protein-losing enteropathy is recognized as a sequela of a known gastrointestinal disorder. In patients in whom the cause is unclear, evaluation is indicated and is guided by the clinical suspicion. Protein-losing enteropathy must be distinguished from other causes of hypoalbuminemia, which include liver disease and nephrotic syndrome, and from heart failure. Protein-losing enteropathy is confirmed by determining the gut alpha-1-antitrypsin clearance (24-hour volume of feces \times stool concentration of alpha-1-antitrypsin \div serum alpha-1-antitrypsin concentration). A clearance of more than 27 mL/24 h is abnormal.

Laboratory evaluation of protein-losing enteropathy includes serum protein electrophoresis, lymphocyte count, and serum cholesterol to look for evidence of lymphatic obstruction. Serum ANA and C3 levels are useful to screen for autoimmune disorders. Stool samples should be examined for ova and parasites. Evidence of malabsorption is evaluated by means of a stool qualitative fecal fat determination. Intestinal imaging is performed with small bowel enteroscopy, CT enterography, or wireless capsule endoscopy of the small intestine. Colonic diseases are excluded with colonoscopy. A CT scan of the abdomen is performed to look for evidence of neoplasms or lymphatic obstruction. Rarely, lymphangiography is helpful. In some situations, laparotomy with full-thickness intestinal biopsy is required to establish a diagnosis.

Treatment is directed at the underlying cause.

Elli L et al. Protein-losing enteropathy. *Curr Opin Gastroenterol.* 2020;36:238. [PMID: 32073507]

Tseng YJ et al. Protein-losing enteropathy and primary intestinal lymphangiectasia. *QJM.* 2020;113:224. [PMID: 31309229]

DISEASES OF THE COLON & RECTUM

(See Chapter 39 for Colorectal Cancer.)

IRRITABLE BOWEL SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Chronic functional disorder characterized by abdominal pain with alterations in bowel habits.
- ▶ Symptoms usually begin in late teens to early twenties.
- ▶ Limited evaluation to exclude organic causes of symptoms.

► General Considerations

IBS can be defined as an idiopathic clinical entity characterized by chronic (more than 3 months) abdominal pain that occurs in association with altered bowel habits. These symptoms may be continuous or intermittent. The 2016 Rome IV consensus definition of IBS is abdominal pain that has two of the following three features: (1) related to defecation, (2) associated with a change in frequency of stool, or (3) associated with a change in form (appearance) of stool. Symptoms of abdominal pain should be present on average at least 1 day per week. Other symptoms supporting the diagnosis include abnormal stool frequency; abnormal stool form (lumpy or hard; loose or watery); abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); and abdominal bloating or a feeling of abdominal distention.

Patients may have other somatic or psychological complaints such as dyspepsia, heartburn, chest pain, headaches, fatigue, myalgias, urologic dysfunction, gynecologic symptoms, anxiety, or depression.

The disorder is a common problem presenting to both gastroenterologists and primary care physicians. Up to 10% of adults have symptoms compatible with the diagnosis, but most never seek medical attention. Approximately two-thirds of patients with IBS are women.

► Pathogenesis

A. Abnormal Motility

A variety of abnormal myoelectrical and motor abnormalities have been identified in the colon and small intestine. In some cases, these are temporally correlated with episodes of abdominal pain or emotional stress. Differences between patients with constipation-predominant (slow intestinal transit) and diarrhea-predominant (rapid intestinal transit) syndromes are reported.

B. Visceral Hypersensitivity

Patients often have a lower visceral pain threshold, reporting abdominal pain at lower volumes of colonic gas inflation or colonic balloon inflation than controls. Many patients complain of bloating and distention, which may be due to several different factors including increased visceral sensitivity, increased gas production, impaired gas transit through the intestine, or impaired rectal expulsion. Many patients also report rectal urgency despite small rectal volumes of stool.

C. Intestinal Inflammation

The intestinal epithelium and immune system interact with the intra-intestinal microbiome, which is made up of an estimated 30,000 different microbial species. It is postulated that dietary factors, medications (antibiotics), or infections may increase intestinal permeability, leading to intestinal inflammation that may contribute to alterations in intestinal motility or visceral hypersensitivity. Increased inflammatory cells have been found in the mucosa, submucosa, and muscularis of some patients with IBS, but their importance is unclear.

Symptoms compatible with IBS develop within 1 year in over 10% of patients after an episode of bacterial gastroenteritis compared with less than 2% of controls. Women and patients with antibiotic exposure or psychological stress at the onset of gastroenteritis appear to be at increased risk for developing “postinfectious” IBS.

Alterations in the intestinal microbiome composition may cause increased postprandial gas as well as bloating and distention due to degradation of undigested, fermentable carbohydrates in the small intestine or colon. A subset of patients with IBS appear to have small intestinal bacterial overgrowth. However, estimates of the proportions of patients affected vary widely in part due to the different methods used to diagnose bacterial overgrowth. In a 2020 meta-analysis of 25 studies of IBS patients who underwent testing for bacterial overgrowth, an increase in breath hydrogen or methane excretion was reported in 62% following lactulose ingestion but in 21% following glucose ingestion, and only 14% using the “gold standard” of jejunal aspirates and bacterial cultures.

D. Psychosocial Abnormalities

More than 50% of patients with irritable bowel who seek medical attention have underlying depression, anxiety, or somatization. Psychological abnormalities may influence how the patient perceives or reacts to illness and minor visceral sensations. Chronic stress may alter intestinal motility or modulate pathways that affect central and spinal processing of visceral afferent sensation.

► Clinical Findings

A. Symptoms and Signs

Irritable bowel is a chronic condition. Symptoms usually begin in the late teens to twenties. The diagnosis is established in the presence of compatible symptoms and the judicious use of tests to exclude organic disease.

Abdominal pain usually is intermittent, crampy, and in the lower abdominal region. As previously stated, pain typically is associated with a change in stool frequency or form and may be improved or worsened by defecation. It does not usually occur at night or interfere with sleep. Patients with IBS may be classified into one of four categories based on the predominant stool habits and stool form: IBS with diarrhea, IBS with constipation, IBS with mixed constipation and diarrhea, or IBS that is not subtyped. It is important to clarify what the patient means by these complaints. Patients with irritable bowel and constipation report infrequent bowel movements (less than three per week), hard or lumpy stools, or straining. Patients with IBS with diarrhea refer to loose or watery stools, frequent stools (more than three per day), urgency, or fecal incontinence. Many patients report that they have a firm stool in the morning followed by progressively looser movements. Complaints of visible distention and bloating are common, though these are not always clinically evident.

The patient should be asked about “alarm symptoms” that suggest a diagnosis other than IBS and warrant further investigation. The acute onset of symptoms raises the

likelihood of organic disease, especially in patients older than 40–50 years. Nocturnal diarrhea, severe constipation or diarrhea, hematochezia, weight loss, and fever are incompatible with a diagnosis of IBS and warrant investigation for underlying disease. Patients who have a family history of cancer, inflammatory bowel disease, or celiac disease should undergo additional evaluation.

A physical examination should be performed to look for evidence of organic disease and to allay the patient’s anxieties. The physical examination usually is normal. Abdominal tenderness, especially in the lower abdomen, is common but not pronounced. A digital rectal examination should be performed in patients with constipation to screen for paradoxical anal squeezing during attempted straining that may suggest pelvic floor dyssynergia. A pelvic examination is recommended for postmenopausal women with recent onset constipation and lower abdominal pain to screen for gynecologic malignancy.

B. Laboratory Findings and Special Examinations

Although the vague nature of symptoms and patient anxiety may prompt clinicians to consider a variety of diagnostic studies, overtesting should be avoided, since the likelihood of serious organic disease is low. Nonetheless, a 2019 AGA practice guideline recommends selected laboratory tests in patients with chronic diarrhea to exclude other diagnoses. A complete blood count should be obtained to screen for iron deficiency anemia. A fecal calprotectin level is recommended to screen for inflammatory bowel disease; a value of greater than 50 mcg/g may warrant further endoscopic evaluation. Serologic testing for celiac disease (TG IgA) should be performed. Stool specimen examinations should be obtained in patients with increased likelihood of parasitic infection (eg, day care workers, campers, foreign travelers) for *Giardia* antigen or for multiple organisms (*Giardia*, *Cryptosporidium*, *Cyclospora*, *Entamoeba histolytica*) using nucleic acid amplification (PCR) tests. If these tests are negative, further testing is not necessary in most patients and education, reassurance, and initial empiric treatment is recommended. Routine sigmoidoscopy or colonoscopy is not recommended in young patients with symptoms of IBS without alarm symptoms but should be considered along with further laboratory testing in patients who do not improve with conservative management. In all patients aged 50 years or older who have not had a previous evaluation, colonoscopy should be obtained to exclude malignancy. When colonoscopy is performed, random mucosal biopsies should be obtained to look for evidence of microscopic colitis (which may have similar symptoms). Routine testing for bacterial overgrowth with hydrogen breath tests is not recommended.

► Differential Diagnosis

A number of disorders may present with similar symptoms. Examples include colonic neoplasia, inflammatory bowel disease (ulcerative colitis, Crohn disease, microscopic colitis), bile-acid diarrhea, hyperthyroidism or hypothyroidism, parasites, malabsorption (especially celiac disease, bacterial overgrowth, lactase deficiency), causes of chronic secretory

diarrhea (carcinoid), and gynecologic disorders (endometriosis, ovarian cancer). Psychiatric disorders such as depression, panic disorder, and anxiety must be considered as well. Women with refractory symptoms have an increased incidence of prior sexual and physical abuse. These diagnoses should be excluded in patients with presumed IBS who do not improve within 2–4 weeks of empiric treatment or in whom subsequent alarm symptoms develop.

Treatment

A. General Measures

As with other functional disorders, the most important interventions the clinician can offer are reassurance, education, and support. This includes identifying and responding to the patient's concerns, careful explanation of the pathophysiology and natural history of the disorder, setting realistic treatment goals, and involving the patient in the treatment process. Because irritable bowel symptoms are chronic, the patient's reasons for seeking consultation at this time should be determined. These may include major life events or recent psychosocial stressors, dietary or medication changes, concerns about serious underlying disease, or reduced quality of life and impairment of daily activities. In discussing with the patient the importance of the mind-gut interaction, it may be helpful to explain that alterations in visceral motility and sensitivity may be exacerbated by environmental, social, or psychological factors such as foods, medications, hormones, and stress. Symptoms such as pain, bloating, and altered bowel habits may lead to anxiety and distress, which in turn may further exacerbate bowel disturbances due to disordered communication between the gut and the central nervous system. Fears that the symptoms will progress, require surgery, or degenerate into serious illness should be allayed. The patient should understand that IBS is a chronic disorder characterized by periods of exacerbation and quiescence. The emphasis should be shifted from finding the cause of the symptoms to finding a way to cope with them. Moderate exercise is beneficial. Clinicians must resist the temptation to chase chronic complaints with new or repeated diagnostic studies.

B. Dietary Therapy

Patients commonly report dietary intolerances. Proposed mechanisms for dietary intolerance include food allergy, hypersensitivity, effects of gut hormones, changes in bacterial flora, increased bacterial gas production (arising in the small or large intestine), and direct chemical irritation. Fatty foods, alcohol, caffeine, spicy foods, and grains are poorly tolerated by many patients with IBS. In patients with diarrhea, bloating, and flatulence, lactose intolerance should be excluded with a hydrogen breath test or a trial of a lactose-free diet. A host of poorly absorbed, fermentable, monosaccharides and short-chain carbohydrates (FODMAPs) may exacerbate bloating, flatulence, and diarrhea in some patients. These include six food groups: fructose (corn syrups, apples, pears, honey, watermelon, raisins), lactose, fructans (garlic, onions, leeks, asparagus, artichokes), wheat-based products (breads, pasta, cereals, cakes), sorbitol (stone fruits), and raffinose (legumes, lentils,

brussel sprouts, soybeans, cabbage). Dietary restriction of these fermentable carbohydrates for 2–4 weeks may improve symptoms (especially abdominal pain and bloating) in 50–65% of patients. Responders should gradually reintroduce different FODMAPs to identify food triggers. Ingestion of alpha-galactosidase supplement ("Beano") with meals containing foods with high galactoside content (eg, beans, peas, lentils, soy) may improve bowel symptoms. Gluten has not been demonstrated to increase bowel symptoms independent of other FODMAPs, and a gluten-free diet is not recommended.

Poorly fermentable soluble fiber (psyllium, oatmeal) improves global symptoms in many patients and is recommended by the 2018 American College of Gastroenterology guideline. Fermentable or insoluble fiber (bran) may increase gas and bloating.

C. Pharmacologic Measures

More than two-thirds of patients with IBS have mild symptoms that respond readily to education, reassurance, and dietary interventions. Drug therapy should be reserved for patients with moderate to severe symptoms that do not respond to conservative measures. These agents should be viewed as being adjunctive rather than curative. Given the wide spectrum of symptoms, no single agent is expected to provide relief in all or even most patients. Nevertheless, therapy targeted at the specific dominant symptom (pain, constipation, or diarrhea) may be beneficial.

1. Antispasmodic agents—Anticholinergic agents are used by some practitioners for treatment of acute episodes of pain or bloating despite a lack of well-designed trials demonstrating efficacy. Available agents include hyoscyamine, 0.125 mg orally (or sublingually as needed) or sustained-release, 0.037 mg or 0.75 mg orally twice daily; dicyclomine, 10–20 mg orally; or methscopolamine, 2.5–5 mg orally before meals and at bedtime. Anticholinergic side effects are common, including urinary retention, constipation, tachycardia, and dry mouth. Hence, these agents should be used with caution in older patients and in patients with constipation. Over-the-counter, enteric-coated peppermint oil formulations (believed to relax smooth intestine) are widely available. In a 2020 randomized controlled trial, a formulation that is released in the small intestine improved abdominal pain in a higher proportion of treated patients (47%) compared with patients given placebo (34%).

2. Antidiarrheal agents—Loperamide (2 mg orally three or four times daily) is effective for the treatment of patients with diarrhea, reducing stool frequency, liquidity, and urgency. It may best be used "prophylactically" in situations in which diarrhea is anticipated (such as stressful situations) or would be inconvenient (social engagements). Increased intracolonic bile acids due to alterations in enterohepatic circulation may contribute to diarrhea in a subset of patients with diarrhea. An empiric trial of bile salt-binding agents (cholestyramine, 2–4 g one to three times daily with meals; colestevam, 625 mg, 1–3 tablets twice daily) may be considered. Eluxadoline (75–100 mg twice daily) is an opioid antagonist that is approved for treatment of IBS with diarrhea. In phase 3 trials, it

decreased abdominal pain and improved stool consistency in approximately 25% of patients versus 16–19% with placebo; however, sphincter of Oddi dysfunction and pancreatitis developed in a small percentage (0.5%) of patients. Given its minimal efficacy, adverse side effect profile, and unproven benefit versus loperamide, further study is needed before its use can be recommended.

3. Anticonstipation agents—Treatment with oral osmotic laxatives polyethylene glycol 3350 (MiraLAX, 17–34 g/day) may increase stool frequency, improve stool consistency, and reduce straining. Lactulose or sorbitol produces increased flatus and distention, which are poorly tolerated in patients with IBS and should be avoided. Lubiprostone (8 mcg orally twice daily), linaclotide (290 mcg orally once daily), plecanatide (3 mg orally once daily), and tegaserod (6 mg orally twice daily) are FDA approved for treatment of IBS with constipation based on modest demonstrated efficacy. Through different mechanisms, they stimulate increased intestinal chloride and fluid secretion, resulting in accelerated colonic transit. In clinical trials, lubiprostone led to global symptom improvement in 18% of patients compared with 10% of patients who received placebo (a therapeutic gain of 8%). Using different FDA-approved endpoints for significant clinical response (30% reduction in abdominal pain and more than three spontaneous bowel movements per week), phase 3 trials of linaclotide and plecanatide have demonstrated similar therapeutic gains: linaclotide 12.5% versus placebo 4% and plecanatide 26% versus placebo 16%. Tegaserod, a 5-HT₄-receptor agonist, was originally approved by the FDA in 2002 for IBS with constipation, but voluntarily withdrawn from the market in 2007 because of cardiovascular safety concerns. But in March 2019, it was reapproved by the FDA for women under age 65 after evaluation of clinical data from 29 placebo-controlled trials and newer treatment outcome data. Patients with intractable constipation should undergo further assessment for slow colonic transit and pelvic floor dysfunction (see Constipation, above).

4. Psychotropic agents—Patients with predominant symptoms of pain or bloating may benefit from low doses of tricyclic antidepressants, which are believed to have effects on motility, visceral sensitivity, and central pain perception that are independent of their psychotropic effects. Because of their anticholinergic effects, these agents may be more useful in patients with diarrhea-predominant than constipation-predominant symptoms. Oral nortriptyline, desipramine, or imipramine may be started at a low dosage of 10 mg at bedtime and increased gradually to 50–150 mg as tolerated. Response rates do not correlate with dosage, and many patients respond to doses of 50 mg or less daily. Side effects are common, and lack of efficacy with one agent does not preclude benefit from another. Agents with higher anticholinergic activity may improve diarrhea but worsen constipation. Improvement should be evident within 4 weeks. The oral serotonin reuptake inhibitors (sertraline, 25–100 mg daily; citalopram, 10–20 mg; paroxetine, 20–50 mg daily; or fluoxetine, 10–40 mg daily) may be used to treat irritable bowel symptoms as well as treat mood disorders. SSRIs may accelerate gastrointestinal transit and improve constipation. Anxiolytics should not

be used chronically in IBS because of their habituation potential. Patients with major depression or anxiety disorders should be identified and treated with therapeutic doses of appropriate agents.

5. Serotonin receptor antagonists—Alosetron is a 5-HT₃ antagonist that is FDA approved for the treatment of women with severe IBS with predominant diarrhea. Unfortunately, due to cases of severe constipation and a small (1:1000) but significant risk of ischemic colitis, alosetron is restricted to women with severe IBS with diarrhea who have not responded to conventional therapies and who have been educated about the relative risks and benefits of the agent. A randomized crossover trial of another 5-HT₃ antagonist, ondansetron 4–8 mg three times daily, showed overall superior symptom improvement, including stool frequency, consistency, and urgency. At this time, 5-HT₃ antagonists may be considered after careful discussion of the risks and benefits in carefully selected patients with severe diarrhea-predominant IBS.

6. Nonabsorbable antibiotics—Rifaximin (550 mg, three times daily for 14 days) may be considered in patients with refractory symptoms, especially bloating. A 2012 meta-analysis identified a 9.9% greater improvement in bloating with rifaximin compared with placebo, a modest gain that is similar to other less expensive therapies. Symptom improvement may be attributable to suppression of bacteria in either the small intestine or colon, resulting in decreased bacterial carbohydrate fermentation, diarrhea, and bloating.

7. Probiotics—Meta-analyses of small controlled clinical trials of probiotics report improved symptoms of pain, bloating, and flatulence in some patients; however, there is no proven benefit. It is hypothesized that alterations in gut flora may reduce symptoms through suppression of inflammation or reduction of bacterial gas production, resulting in reduced distention, flatus, and visceral sensitivity. A 2018 American College of Gastroenterology guideline gave probiotics a weak recommendation, but a 2020 AGA guideline recommended use only within clinical trials.

D. Psychological Therapies

Cognitive-behavioral therapies, relaxation techniques, yoga, and hypnotherapy appear to be beneficial in some patients. Patients with underlying psychological abnormalities may benefit from evaluation by a psychiatrist or psychologist. Patients with severe disability should be referred to a pain treatment center.

► Prognosis

Most patients with IBS learn to cope with their symptoms and lead productive lives.

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in people who have received antibiotics that disrupt the normal bowel flora and thus allow bacterium to flourish. Although almost all antibiotics have been implicated, colitis most commonly develops after use of ampicillin, clindamycin, third-generation cephalosporins, and fluoroquinolones. Symptoms usually begin during or shortly after antibiotic therapy but may be delayed for up to 8 weeks. All patients with acute diarrhea should be asked about recent antibiotic exposure. Patients who are elderly; debilitated; immunocompromised; receiving multiple antibiotics or prolonged (more than 10 days) antibiotic therapy; receiving enteral tube feedings, proton pump inhibitors, or chemotherapy; or who have inflammatory bowel disease have a higher risk of acquiring *C difficile* and developing *C difficile*-associated diarrhea.

Pathogenic strains of *C difficile* produce two toxins: toxin TcdA is an enterotoxin and toxin TcdB is a cytotoxin. A more virulent strain of *C difficile* (NAP1) that contains an 18-base pair deletion of the TcdC inhibitory gene results in higher toxin A and B production. This hypervirulent strain is more prevalent among hospital-associated infections (31%) than community-acquired infections (19%) and has been associated with outbreaks of severe disease with up to 7% mortality.

► Clinical Findings

A. Symptoms and Signs

Most patients report mild to moderate greenish, foul-smelling watery diarrhea 5–15 times per day with lower abdominal cramps. Physical examination is normal or reveals mild left lower quadrant tenderness. The stools may have mucus but seldom gross blood. Over half of hospitalized patients diagnosed with *C difficile* colitis have severe disease as defined by a white blood count greater than 15,000/mcL ($15 \times 10^9/L$) or serum creatinine greater than 1.5 g/dL.

Fulminant disease occurs in up to 10 % of patients. It is characterized by fever; hemodynamic instability; and abdominal distention, pain, and tenderness. Most patients have profuse diarrhea (up to 30 stools/day); however, diarrhea may be absent or appear to be improving in patients with fulminant disease or ileus. Laboratory data suggestive of severe disease include a white blood count greater than 30,000/mcL ($30 \times 10^9/L$), serum albumin less than 2.5 g/dL (due to protein-losing enteropathy), elevated serum lactate, and rising serum creatinine.

B. Special Examinations

1. Stool studies—Stool testing for *C difficile* is recommended in hospitalized patients with dysentery or three or more liquid stools within 24 hours or outpatients with diarrhea persisting longer than 1 week. Three types of diagnostic tests are in common use: (1) an immunoassay for glutamate dehydrogenase (GDH) protein has high sensitivity and negative predictive value (95%) for the detection of toxigenic and nontoxigenic *C difficile*, though it does not distinguish active infection with toxin secretion from colonization; (2) PCR tests amplify the *C difficile* toxin gene (usually *TcdB*); they have extremely high sensitivity (97–99%) for detection of *C difficile* as well as the

ANTIBIOTIC-ASSOCIATED COLITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Most cases of antibiotic-associated diarrhea are not attributable to *C difficile* and are usually mild and self-limited.
- ▶ Symptoms of antibiotic-associated colitis vary from mild to fulminant; almost all colitis is attributable to *C difficile*.
- ▶ Diagnosis in most cases established by stool assay.

► General Considerations

Antibiotic-associated diarrhea is a common clinical occurrence. Characteristically, the diarrhea occurs during the period of antibiotic exposure, is dose related, and resolves spontaneously after discontinuation of the antibiotic. In most cases, this diarrhea is mild, self-limited, and does not require any specific laboratory evaluation or treatment. Stool examination usually reveals no fecal leukocytes, and stool cultures reveal no pathogens. Although *C difficile* is identified in the stool of 15–25% of cases of antibiotic-associated diarrhea, it is also identified in 5–10% of patients treated with antibiotics who do not have diarrhea. Most cases of antibiotic-associated diarrhea are due to changes in colonic bacterial fermentation of carbohydrates and are not due to *C difficile*.

Antibiotic-associated colitis is a significant clinical problem almost always caused by *C difficile* infection that colonizes the colon and releases two toxins: TcdA and TcdB. Found throughout hospitals in patient rooms and bathrooms, *C difficile* is readily transmitted from patient to patient by hospital personnel. Fastidious hand washing and use of disposable gloves are helpful in minimizing transmission and reducing infections in hospitalized patients. In hospitalized patients, *C difficile* colitis occurs in approximately 20% of those who are colonized at admission and 3.5% of those not colonized. In both hospital-associated and community infections, most episodes of colitis occur

ability to detect the hypervirulent NAP1 strain but like the GDH assay cannot distinguish active infection from colonization; (3) rapid enzyme immunoassays (EIAs) detect the presence of *C difficile*-toxins TcdA and TcdB with 75–95% sensitivity, confirming active toxin-secreting infection. As the initial diagnostic test, most laboratories screen for *C difficile* with either the PCR toxin gene test or the GDH protein assay. A negative PCR or GDH assay effectively excludes infection. Treatment based on PCR or GDH testing alone may result in unnecessary treatment of patients with *C difficile* colonization. Therefore, laboratories may perform secondary testing with toxin EIA to distinguish colonization from active toxin-producing infection.

2. Flexible sigmoidoscopy—Flexible sigmoidoscopy is not needed in patients who have typical symptoms and a positive stool test. It may clarify the diagnosis in patients with positive *C difficile* toxin assays who have atypical symptoms or who have persistent diarrhea despite appropriate therapy. In patients with mild to moderate symptoms, there may be no abnormalities or only patchy or diffuse, nonspecific colitis indistinguishable from other causes. In patients with severe illness, true **pseudomembranous colitis** is seen.

3. Imaging studies—Abdominal radiographs or noncontrast abdominal CT scans are obtained in patients with severe or fulminant symptoms to look for evidence of colonic dilation and wall thickening. Abdominal CT also is useful in the evaluation of hospitalized patients with abdominal pain or ileus without significant diarrhea, in whom the presence of colonic wall thickening suggests unsuspected *C difficile* colitis. CT scanning is also useful in the detection of possible perforation.

placed on strict contact precautions and health care workers should apply careful handwashing before and after contact. If possible, therapy of the inciting antibiotic should be discontinued as soon as possible. The treatment of an initial episode of *C difficile* colitis is determined by the severity of disease. For patients with nonsevere disease, oral fidaxomicin (200 mg orally two times daily) and vancomycin (125 mg orally four times daily) are equally effective for initial treatment, but recurrence rates are lower with fidaxomicin than vancomycin (15% vs 25%). Fidaxomicin may be preferred as first-line treatment for patients believed to be at higher risk for recurrent disease. Recommended treatment duration is 10 days in most situations but is extended in patients requiring prolonged antibiotic therapy for other infections. Metronidazole (500 mg orally three times daily) is no longer recommended for initial therapy except when vancomycin or fidaxomicin is unavailable. Symptomatic improvement occurs in most patients within 72 hours. Following treatment, stool assays may remain positive for several weeks after symptom resolution.

For patients with fulminant disease, vancomycin 500 mg orally four times daily along with metronidazole 500 mg intravenously every 8 hours are recommended. In patient with ileus, vancomycin may be administered by nasoenteric tube and by rectal enema (500 mg in 100 mL normal saline by enema every 6 hours). The efficacy of fidaxomicin for severe or fulminant disease requires further investigation. Early surgical consultation is recommended for all patients with severe or fulminant disease. Total abdominal colectomy or loop ileostomy with colonic lavage may be required in patients with toxic megacolon, perforation, sepsis, or hemorrhage.

Differential Diagnosis

In the hospitalized patient in whom acute diarrhea develops after admission, the differential diagnosis includes simple antibiotic-associated diarrhea (not related to *C difficile*), enteral feedings, medications, and ischemic colitis. Other infectious causes are unusual in hospitalized patients in whom diarrhea develops more than 72 hours after admission, and it is not cost-effective to obtain stool cultures unless tests for *C difficile* are negative. *Klebsiella oxytoca* may cause a distinct form of antibiotic-associated hemorrhagic colitis that is segmental (usually in the right or transverse colon); spares the rectum; and is more common in younger, healthier outpatients.

Treatment of Relapse

Up to 20% of patients have a relapse of diarrhea from *C difficile* within 8 weeks after stopping initial therapy. This may be due to reinfection or failure to eradicate the organism. Current Infectious Disease Society of America guidelines recommend that the first recurrence be treated with fidaxomicin 200 mg orally twice daily for 10 days or with a prolonged tapering regimen of vancomycin 125 mg orally four times daily for 14 days; twice daily for 7 days; once daily for 7 days; then every other 2 or 3 days for 2–8 weeks. Second recurrence should be treated with an additional vancomycin tapering regimen, as above.

For patients with three or more relapses, guidelines recommend consideration of fecal microbiota transplantation (FMT), in which a suspension of fecal bacteria from a healthy donor is given to the patient with infection. Fecal specimens that have been screened for infectious agents are commercially available. The fecal microbiota may be instilled into the patient by one of three methods: (1) infusion through a colonoscope into the terminal ileum and colon, (2) infusion through a nasoenteric tube into the duodenum, or (3) ingestion of multiple freeze-dried capsules. Due to its efficacy and relative safety and ease of administration, the oral capsule method has become the preferred mode of fecal administration in most patients. Using all three infusion modalities, multiple case series reported disease remission after a single treatment in over

Complications

Severe colitis may progress quickly to fulminant disease, resulting in hemodynamic instability, respiratory failure, metabolic acidosis, megacolon (more than 7-cm diameter), perforation, and death. Chronic untreated colitis may result in weight loss and protein-losing enteropathy.

Treatment

A. Initial Treatment

To reduce transmission within health care facilities, patients with suspected or proven *C difficile* infection should be

90% of patients with recurrent *C. difficile* infection. Furthermore, randomized studies have demonstrated significantly higher resolution of *C. difficile* diarrhea with FMT (94%) than vancomycin (31%) and with FMT (92%) versus fidaxomicin (42%) or vancomycin (19%). However, FMT carries the potential risk of transmission of serious, even sometimes fatal, infection. Clinicians considering offering FMT must discuss with their patient this possible uncommon but very serious risk. Nonetheless, with proper screening and stool testing of donors, the risk of infections appears to be very low.

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INFLAMMATORY BOWEL DISEASE

The term “inflammatory bowel disease” includes ulcerative colitis and Crohn disease. In the United States, there are approximately 1.6 million people with inflammatory bowel disease with adjusted annual incidences of 12.2 cases/100,000 and 10.7 cases/100,000 person-years for ulcerative colitis and Crohn disease, respectively. Ulcerative colitis is a chronic, recurrent disease characterized by diffuse mucosal inflammation involving only the colon. Ulcerative colitis invariably involves the rectum and may extend proximally in a continuous fashion to involve part or all of the colon. Crohn disease is a chronic, recurrent disease characterized by patchy transmural inflammation involving any segment of the gastrointestinal tract from the mouth to the anus.

Crohn disease and ulcerative colitis may be associated in 50% of patients with a number of extraintestinal manifestations, including oral ulcers, oligoarticular or polyarticular nondeforming peripheral arthritis, spondylitis or sacroiliitis, episcleritis or uveitis, erythema nodosum, pyoderma gangrenosum, hepatitis and sclerosing cholangitis, and thromboembolic events.

► Pharmacologic Therapy

Although ulcerative colitis and Crohn disease appear to be distinct entities, several pharmacologic agents are used to treat both. Despite extensive research, there are still no specific therapies for these diseases. The mainstays of therapy are 5-aminosalicylic acid derivatives, corticosteroids, immunomodulating agents (such as mercaptopurine or azathioprine and methotrexate), and biologic agents.

A. 5-Aminosalicylic Acid (5-ASA)

5-ASA is a topically active agent that has a variety of anti-inflammatory effects. It is readily absorbed from the small intestine but demonstrates minimal colonic absorption. Several oral and topical compounds have been designed to target delivery of 5-ASA to the colon or distal small intestine.

1. Oral formulations—Mesalamine compounds are oral 5-ASA formulations that are either coated in various pH-sensitive resins (Asacol, Apriso, and Lialda) that release 5-ASA throughout the colon or packaged in timed-release capsules (Pentasa) that release 5-ASA in the small intestine and colon. Side effects of these compounds are uncommon but include nausea, rash, diarrhea, pancreatitis, and acute interstitial nephritis. Sulfasalazine and balsalazide are oral formulations that contain 5-ASA linked by an azo bond to another agent (sulfaipyridine or an inert peptide, respectively) in order to prevent small intestine absorption. Following cleavage of the azo bond by colonic bacteria, 5-ASA is released in the colon. The sulfaipyridine group is absorbed and may cause side effects in 15–30% of patients, including nausea, oligospermia, leukopenia, agranulocytosis, impaired folate metabolism, and hypersensitivity (fever, rash, hemolytic anemia, pneumonitis). Because of its side effects, sulfasalazine is used less frequently than other 5-ASA agents.

2. Topical mesalamine—5-ASA is provided in the form of suppositories (Canasa; 1000 mg) and enemas (Rowasa; 4 g/60 mL). These formulations can deliver much higher concentrations of 5-ASA to the distal colon than oral compounds. Side effects are uncommon.

B. Corticosteroids

A variety of intravenous, oral, and topical corticosteroid formulations have been used in inflammatory bowel disease. They have utility in the short-term treatment of moderate to severe disease. However, long-term use is associated with serious, potentially irreversible side effects and is to be avoided. The agents, route of administration, duration of use, and tapering regimens used are based more on personal bias and experience than on data from rigorous clinical trials. In hospitalized adult patients with severe disease, current guidelines recommend intravenous methylprednisolone 40–60 mg/day, which may be given in single or divided doses. Oral formulations are prednisone or methylprednisolone. Budesonide is an oral corticosteroid with high topical anti-inflammatory activity but low systemic activity due to high first-pass hepatic metabolism. An enteric-coated formulation is available (Entocort) that targets delivery to the terminal ileum and proximal colon. An enteric coated, multi-matrix, delayed-release formulation (budesonide Multi Matrix [MMX] formulation [Uceris]) is available that releases budesonide throughout the colon. Topical preparations are provided as hydrocortisone suppositories (100 mg), foam (90 mg), and enemas (100 mg) and as budesonide foam (2 mg).

C. Immunomodulating Drugs and Other Small Molecules

1. Thiopurines (mercaptopurine and azathioprine)—These drugs are used in many patients with moderate to

severe Crohn disease and ulcerative colitis either alone or in combination with anti-TNF agents. Thiopurines are used alone in patients who are corticosteroid-dependent in an attempt to reduce or withdraw corticosteroids and in patients in remission to reduce the risk of disease recurrence. Thiopurines are used in combination with biologic agents (especially anti-TNF agents) to reduce antibody formation against the biologic agent and to increase the likelihood of clinical remission through increased anti-TNF drug levels and possible synergistic effects. Side effects of mercaptopurine and azathioprine, including allergic reactions (fever, rash, or arthralgias) and nonallergic reactions (nausea, vomiting, pancreatitis, hepatotoxicity, bone marrow suppression, infections), occur in 15% of patients. Thiopurines are associated with up to a 2.5-fold increased risk of non-Hodgkin lymphomas (0.5/1000 patient-years). The risk rises after 1–2 years of exposure and is higher in men younger than age 30 years and patients older than age 50 years. Thiopurines also are associated with a risk of human papillomavirus (HPV)-related cervical dysplasia and with an increased risk of non-melanoma skin cancer. Younger patients also are at risk for severe primary Epstein-Barr virus (EBV) infection, if not previously exposed.

About 1 person in 300 has a homozygous mutation of one of the enzymes that metabolizes thiopurine methyltransferase (TPMT), placing them at risk for profound immunosuppression; 1 person in 9 is heterozygous for TPMT, resulting in intermediate enzyme activity. Measurement of TPMT functional activity is recommended prior to initiation of therapy. Treatment should be withheld in patients with absent TPMT activity. The most effective dose of mercaptopurine is 1–1.5 mg/kg. For azathioprine, it is 2–3 mg/kg daily. For patients with normal TPMT activity, both drugs may be initiated at the weight-calculated dose. A complete blood count should be obtained weekly for 4 weeks, biweekly for 4 weeks, and then every 1–3 months for the duration of therapy. Liver biochemical tests should be measured periodically. Some clinicians prefer gradual dose escalation, especially for patients with intermediate TPMT activity or for whom TPMT measurement is not available; both drugs may be started at 25 mg/day and increased by 25 mg every 1–2 weeks while monitoring for myelosuppression until the target dose is reached. If the white blood count falls below 4000/mcL ($4.0 \times 10^9/L$) or the platelet count falls below 100,000/mcL ($100 \times 10^9/L$), the medication should be held for at least 1 week before reducing the daily dose by 25–50 mg. Measurement of thiopurine metabolites (6-TG and 6-MMP) is of unproved value in most patients but is recommended in patients who have not responded to standard, weight-based dosing or in whom adverse effects develop.

2. Methotrexate—Low-dose oral methotrexate is used in combination with biologic agents to prevent immunogenicity. Methotrexate is an analog of dihydrofolic acid. Side effects of methotrexate include nausea, vomiting, stomatitis, infections, bone marrow suppression, hepatic fibrosis, and life-threatening pneumonitis. A complete blood count and liver chemistries should be monitored every 3 months. Folate supplementation (1 mg/day) should be administered.

Because methotrexate is teratogenic, it should be discontinued in men and women at least 6 months before conception and during pregnancy.

3. Janus kinase inhibitors—Tofacitinib is a nonbiologic small-molecule inhibitor of Janus kinase (JAK 1/3), which is involved through the JAK-STAT pathway in modulation of multiple interleukins. It is currently approved by the FDA as second-line therapy for the treatment of moderate to severe ulcerative colitis (not Crohn disease) that has not responded to anti-TNF therapy. It has rapid oral absorption and lacks immunogenicity. The FDA has issued a black box warning about an increased risk of blood clots and deaths in rheumatoid arthritis patients taking tofacitinib 10 mg orally twice daily compared with patients taking 5 mg orally twice daily of anti-TNF agents. Tofacitinib should not be prescribed to patients deemed at higher risk for thrombosis. It has a low risk of adverse events, including infections, with the exception of herpes zoster (it occurs in up to 5% of patients). Vaccination with inactivated (not live) recombinant zoster (Shingrix) is recommended in all patients older than 50 years and in younger patients with other risk factors for reactivation.

D. Biologic Therapies

A number of biologic therapies are available or in clinical testing that target various components of the immune system. Biologic agents are highly effective for patients with moderate to severe disease and when administered early in the disease course may improve the natural history of disease. The potential benefits of these agents must be weighed with their high cost and risk of rare but serious and potentially life-threatening side effects.

1. Anti-TNF therapies—Four monoclonal antibodies to TNF currently are available for the treatment of inflammatory bowel disease: infliximab, adalimumab, golimumab, and certolizumab. All four agents bind and neutralize soluble as well as membrane-bound TNF on macrophages and activated T lymphocytes, thereby preventing TNF stimulation of effector cells.

Infliximab is a chimeric (75% human/25% mouse) IgG₁ antibody that is administered by intravenous infusion. A three-dose regimen of 5 mg/kg administered at 0, 2, and 6 weeks is recommended for acute induction, followed by infusions every 8 weeks for maintenance therapy. Acute infusion reactions occur in 5–10% of infusions but occur less commonly in patients receiving regularly scheduled infusions or concomitant immunomodulators (ie, azathioprine or methotrexate). Most reactions are mild and can be treated by slowing the infusion rate and administering acetaminophen and diphenhydramine. Severe reactions (hypotension, severe shortness of breath, rigors, severe chest discomfort) occur in less than 1% and may require oxygen, diphenhydramine, hydrocortisone, and epinephrine. Delayed serum sickness-like reactions occur in 1%. With repeated, intermittent intravenous injections, antibodies to infliximab develop in up to 40% of patients, which are associated with a shortened duration or loss of response and increased risk of acute or delayed infusion reactions. Giving infliximab in a regularly scheduled

maintenance therapy (eg, every 8 weeks) or in combination with other immunomodulating agents (azathioprine, mercaptopurine, or methotrexate) significantly reduces the development of antibodies to less than 10%.

Adalimumab and golimumab are fully human IgG₁ antibodies that are administered by subcutaneous injection. For adalimumab, a dose of 160 mg at week 0 and 80 mg at week 2 is recommended for acute induction, followed by maintenance therapy with 40 mg subcutaneously every other week. For golimumab, a dose of 200 mg at week 0 and 100 mg at week 2 is recommended for acute induction, followed by maintenance therapy with 100 mg subcutaneously every 4 weeks.

Certolizumab is a fusion compound in which the Fab1 portion of a chimeric (95% human/5% mouse) TNF-antibody is bound to polyethylene glycol in order to prolong the drug half-life. However, certolizumab is infrequently used due to lower clinical efficacy.

Acute and delayed hypersensitivity reactions are rare with subcutaneous anti-TNF therapies. Antibodies to adalimumab or golimumab develop in 5% of patients and to certolizumab in 10%, which may lead to shortened duration or loss of response to the drug.

Serious infections with anti-TNF therapies may occur in 2–5% of patients, including sepsis, pneumonia, abscess, and cellulitis; however, controlled studies suggest the increased risk may be attributable to increased severity of disease and concomitant use of corticosteroids or immunomodulators. Patients treated with anti-TNF therapies are at increased risk for the development of opportunistic infections with intracellular bacterial pathogens including tuberculosis, mycoses (candidiasis, histoplasmosis, coccidioidomycosis, nocardiosis), and listeriosis, and with reactivation of viral infections, including hepatitis B, herpes simplex, varicella zoster, and EBV. Prior to use of these agents, patients should be screened for latent tuberculosis with PPD testing and a chest radiograph. Antinuclear and anti-DNA antibodies occur in a large percentage of patients; however, the development of drug-induced lupus is rare. All agents may cause severe hepatic reactions leading to acute hepatic failure; liver biochemical tests should be monitored routinely during therapy. Anti-TNF therapies may increase the risk of skin cancer, hence annual dermatologic examinations are recommended. There may be a small risk of non-Hodgkin lymphoma in patients taking anti-TNF monotherapy; however, the risk is much higher in patients receiving a combination of anti-TNF and a thiopurine (6.1-fold increase; 0.95/1000 person-years). Rare cases of optic neuritis and demyelinating diseases, including multiple sclerosis have been reported. Anti-TNF therapies may worsen heart failure in patients with cardiac disease.

In patients with active inflammatory bowel disease, monitoring of anti-TNF trough levels and any anti-drug antibodies is useful to optimize drug levels and guide therapy. Therapeutic drug monitoring is indicated in patients who have poor clinical response or who have lost clinical response. Patients with high titers of anti-drug antibodies should be switched to a different anti-TNF agent. Anti-TNF therapy is considered to have failed when patients have a poor response despite adequate anti-TNF

trough concentrations; another class of drugs should be tried. Increasingly, experts recommend proactive measurement of drug and antibody concentrations in all patients to optimize clinical response and minimize drug antibody formation (more common at low drug levels). At present, recommended trough concentrations during maintenance therapy are greater than 5–7 mcg/mL for infliximab, greater than 7–10 mcg/mL for adalimumab, and greater than 1 mcg/mL for golimumab.

2. Anti-integrins—Anti-integrins decrease the trafficking of circulating leukocytes through the vasculature, reducing chronic inflammation. Vedolizumab is FDA approved for patients with moderately active ulcerative colitis or Crohn disease who have an inadequate response to or intolerance of corticosteroids, immunomodulators, or anti-TNF agents. Induction therapy is given as a 300-mg intravenous dose at weeks 0, 2, and 6. This is followed by maintenance therapy of 300 mg intravenously every 4–8 weeks based on clinical response or serum trough concentrations. Thus far, vedolizumab does not appear to be associated with an increased risk of serious infections or malignancy. Infusion reactions are uncommon. Antibodies develop in 5%, which may interfere with drug efficacy.

3. Anti-IL-12/23 antibody—Ustekinumab is a human IgG₁ monoclonal antibody that binds the p40 subunit of IL-12 and IL-23, interfering with their receptor binding on T cells, NK cells, and antigen presenting cells. Ustekinumab is FDA approved for the treatment of patients with moderate to severe Crohn disease and for those with moderate to severe ulcerative colitis. Induction therapy is given as a single, weight-based intravenous dose (approximately 5–7 mg/kg), followed by 90 mg every 8 weeks by subcutaneous injection. There has been no demonstrated increase in severe infections or malignancy, and other serious events are rare. Antibodies to ustekinumab develop in less than 5% of patients but their impact on treatment efficacy is uncertain.

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► Social Support for Patients

Inflammatory bowel disease is a lifelong illness that can have profound emotional and social impacts on the

individual. Patients should be encouraged to become involved in the Crohn's and Colitis Foundation of America (CCFA). National headquarters may be contacted at 733 Third Avenue, Suite 510, New York, NY 10017; phone 800-932-2423. <https://www.crohnscolitisfoundation.org/>

1. Crohn Disease



ESSENTIALS OF DIAGNOSIS

- ▶ Insidious onset.
- ▶ Intermittent bouts of low-grade fever, diarrhea, and right lower quadrant pain.
- ▶ Right lower quadrant mass and tenderness.
- ▶ Perianal disease with abscess, fistulas.
- ▶ Radiographic or endoscopic evidence of ulceration, stricturing, or fistulas of the small intestine or colon.

► General Considerations

One-third of cases of Crohn disease involve the small bowel only, most commonly the terminal ileum (ileitis). Half of all cases involve the small bowel and colon, most often the terminal ileum and adjacent proximal ascending colon (ileocolitis). In 20% of cases, the colon alone is affected. One-third of patients have associated perianal disease (fistulas, fissures, abscesses). Less than 5% of patients have symptomatic involvement of the upper intestinal tract. Unlike ulcerative colitis, Crohn disease is a transmural process that can result in mucosal inflammation and ulceration, stricturing, fistula development, and abscess formation. Cigarette smoking is strongly associated with the development of Crohn disease, resistance to medical therapy, and early disease relapse.

► Clinical Findings

A. Symptoms and Signs

Because of the variable location of involvement and severity of inflammation, Crohn disease may present with a variety of symptoms and signs. In eliciting the history, the clinician should take particular note of fevers, the patient's general sense of well-being, weight loss, the presence of abdominal pain, the number of liquid bowel movements per day, and prior surgical resections. Physical examination should focus on the patient's temperature, weight, and nutritional status, the presence of abdominal tenderness or mass, rectal examination, and extraintestinal manifestations. Approximately 20–30% of patients have an indolent, nonprogressive course. The majority will require specific therapies (often biologic agents) to reduce inflammation, improve quality of life, and reduce the risk of surgery and hospitalization. Most commonly, there is one or a combination of the following clinical constellations.

1. Luminous inflammatory disease—This is the most common presentation at diagnosis (60–80%). Patients report

malaise, weight loss, and loss of energy. In patients with ileitis or ileocolitis, there may be diarrhea, which is usually nonbloody and often intermittent. In patients with colitis involving the rectum or left colon, there may be bloody diarrhea and fecal urgency, which may mimic the symptoms of ulcerative colitis. Cramping or steady right lower quadrant or periumbilical pain is common. Physical examination reveals focal tenderness, usually in the right lower quadrant. A palpable, tender mass that represents thickened or matted loops of inflamed intestine may be present in the lower abdomen.

2. Intestinal stricturing—Narrowing of the small bowel may occur as a result of inflammation or fibrotic stenosis. Patients report postprandial bloating, cramping pains, and loud borborygmi. This may occur in patients with active inflammatory symptoms or later in the disease from chronic fibrosis without other systemic symptoms or signs of inflammation.

3. Penetrating disease and fistulae—Sinus tracts that penetrate through the bowel, where they may be contained or form fistulas to adjacent structures, develop in a subset of patients. Penetration through the bowel can result in an intra-abdominal or retroperitoneal phlegmon or abscess manifested by fevers, chills, a tender abdominal mass, and leukocytosis. Fistulas between the small intestine and colon commonly are asymptomatic, but can result in diarrhea, weight loss, bacterial overgrowth, and malnutrition. Fistulas to the bladder produce recurrent infections. Fistulas to the vagina result in malodorous drainage and problems with personal hygiene. Fistulas to the skin usually occur at the site of surgical scars.

4. Perianal disease—One-third of patients with either large or small bowel involvement develop perianal disease manifested by large painful skin tags, anal fissures, perianal abscesses, and fistulas.

5. Extraintestinal manifestations—Extraintestinal manifestations may include arthralgias, arthritis, iritis or uveitis, pyoderma gangrenosum, or erythema nodosum. Oral aphthous lesions are common.

B. Laboratory Findings

Laboratory values may reflect inflammatory activity or nutritional complications of disease. A complete blood count and serum albumin should be obtained in all patients. Anemia may reflect chronic inflammation, mucosal blood loss, iron deficiency, or vitamin B₁₂ malabsorption secondary to terminal ileal inflammation or resection. Leukocytosis may reflect inflammation or abscess formation or may be secondary to corticosteroid therapy. Hypoalbuminemia may be due to intestinal protein loss, malabsorption, bacterial overgrowth, or chronic inflammation. The sedimentation rate or C-reactive protein level is elevated in many patients during active inflammation; however, one-third have a normal C-reactive protein level. Fecal calprotectin is an excellent noninvasive test. Elevated levels are correlated with active inflammation as demonstrated by ileocolonoscopy or radiologic CT or MR enterography. Stool specimens are sent for examination for

routine pathogens and *C difficile* toxin by microscopy, culture, and toxin assay or by rapid multiplex PCR diagnostic assessment.

C. Special Diagnostic Studies

In most patients, the initial diagnosis of Crohn disease is based on a compatible clinical picture with supporting endoscopic, pathologic, and radiographic findings. Colonoscopy usually is performed first to evaluate the colon and terminal ileum and to obtain mucosal biopsies. Typical endoscopic findings include aphthoid, linear or stellate ulcers, strictures, and segmental involvement with areas of normal-appearing mucosa adjacent to inflamed mucosa. Large or deep mucosal ulcers portend a higher risk for progressive disease. In 10% of cases, it may be difficult to distinguish ulcerative colitis from Crohn disease. Granulomas on biopsy are present in less than 25% of patients but are highly suggestive of Crohn disease. CT or MR enterography is obtained in patients with suspected small bowel involvement. Suggestive findings include ulcerations, strictures, and fistulas; in addition, CT or MR enterography may identify bowel wall thickening and vascularity, mucosal enhancement, and fat stranding. MR enterography, where available, may be preferred due its lack of radiation exposure. Capsule imaging may help establish a diagnosis when clinical suspicion for small bowel involvement is high but radiographs are normal or nondiagnostic. Barium upper gastrointestinal series with small bowel follow through should no longer be performed except where CT or MR enterography is unavailable.

► Complications

A. Abscess

The presence of a tender abdominal mass with fever and leukocytosis suggests an abscess. Emergent CT or MR of the abdomen is necessary to confirm the diagnosis. Patients should be given broad-spectrum antibiotics. Smaller abscesses (less than 3 cm) respond to antibiotic therapy but larger abscesses usually require percutaneous or surgical drainage.

B. Obstruction

Small bowel obstruction may develop secondary to active inflammation or chronic fibrotic stricturing and is often acutely precipitated by dietary indiscretion. Patients should be given intravenous fluids with nasogastric suction. Systemic corticosteroids are indicated in patients with symptoms or signs of active inflammation but are unhelpful in patients with inactive, fixed disease. Patients unimproved on medical management require surgical resection of the stenotic area or stricturoplasty.

C. Abdominal and Rectovaginal Fistulas

Many fistulas are asymptomatic and require no specific therapy. For symptomatic fistulas, medical therapy is effective in a subset of patients and is usually tried first in outpatients who otherwise are stable. Anti-TNF agents may promote closure in up to 60% within 10 weeks; however, relapse occurs in over one-half of patients within 1 year

despite continued therapy. Surgical therapy is required for symptomatic fistulas that do not respond to medical therapy. Fistulas that arise above (proximal to) areas of intestinal stricturing commonly require surgical treatment.

D. Perianal Disease

Patients with fissures, fistulas, and skin tags commonly have perianal discomfort. Successful treatment of active intestinal disease also may improve perianal disease. Specific treatment of perianal disease can be difficult and is best approached jointly with a surgeon with an expertise in colorectal disorders. Pelvic MRI is the best noninvasive study for evaluating perianal fistulas. Patients should be instructed on proper perianal skin care, including gentle wiping with a premoistened pad (baby wipes) followed by drying with a cool hair dryer, daily cleansing with sitz baths or a water wash, and use of perianal cotton balls or pads to absorb drainage. Oral antibiotics (metronidazole, 250 mg three times daily, or ciprofloxacin, 500 mg twice daily) may promote symptom improvement or healing in patients with fissures or uncomplicated fistulas; however, recurrent symptoms are common. Immunomodulators or anti-TNF agents or both promote short-term symptomatic improvement from anal fistulas in two-thirds of patients and complete closure in up to one-half of patients; however, less than one-third maintain symptomatic remission during long-term maintenance treatment.

Anorectal abscesses should be suspected in patients with severe, constant perianal pain, or perianal pain in association with fever. Superficial abscesses are evident on perianal examination, but deep perirectal abscesses may be detected by digital examination or pelvic CT or MR scan. Depending on the abscess location, surgical drainage may be achieved by incision, or catheter or seton placement. Surgery should be considered for patients with severe, refractory symptoms but is best approached after medical therapy of the Crohn disease has been optimized.

E. Carcinoma

Patients with colonic Crohn disease are at increased risk for developing colon carcinoma; hence, annual screening colonoscopy to detect dysplasia or cancer is recommended for patients with a history of 8 or more years of Crohn colitis. Patients with Crohn disease have an increased risk of lymphoma and of small bowel adenocarcinoma; however, both are rare.

F. Hemorrhage

Unlike ulcerative colitis, severe hemorrhage is unusual in Crohn disease.

G. Malabsorption

Malabsorption may arise after extensive surgical resections of the small intestine and from bacterial overgrowth in patients with enterocolonic fistulas, strictures, and stasis resulting in bacterial overgrowth. Serum levels of vitamins A, D, and B_{12} should be obtained at diagnosis and monitored periodically in patients with ileal inflammation or resection.

Differential Diagnosis

Chronic cramping abdominal pain and diarrhea are typical of both IBS and Crohn disease, but radiographic examinations are normal in the former. Celiac disease may cause diarrhea with malabsorption. Acute fever and right lower quadrant pain may resemble appendicitis or *Yersinia enterocolitica* enteritis. Intestinal lymphoma causes fever, pain, weight loss, and abnormal small bowel radiographs that may mimic Crohn disease. Patients with undiagnosed AIDS may present with fever and diarrhea. Segmental colitis may be caused by tuberculosis, *E histolytica*, *Chlamydia*, or ischemic colitis. *C difficile* or CMV infection may develop in patients with inflammatory bowel disease, mimicking disease recurrence. In patients from tuberculosis-endemic countries, it can be extremely difficult to distinguish active intestinal tuberculosis from Crohn disease, even with biopsies and PCR analyses. Diverticulitis or appendicitis with abscess formation may be difficult to distinguish acutely from Crohn disease. NSAIDs may exacerbate inflammatory bowel disease and may also cause NSAID-induced colitis characterized by small bowel or colonic ulcers, erosion, or strictures that tend to be most severe in the terminal ileum and right colon.

Treatment of Active Disease

Crohn disease is a chronic lifelong illness characterized by exacerbations and periods of remission. As no specific therapy exists, current treatment is directed toward symptomatic improvement and control of the disease process, in order to improve quality of life and reduce disease progression and complications. Most patients have moderate to severe disease with increased risk of progression to intestinal complications. However, 20–30% of patients have mild, intermittent disease with a nonprogressive course. Risk factors for an aggressive disease course include (1) young age at disease onset, early need for corticosteroids, perianal disease, strictureting disease, or upper gastrointestinal involvement; (2) laboratory markers of severe inflammation, including low albumin or hemoglobin, or high C-reactive protein; or (3) endoscopic findings of deep ulcerations. Choice of therapies therefore depends on the disease severity, patient age and comorbidities, and patient preference. Sustained clinical remission with intestinal mucosal healing should be the therapeutic goal in most patients; however, this cannot always be achieved. Early introduction of biologic therapy should be strongly considered in patients who have moderate to severe disease, most especially those with risk factors for a progressive course. The pharmacology of medications used in Crohn disease treatment, including mechanisms of action, adverse effects, dosing, and monitoring, are detailed in Inflammatory Bowel Disease: Pharmacologic Therapy. All patients with Crohn disease should be counseled to discontinue cigarettes.

A. Mild/Low-Risk Disease

Patients may be characterized as having mild disease with a low-risk of disease progression if they have mild symptoms, no significant weight loss, normal or only mildly elevated inflammatory markers (C-reactive protein, fecal calprotectin, serum albumin), absence of intestinal complications

(stricturing, abscess, fistula, perianal disease), and limited intestinal involvement with superficial mucosal ulcers.

1. Nutrition—Patients should eat a well-balanced diet with as few restrictions as possible. Eating smaller but more frequent meals may be helpful. Patients with diarrhea should be encouraged to drink fluids to avoid dehydration. Many patients report that certain foods worsen symptoms, especially fried or greasy foods. Because lactose intolerance is common, a trial off dairy products is warranted if flatulence or diarrhea is a prominent complaint. Probiotics have not proven beneficial for Crohn disease.

2. Symptomatic therapy—Loperamide (2–4 mg) may be given for diarrhea as needed up to four times daily.

3. Drug therapy—It is recommended that therapy for mild, low-risk Crohn disease begin with medications that are less potent but have a lower risk of adverse effects. Recommended drug treatment depends on the location of disease involvement.

A. TERMINAL ILEUM OR ASCENDING COLON DISEASE—For patients with mild disease involving the terminal ileum or ascending colon, initial treatment is recommended with extended-release budesonide (Entocort), 9 mg once daily for 8 weeks, which induces remission in 50–70% of patients. If disease remission is achieved, budesonide is tapered over 2–4 weeks in 3 mg increments and the patient observed. For treatment of mild ileocolonic Crohn disease, 5-ASA agents remain in widespread clinical use despite an absence of clinical trial data supporting their efficacy. Formulations that release mesalamine in the distal small intestine (Asacol 2.4–4.8 g/day or Pentasa 2–4 g/day) are most often prescribed.

B. LEFT-SIDED OR DIFFUSE COLITIS—For patients with mild colitis that is diffuse or involves only the left-side of the colon, oral corticosteroids (prednisone or prednisolone) are recommended. The initial dose of either agent is 40 mg once daily for 1–2 weeks, followed in those who respond by gradual tapering of 5–10 mg/week over 4–8 weeks. Sulfasalazine (1.5–3 g orally twice daily) appears effective in improving symptoms and inducing remission in patients with mild Crohn disease involving the colon (not small intestine) and is recommended in current treatment guidelines. Sulfasalazine is associated with potentially severe side effects in up to 30% of patients (see Inflammatory Bowel Disease: Pharmacologic Therapy). For patients who respond, sulfasalazine 2–4 g/day may be continued as long-term maintenance. Because of sulfasalazine's side effects, many clinicians prescribe other oral 5-ASA agents for mild Crohn colitis despite an absence of clinical data supporting efficacy. Such agents include those that release 5-ASA throughout the colon: delayed-release mesalamine (Lialda or Asacol 2.4–4.8 g/day; Apriso 2.25–4.5 g/day) and balsalazide 2.25 g three times daily.

C. LONG-TERM FOLLOW UP—In patients with mild Crohn disease who respond to initial therapy with budesonide or prednisone, treatment should be discontinued and the patient monitored periodically for disease recurrence (symptoms, C-reactive protein, fecal calprotectin, or endoscopy every 1–2 years). Patients who respond to treatment with

sulfasalazine or other 5-ASA formulations should continue long-term maintenance therapy. Patients with mild disease who either do not respond to initial therapy or who experience symptom relapse more than once every 1–2 years) following tapering of corticosteroids should be reclassified as moderate- to high-risk for disease progression and ‘stepped up’ to more potent therapies (oral corticosteroids, immunomodulators, or biologic agents).

B. Moderate to Severe/High-Risk Crohn Disease

Moderate to severe disease may be characterized by frequent diarrhea, weight loss, daily abdominal pain, abdominal tenderness, and perianal disease. Evidence of significant inflammation includes elevated C-reactive protein; anemia; low serum albumin; or the findings of deep ulceration, stricture, or penetrating disease on endoscopy or radiologic imaging. Patients characterized as having moderate to severe Crohn disease are at high risk for the development of intestinal complications and therefore warrant early aggressive “top down” management with biologic agents or immunomodulators (or both) in an effort to promote sustained clinical remission.

1. Nutrition—Patients with obstructive symptoms should be placed on a low-roughage diet, ie, no raw fruits or vegetables, popcorn, nuts, etc. TPN sometimes is used short term in patients with active disease and progressive weight loss, especially those awaiting surgery who have malnutrition but cannot tolerate enteral feedings because of high-grade obstruction, high-output fistulas, severe diarrhea, or abdominal pain. Parenteral vitamin B₁₂ (1000 mcg subcutaneously per month) and oral vitamin D supplementation commonly are needed for patients with previous ileal resection or extensive terminal ileal disease.

2. Symptomatic therapy—Involvement of the terminal ileum with Crohn disease or prior ileal resection may lead to reduced absorption of bile acids that may induce secretory diarrhea from the colon. Secretory diarrhea responds to agents that bind the malabsorbed bile salts: cholestyramine 2–4 g or colestipol 1–2 g one to three times daily with meals; colesvelam, 625 mg, one to three tablets twice daily. Patients with extensive ileal disease (requiring more than 100 cm of ileal resection) have severe bile salt malabsorption causing steatorrhea. Such patients may benefit from a low-fat diet; bile salt-binding agents exacerbate the diarrhea and should not be given. Patients with Crohn disease are at risk for the development of small intestinal bacterial overgrowth due to enteral fistulas, ileal resection, and impaired motility and may benefit from a course of broad-spectrum antibiotics (see *Bacterial Overgrowth*, above). Other causes of diarrhea include lactase deficiency and short bowel syndrome. Use of oral antidiarrheal agents may provide benefit in some patients.

3. Drug therapy—The goal of drug treatment for moderate to severe, high-risk Crohn disease is to induce and maintain clinical disease remission, including mucosal healing, whenever possible.

A. CORTICOSTEROIDS—Corticosteroids dramatically suppress the acute clinical symptoms and signs in most patients with both small and large bowel disease; however,

they do not alter the natural history of the underlying disease. Because of their rapidity of onset, corticosteroids commonly are used in patients with moderate to severe disease to promote early symptomatic improvement while other disease-modifying agents with slower onset of action are initiated. Hospitalization is warranted in some patients with symptoms or signs of severe disease, especially those with high fever, persistent vomiting, evidence of intestinal obstruction, severe weight loss, severe abdominal tenderness, or suspicion of an abscess. In patients with a tender, palpable inflammatory abdominal mass, CT scan of the abdomen should be obtained prior to administering corticosteroids to rule out an abscess. If no abscess is identified, parenteral corticosteroids (methylprednisolone 40–60 mg daily) should be administered as described for ulcerative colitis. Outpatients with moderate to severe disease may be treated with oral prednisone or methylprednisolone, 40 mg/day for 1–2 weeks followed by slow tapering of 5–10 mg/week over 4–8 weeks as described above for mild Crohn disease. Remission or significant improvement occurs in greater than 80% of patients after 8–16 weeks of therapy. It is recommended in most patients that a biologic agent be initiated as the corticosteroid is tapered and withdrawn. Use of long-term low corticosteroid doses should be avoided because of associated complications. If a decision is made not to initiate a biologic agent, long-term treatment with an immunomodulator (azathioprine, mercaptopurine, or methotrexate) is recommended to attempt to provide a steroid-free disease maintenance. However, approximately 20% of patients cannot be completely withdrawn from corticosteroids without experiencing a symptomatic flare-up.

B. BIOLOGIC THERAPIES—Induction therapy with a biologic agent is recommended for almost all patients with moderate to severe Crohn disease; those with a favorable clinical response to induction treatment should be maintained on long-term therapy with a goal of achieving clinical and endoscopic remission. Current treatment options include anti-TNF monoclonal antibodies (infliximab, adalimumab, certolizumab), anti-integrin monoclonal antibody (vedolizumab), and anti-IL 12/23 monoclonal antibody (ustekinumab) (see *Inflammatory Bowel Disease: Pharmacology*, above). In the absence of head-to-head comparative trials of these agents, relative differences in efficacy and safety are suggested by network meta-analyses. The choice of biologic agent depends on the disease severity, patient age and comorbidities, patient preference, and drug cost/pharmacy tiering.

(1) Anti-TNF therapies—For most patients with moderate to severe Crohn disease, two anti-TNF therapies (infliximab or adalimumab) are recommended as the preferred first-line agents to induce remission either as monotherapy or in combination with immunomodulating agents (azathioprine, mercaptopurine, or methotrexate). Up to two-thirds of patients have significant clinical improvement during acute induction therapy (see *Inflammatory Bowel Disease: Pharmacology* above for dosing). Although direct comparisons of these anti-TNF agents are unavailable, indirect evidence suggests that intravenous, weight-based infliximab infusion may be preferred to subcutaneous,

fixed-dose adalimumab for patients with severe disease, extraintestinal manifestations, perianal disease, or obesity. Certolizumab appears inferior to other anti-TNF agents. Compared with anti-TNF monotherapy, clinical trials suggest that combination of an anti-TNF agent (infliximab or adalimumab) with an immunomodulator (azathioprine, mercaptopurine, or methotrexate) achieves higher rates of clinical and mucosal healing. This benefit is ascribed to increased anti-TNF serum drug levels, reduced development of neutralizing, anti-TNF antibodies, and synergistic anti-inflammatory effects. Despite these benefits, the role of combination therapy versus monotherapy is controversial due to an increased risk of adverse events, including myelosuppression, infections, and malignancies (lymphoma, skin cancer). Due to the complexity and higher risks of combination therapy, many clinicians prefer monotherapy with drug monitoring to optimize anti-TNF trough levels and reduce the risk of developing anti-drug antibodies. Retrospective clinical trial data suggest that remission rates are similar between combination therapy and anti-TNF monotherapy when adjusted for trough levels. Combination therapy is favored for patients at higher risk for disease progression or who previously developed antibodies to a biologic agent.

After initial clinical response, symptom relapse occurs in more than 80% of patients within 1 year in the absence of further maintenance therapy. Therefore, scheduled maintenance therapy is usually recommended (eg, infliximab, 5 mg/kg infusion every 8 weeks; or adalimumab, 40 mg subcutaneous injection every 1–2 weeks). With long-term maintenance therapy, approximately two-thirds of patients have continued clinical response and up to one-half have complete symptom remission. Serum anti-TNF trough levels and drug antibody levels may guide therapy in patients who have lost response. Patients with low serum anti-TNF trough levels and absent drug antibodies should receive increased anti-TNF dosing (infliximab 10 mg/kg; adalimumab 80 mg) or decreased dosing intervals (infliximab every 6 weeks; adalimumab every week). Patients with high antibodies to the anti-TNF agent and low anti-TNF trough levels should be switched to another anti-TNF agent. Patients with inadequate response despite adequate anti-TNF trough levels should be changed to an alternative biologic agent, such as vedolizumab or ustekinumab. In patients receiving combination therapy, consideration should be given to stopping or reducing the dose of the immunomodulating agent after 6–12 months for patients in remission, most especially men younger than age 30 years who have a higher risk of hepatosplenic T-cell lymphoma and for adults older than age 50–60 years in whom there is a higher risk of lymphoma and of infectious complications.

(2) *Anti-integrins*—Vedolizumab may be preferred as first-line agent for induction therapy in patients with moderate Crohn disease who are deemed at increased risk for complications from anti-TNF therapy due to advanced age, multiple comorbidities, or prior malignancy. Vedolizumab may also be used as a second- or third-line agent in patients who have not responded or lost response to anti-TNF agents or ustekinumab. In a phase 3 trial, among patients demonstrating initial clinical improvement with

vedolizumab induction therapy, 39% of patients treated with long-term vedolizumab (300 mg every 8 weeks) were in remission at 1 year compared with 21.6% of patients given placebo. Vedolizumab may be less effective than anti-TNF or ustekinumab in the treatment of fistulous disease.

(3) *Anti-IL-12/IL-23 antibody*—Ustekinumab is approved by the FDA for treatment of patients with moderate to severe Crohn disease who have not responded to or are intolerant of conventional therapies. It may also be appropriate as first-line induction therapy for patients with severe Crohn disease who are deemed to be at increased risk for complications of anti-TNF therapy. In a phase 3 trial involving 741 patients with Crohn disease in whom anti-TNF therapy failed, clinical response was seen in 34% of patients 6 weeks after a single dose of intravenous ustekinumab compared to 21.5% with placebo. In a second phase 3 trial composed of patients in whom conventional therapy with immunomodulators or corticosteroids (but not anti-TNF) had failed, clinical improvement occurred in 55% compared to 28.7% with placebo. Among patients from both induction trials who were enrolled in a chronic maintenance trial (ustekinumab versus placebo subcutaneously every 8 weeks), 53% of those given ustekinumab were in clinical remission at week 44 versus 36% given the placebo.

► Indications for Surgery

Over 50% of patients will require at least one surgical procedure. The main indications for surgery are intractability to medical therapy, intra-abdominal abscess, massive bleeding, symptomatic refractory internal or perianal fistulas, and intestinal obstruction. Patients with chronic obstructive symptoms due to a short segment of ileal stenosis are best treated with resection or stricturoplasty (rather than long-term medical therapy), which promotes rapid return of well-being and elimination of corticosteroids. After surgery, endoscopic evidence of recurrence occurs in 60% within 1 year. Endoscopic recurrence precedes clinical recurrence by months to years; clinical recurrence occurs in 20% of patients within 1 year and 80% within 10–15 years. Therapy with metronidazole, 250 mg three times daily for 3 months, or long-term therapy with immunomodulators (mercaptopurine or azathioprine) has only been modestly effective in preventing clinical and endoscopic recurrence after ileocolic resection. In a 2016 controlled trial of 297 patients undergoing ileocolonic resection, endoscopic recurrence occurred in 30% of patients treated with infliximab every 8 weeks compared with 60% treated with placebo. It may be reasonable to initiate empiric infliximab postoperatively for patients at high risk for disease recurrence and to perform endoscopy in low-risk patients 6 months after surgery in order to identify patients with early endoscopic recurrence who may benefit from anti-TNF therapy.

► Prognosis

With proper medical and surgical treatment, the majority of patients are able to cope with this chronic disease and its complications and lead productive lives. Few patients die as a direct consequence of the disease.

► When to Refer

- For expertise in endoscopic procedures or capsule endoscopy.
- For follow-up of any patient requiring hospitalization.
- Patients with moderate to severe disease for whom therapy with immunomodulators or biologic agents is being considered.
- When surgery may be necessary.

► When to Admit

- An intestinal obstruction is suspected.
- An intra-abdominal or perirectal abscess is suspected.
- A serious infectious complication is suspected, especially in patients who are immunocompromised due to concomitant use of corticosteroids, immunomodulators, or anti-TNF agents.
- Patients with severe symptoms of diarrhea, dehydration, weight loss, or abdominal pain.
- Patients with severe or persisting symptoms despite treatment with corticosteroids.

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2. Ulcerative Colitis

ESSENTIALS OF DIAGNOSIS			
			
▶ Bloody diarrhea.	Mild	Moderate	Severe
▶ Lower abdominal cramps and fecal urgency.	< 4	4–6	> 6 (mostly bloody)
▶ Anemia, low serum albumin.	< 90	90–100	> 100
▶ Negative stool studies for pathogens.	Normal	30–40	< 30
▶ Sigmoidoscopy is the key to diagnosis.	None	1–10	> 10
	Normal	99–100	> 100
	< 20	20–30	> 30
	Normal	3–3.5	< 3

► General Considerations

Ulcerative colitis is an idiopathic inflammatory condition that involves the mucosal surface of the colon, resulting in diffuse friability and erosions with bleeding. Approximately one-fourth of patients have disease confined to the rectosigmoid region (proctosigmoiditis); one-half have disease that extends to the splenic flexure (left-sided colitis); and one-fourth have disease that extends more proximally (extensive colitis). In patients with distal colitis, the disease progresses with time to more extensive involvement in 25%. There is some correlation between disease extent and symptom severity. In most patients, the disease is characterized by periods of symptomatic flare-ups and periods of mild activity or remission. Approximately 15% of patients may have an aggressive course with increased risk of hospitalization or surgery. Of patients hospitalized with severe colitis, colectomy is required in up to 30% for unresponsive or "fulminant" disease. Ulcerative colitis is more common in nonsmokers and former smokers. Disease severity may be lower in active smokers and may worsen in patients who stop smoking. Appendectomy before the age of 20 years for acute appendicitis is associated with a reduced risk of developing ulcerative colitis.

► Clinical Findings

A. Symptoms and Signs

The clinical profile in ulcerative colitis is highly variable. Bloody diarrhea is the hallmark. Several clinical and laboratory parameters help classify patients as having mild, moderate, or severe disease (Table 15–12). Patients should be asked about stool frequency, the presence and amount of rectal bleeding, cramps, abdominal pain, fecal urgency, tenesmus, and extraintestinal symptoms. Physical examination should focus on the patient's volume status as determined by orthostatic blood pressure and pulse measurements and by nutritional status. On abdominal examination, the clinician should look for tenderness and evidence of peritoneal inflammation. Red blood may be present on digital rectal examination.

1. Mild to moderate disease—Patients with mild to moderate disease have fewer than four to six bowel movements

Table 15–12. Ulcerative colitis: assessment of disease activity.

	Mild	Moderate	Severe
Stool frequency (per day)	< 4	4–6	> 6 (mostly bloody)
Pulse (beats/min)	< 90	90–100	> 100
Hematocrit (%)	Normal	30–40	< 30
Weight loss (%)	None	1–10	> 10
Temperature (°F)	Normal	99–100	> 100
ESR (mm/h)	< 20	20–30	> 30
Albumin (g/dL)	Normal	3–3.5	< 3

ESR, erythrocyte sedimentation rate.

per day, mild to moderate rectal bleeding, and no constitutional symptoms. Stools may be formed or loose in consistency. Because of rectal inflammation, there is fecal urgency and tenesmus. Left lower quadrant cramps relieved by defecation are common, but there is no significant abdominal pain or tenderness. There may be mild anemia and hypoalbuminemia.

2. Severe disease—Patients with severe disease have more than six bloody bowel movements per day, resulting in severe anemia, hypovolemia, and impaired nutrition with hypoalbuminemia. Abdominal pain and tenderness are present. “Fulminant colitis” is a subset of severe disease characterized by rapidly worsening symptoms with signs of toxicity.

B. Laboratory Findings

The degree of abnormality of the hematocrit, serum albumin, and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) reflects disease severity (Table 15–12).

C. Endoscopy

In acute colitis, the diagnosis is readily established by sigmoidoscopy. The mucosal appearance is characterized by edema, friability, mucopus, and erosions. The “Mayo” endoscopic scoring system is commonly used in clinical practice and therapeutic trials. A score of 0 indicates normal or inactive colitis; 1 indicates erythema, decreased vascularity; 2 indicates friability, marked erythema, erosions; and 3 indicates ulcerations, severe friability, spontaneous bleeding. Mayo endoscopic scores 1–2 are consistent with mild to moderate disease clinical activity, and Mayo scores 2–3 are usually seen in patients with moderate to severe clinical activity. Colonoscopy should not be performed in patients with fulminant disease because of the risk of perforation. After patients have demonstrated improvement on therapy, colonoscopy is performed to determine the extent of disease.

D. Imaging

Abdominal imaging with plain radiographs or CT is obtained in patients with severe colitis to look for significant colonic dilation. Barium enemas are of little utility in the evaluation of acute ulcerative colitis and may precipitate toxic megacolon in patients with severe disease.

Differential Diagnosis

The initial presentation of ulcerative colitis is indistinguishable from other causes of colitis, clinically as well as endoscopically. Thus, the diagnosis of idiopathic ulcerative colitis is reached after excluding other known causes of colitis. Infectious colitis should be excluded by sending stool specimens for routine testing to exclude *Salmonella*, *Shigella*, *Campylobacter*, *E coli* O157, *C difficile*, and amebiasis. Where available, microbial assessment using multiplex molecular techniques provides results within 1–4 hours with excellent sensitivity and is preferred to conventional labor-intensive stool microscopy, culture, and toxin testing.

CMV colitis occurs in immunocompromised patients, including patients receiving prolonged corticosteroid therapy, and is diagnosed on mucosal biopsy. Gonorrhea, chlamydial infection, herpes, and syphilis are considerations in sexually active patients with proctitis. In elderly patients with cardiovascular disease, ischemic colitis may involve the rectosigmoid. A history of radiation to the pelvic region can result in proctitis months to years later. Crohn disease involving the colon but not the small intestine may be confused with ulcerative colitis. In 10% of patients, a distinction between Crohn disease and ulcerative colitis may not be possible.

Treatment

There are three main treatment objectives: (1) to terminate the acute, symptomatic attack; (2) to achieve complete remission of clinical and endoscopic disease activity; and (3) to prevent recurrence of attacks. The treatment of acute ulcerative colitis depends on the extent of colonic involvement and the severity of illness. Patients with systemic signs of inflammation (ie, anemia, low serum albumin, elevated C-reactive protein or erythrocyte sedimentation rate levels) and ulcerations with extensive disease on colonoscopy are at increased risk for hospitalization or surgery, and early aggressive therapy with biologic agents is warranted.

A. Mild to Moderate Distal Colitis

Patients with disease confined to the rectum or rectosigmoid region generally have mild to moderate but distressing symptoms. Patients may be treated with topical mesalamine, topical corticosteroids, or oral aminosalicylates (5-ASA) according to patient preference and cost considerations. Topical mesalamine is the drug of choice and is superior to topical corticosteroids and oral 5-ASA. Mesalamine is administered as a suppository, 1000 mg once daily at bedtime for proctitis, and as an enema, 4 g at bedtime for proctosigmoiditis, for 4–8 weeks, with 75% of patients improving. Patients who either decline or are unable to manage topical therapy may be treated with oral 5-ASA, as discussed below. Although topical corticosteroids are a less expensive alternative to mesalamine, they are also less effective. Hydrocortisone enema or foam (80–100 mg) or budesonide foam are prescribed for proctitis or proctosigmoiditis. Systemic effects from short-term use are very slight. For patients with distal disease who do not improve with topical or oral mesalamine therapy, the following options may be considered: (1) a combination of a topical agent with an oral 5-ASA agent; (2) topical corticosteroid; or (3) addition of oral prednisone (as described below) or budesonide MMX 9 mg/day for 4–8 weeks to rectal and oral 5-ASA.

Most patients with proctitis or proctosigmoiditis who achieve complete remission with oral or rectal 5-ASA should continue indefinitely on the same therapy to reduce the likelihood of symptomatic relapse. Maintenance treatment with 5-ASA reduces the 12-month relapse rate from 75% to less than 40%. Some patients, however, may prefer intermittent therapy for symptomatic relapse. Topical corticosteroids are ineffective for maintaining remission of distal colitis.

B. Mild to Moderate Colitis

1. 5-ASA agents—Disease extending above the sigmoid colon is best treated with both an oral and rectal 5-ASA agent. For induction of remission, the optimal dose of oral 5-ASA (mesalamine or balsalazide) is 2–3 g once daily in combination with mesalamine 1 g suppository or 4 g enema at bedtime. Most patients improve within 4–8 weeks. Some patients may prefer to initiate therapy with an oral agent, adding topical therapy if initial response is inadequate. These agents achieve clinical improvement in 75% of patients and remission in 20–30%. Oral sulfasalazine (1.5–2 g twice daily) is uncommonly used due to its side effects but is sometimes prescribed in patients with significant arthritis. To minimize side effects, sulfasalazine is begun at a dosage of 500 mg twice daily and increased gradually over 1–2 weeks to 2 g twice daily. Folic acid, 1 mg/day orally, should be administered to all patients taking sulfasalazine.

2. Corticosteroids—Patients with mild to moderate colitis who do not improve within 4–8 weeks of 5-ASA therapy should have an oral corticosteroid therapy added with budesonide MMX or prednisone. Budesonide MMX (Uceris) 9 mg/day orally for 4–8 weeks may be preferred in mild to moderate colitis due to its low incidence of corticosteroid-associated side effects, especially in those for whom other systemic corticosteroids are deemed high risk. For patients who require more than one course of corticosteroid therapy every 1–2 years for symptomatic relapse, treatment should be “stepped up” to include a thiopurine (azathioprine or mercaptopurine) or a biologic agent, as described below for Moderate to Severe Colitis.

C. Moderate to Severe Colitis

1. Corticosteroids—An oral corticosteroid (prednisone or methylprednisolone) is commonly prescribed as the first-line agent for nonhospitalized patients with moderate to severe colitis or as second-line therapy in patients in whom initial 5-ASA therapy was ineffective. The initial oral dose of prednisone is 40 mg daily. Rapid improvement is observed in most cases within 2 weeks. Thereafter, tapering of prednisone should proceed by 5–10 mg/wk. After tapering to 20 mg/day, slower tapering (2.5 mg/wk) is sometimes required. Complete tapering of prednisone without symptomatic flare-ups is possible in the majority of patients. Corticosteroids should not be continued long-term to control symptoms because of an unacceptable risk of adverse events. Patients achieving remission should be maintained on oral mesalamine (2–4 g/day). Up to 30% of patients either do not respond to prednisone or have symptomatic flares during tapering that prevent its complete withdrawal. The addition of a thiopurine (azathioprine or mercaptopurine) is sometimes used to promote complete steroid withdrawal and maintain long-term remission. Tofacitinib or biologic agents are recommended for patients in whom corticosteroids cannot be completely withdrawn or who require more than one course of corticosteroids every 1–2 years.

2. Biologic agents—Anti-TNF antibodies (infliximab, adalimumab, golimumab), vedolizumab (integrin antibody),

ustekinumab (IL-12/23 antibody) and tofacitinib (Janus kinase inhibitor) have demonstrated efficacy for treatment of moderate to severe colitis. The preferred agent depends on several considerations: prior exposure and response to biologic agents; disease severity; patient comorbidities; preferred mode of administration (intravenous, subcutaneous, oral); and pharmacy/insurance company tiering.

A. TREATMENT OF PATIENTS NAÏVE TO PRIOR BIOLOGIC THERAPY—A 2020 AGA guideline recommends either infliximab or vedolizumab as first-line therapies for moderate to severe colitis based on their efficacy and safety profiles. These two agents had the highest rankings of all biologic agents for induction of clinical remission in a 2020 network meta-analysis. Although infliximab may be the more effective agent (especially for severe disease), vedolizumab may be the preferred first-line therapy in patients who are elderly or have increased medical comorbidities due to its significantly lower incidence of infectious complications.

An induction regimen of infliximab (5 mg/kg administered at 0, 2, and 6 weeks) results in clinical response in 65% of patients. During long-term maintenance treatment with infliximab (5–10 mg/kg every 4–8 weeks), clinical improvement or remission is achieved in approximately 50% of patients. Network meta-analyses suggest superiority of infliximab (weight-based, intravenous infusion) over the other anti-TNF agents adalimumab and golimumab (fixed-dose, subcutaneous injection). Treatment with adalimumab or golimumab may nonetheless be selected in patients with moderate (not severe) disease who prefer the convenience of subcutaneous, self-injection.

Vedolizumab induction (300 mg intravenously at 0, 2, and 6 weeks) led to clinical improvement in 47.1% of patients compared with 25.5% who were given placebo. Among patients who demonstrated initial clinical improvement, 41.8% of those given long-term maintenance treatment with vedolizumab (300 mg intravenously every 8 weeks) were in clinical remission at 1 year compared with 15.9% of those given placebo. The 2019 VARSITY trial randomized patients with moderate to severe ulcerative colitis to induction and maintenance therapy with vedolizumab versus adalimumab. At 1 year, clinical remission (31.3% vs 22.5%) and endoscopic improvement (39.7% vs 27.7%) were seen in significantly more patients treated with vedolizumab than adalimumab. This was the first controlled trial in ulcerative colitis comparing agents from different biologic classes. Due to its efficacy and superior safety profile, vedolizumab may become the preferred first-line biologic agent for the treatment of moderate ulcerative colitis.

When initiating induction therapy with anti-TNF agents, many clinicians add an immunomodulator (azathioprine, mercaptopurine, or methotrexate) for the first year to increase the likelihood of disease remission and to reduce the development of antibodies that may result in secondary loss of response to anti-TNF therapies. If monotherapy is preferred, proactive drug monitoring of serum trough levels and anti-drug antibody titers should be obtained during induction and maintenance therapy in order to optimize drug dosing. Vedolizumab and ustekinumab have a lower

incidence of anti-drug antibodies; hence, the benefit of immunomodulator cotherapy is uncertain.

B. SECOND-LINE TREATMENT FOR PATIENTS WHO HAVE NOT RESPONDED TO INFILIXIMAB—In patients with moderate to severe colitis who have not responded to or lost response to infliximab, the 2020 AGA treatment guideline recommends ustekinumab or tofacitinib rather than vedolizumab or adalimumab as second-line therapy based on network meta-analyses. In phase 3 trials, the clinical response rates at 8 weeks following intravenous administration of ustekinumab 6 mg/kg vs placebo were 62% vs 31%, respectively. Among responders who entered long-term maintenance treatment with ustekinumab 90 mg or placebo subcutaneous injection every 8 weeks, clinical remission was significantly higher with ustekinumab (44%) than with placebo (24%).

Tofacitinib, an oral, small-molecule JAK 1/3 inhibitor, was approved by the FDA in 2018 for the treatment of moderate to severe ulcerative colitis. However, in 2019 the FDA issued a black box warning about an increased risk of thrombosis and death in rheumatoid arthritis patients treated with tofacitinib 10 mg orally twice daily for prolonged periods. Therefore, the 2020 AGA treatment guideline recommends that tofacitinib currently be restricted to second-line therapy in patients who have not responded or who have lost response to anti-TNF therapy. A network meta-analysis of controlled trials found that tofacitinib ranked highest among biologic therapies for induction of remission in patients who have received anti-TNF therapy.

3. Probiotics—Probiotics have not demonstrated significant benefit versus placebo in the treatment of mild to moderate ulcerative colitis in randomized, controlled trials.

D. Severe and Fulminant Colitis

About 15% of patients with ulcerative colitis have a more severe course. Of these, a small subset has a fulminant course with rapid progression of symptoms over 1–2 weeks and signs of severe toxicity. These patients appear quite ill, with fever, prominent hypovolemia, hemorrhage requiring transfusion, and abdominal distention with tenderness. Toxic megacolon develops in less than 2% of cases of ulcerative colitis. It is characterized by colonic dilation of more than 6 cm on plain films with signs of toxicity.

1. General measures—Discontinue all oral intake for 24–48 hours or until the patient demonstrates clinical improvement. TPN is indicated only in patients with poor nutritional status or if feedings cannot be reinstated within 7–10 days. All opioid or anticholinergic agents should be discontinued. Restore circulating volume with fluids, correct electrolyte abnormalities, and consider transfusion for significant anemia (hematocrit less than 25–28%). A plain abdominal radiograph or CT scan should be ordered on admission to look for evidence of colonic dilation. Send stools for assessment of bacterial pathogens, *C difficile* and parasites, either by conventional bacterial culture, *C difficile* toxin assay, and ova and parasite examinations or by rapid, multiplex PCR assay. CMV

superinfection should be considered in patients receiving long-term immunosuppressive therapy who are unresponsive to corticosteroid therapy. Due to a high risk of venous thromboembolic (VTE) disease, VTE prophylaxis should be administered to all hospitalized patients with inflammatory bowel disease. Surgical consultation should be sought for all patients with severe disease.

Patients with fulminant disease are at higher risk for perforation or toxic megacolon and must be monitored closely. Abdominal examinations should be repeated to look for evidence of worsening distention or pain. A 2020 AGA guideline does not recommend the use of empiric broad-spectrum antibiotics in the absence of confirmed infection. In addition to the therapies outlined above, nasogastric suction should be initiated. Patients should be instructed to roll from side to side and onto the abdomen in an effort to decompress the distended colon. Serial abdominal plain films should be obtained to look for worsening dilation or signs of ischemia. Patients with fulminant disease or toxic megacolon who worsen or do not improve within 48–72 hours should undergo surgery to prevent perforation. If the operation is performed before perforation, the mortality rate should be low.

2. Corticosteroid therapy—Methylprednisolone, 40–60 mg, is administered intravenously. There appears to be no difference in efficacy between single-dose, divided dose, or continuous infusion regimens. Higher or “pulse” doses are of no benefit. Hydrocortisone enemas (100 mg) may also be administered twice daily for treatment of urgency or tenesmus. Clinical improvement with systemic corticosteroids should be evident within 3–5 days in 50–75% of patients. Once symptomatic improvement has occurred, oral fluids are reconstituted. If fluids are well tolerated, intravenous corticosteroids are discontinued and the patient is started on oral prednisone (as described for moderate disease). Patients without significant improvement within 3–5 days of intravenous corticosteroid therapy should be referred for surgery or considered for anti-TNF therapies or cyclosporine.

3. Anti-TNF therapies—Infusion of infliximab, 5–10 mg/kg, has been shown in uncontrolled and controlled studies to be effective in treating severe colitis in patients who did not improve within 4–7 days of intravenous corticosteroid therapy. In a controlled study of patients hospitalized for ulcerative colitis, colectomy was required within 3 months in 69% who received placebo therapy, compared with 47% who received infliximab. Thus, infliximab therapy should be considered in patients with severe ulcerative colitis who have not improved with intravenous corticosteroid therapy. Recent studies have demonstrated more rapid clearance of infliximab in patients with severe ulcerative colitis. Uncontrolled trials have found lower colectomy rates in patients administered higher doses of infliximab (three infusions of 5–10 mg/kg within 2–3 weeks) than with conventional dosing (5 mg/kg at 0, 2, and 6 weeks).

4. Cyclosporine—Intravenous cyclosporine (2–4 mg/kg/day as a continuous infusion) benefits 60–75% of patients with severe colitis who have not improved after 7–10 days of corticosteroids, but it is associated with significant toxicity (nephrotoxicity, seizures, infection, hypertension). Up to two-thirds

of responders may be maintained in remission with a combination of oral cyclosporine for 3 months and long-term therapy with mercaptopurine or azathioprine. A 2011 randomized study of patients with severe colitis refractory to intravenous corticosteroids found similar response rates (85%) with cyclosporine and infliximab therapy.

5. Surgical therapy—Patients with severe disease who do not improve after corticosteroid, infliximab, or cyclosporine therapy are unlikely to respond to further medical therapy, and surgery is recommended.

► Risk of Colon Cancer

In patients with ulcerative colitis with disease proximal to the rectum and in patients with Crohn colitis, there is an increased risk of developing colon carcinoma. Although older meta-analyses from referral centers reported a high risk (8% after 20 years), more recent systematic reviews of population-based studies report a 2.4-fold increased risk (1.4% after a mean of 14 years of follow-up). Retrospective studies suggest that the risk of colon cancer may be reduced in patients treated with long-term 5-ASA therapy. Ingestion of folic acid, 1 mg/day, also is associated with a decreased risk of cancer development. Colonoscopies are recommended every 1–2 years in patients with colitis, beginning 8 years after diagnosis. Several prospective studies demonstrate that dye spraying with methylene blue or indigo carmine (“chromoendoscopy”) enhances the detection of subtle mucosal lesions, thereby significantly increasing the detection of dysplasia compared with standard colonoscopy. At colonoscopy, all polypoid and nonpolypoid lesions should be resected, when possible, and biopsies obtained of endoscopically unresectable lesions.

► Surgery in Ulcerative Colitis

Surgery is required in 25% of patients. Severe hemorrhage, perforation, and documented carcinoma are absolute indications for surgery. Surgery is indicated also in patients with fulminant colitis or toxic megacolon that does not improve within 48–72 hours, in patients with invisible flat dysplasia or non-endoscopically resectable dysplastic lesions on surveillance colonoscopy, and in patients with refractory disease requiring long-term corticosteroids to control symptoms.

Although total proctocolectomy (with placement of an ileostomy) provides complete cure of the disease, most patients seek to avoid it out of concern for the impact it may have on their bowel function, their self-image, and their social interactions. After complete colectomy, patients may have a standard ileostomy with an external appliance, a continent ileostomy, or an internal ileal pouch that is anastomosed to the anal canal (ileal pouch–anal anastomosis). The latter maintains intestinal continuity, thereby obviating an ostomy. Under optimal circumstances, patients have five to seven loose bowel movements per day without incontinence. Endoscopic or histologic inflammation in the ileal pouch (“pouchitis”) develops in over 40% of patients within 1 year and in up to 80% over the long term, resulting in increased stool frequency, fecal urgency,

cramping, and bleeding, but usually resolves with a 2-week course of oral metronidazole (250–500 mg three times daily) or ciprofloxacin (500 mg twice daily). Patients with frequently relapsing pouchitis may need continuous antibiotics. Probiotics do not appear to be of benefit.

► Prognosis

Ulcerative colitis is a lifelong disease characterized by exacerbations and remissions. For most patients, the disease is readily controlled by medical therapy without need for surgery. The majority never require hospitalization. A subset of patients with more severe disease will require surgery, which results in complete cure of the disease. Properly managed, most patients with ulcerative colitis lead close to normal productive lives.

► When to Refer

- Colonoscopy: for evaluation of activity and extent of active disease and for surveillance for neoplasia in patients with quiescent disease for more than 8–10 years.
- For follow-up of any patient requiring hospitalization.
- When surgical colectomy is indicated.

► When to Admit

- Patients with severe disease manifested by frequent bloody stools, anemia, weight loss, and fever.
- Patients with fulminant disease manifested by rapid progression of symptoms, worsening abdominal pain, distention, high fever, and tachycardia.
- Patients with moderate to severe symptoms that do not respond to oral corticosteroids and require a trial of bowel rest and intravenous corticosteroids.

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Singh S et al. First- and second-line pharmacotherapies for patients with moderate to severe active ulcerative colitis: an updated network meta-analysis. *Clin Gastroenterol Hepatol.* 2020;18:2179. [PMID: 31945470]

3. Microscopic Colitis

Microscopic colitis is an idiopathic condition that is found in up to 15% of patients who have chronic or intermittent watery diarrhea with normal-appearing mucosa at endoscopy. There are two major subtypes—lymphocytic colitis

and collagenous colitis. In both, histologic evaluation of mucosal biopsies reveals chronic inflammation (lymphocytes, plasma cells) in the lamina propria and increased intraepithelial lymphocytes. **Collagenous colitis** is further characterized by the presence of a thickened band (greater than 10 mcm) of subepithelial collagen. Both forms occur more commonly in women, especially in the fifth to sixth decades. Symptoms tend to be chronic or recurrent but may remit in most patients after several years. A more severe illness characterized by abdominal pain, fatigue, dehydration, and weight loss may develop in a subset of patients. The cause of **microscopic colitis** usually is unknown. Several medications have been implicated as etiologic agents, including NSAIDs, proton pump inhibitors, low-dose aspirin, selective serotonin reuptake inhibitors, ACE inhibitors, beta-blockers, and menopausal estrogen hormonal therapy. Diarrhea usually abates within 30 days of stopping the offending medication. Celiac disease may be present in 2–9% of patients and should be excluded with serologic testing (anti-tissue transglutaminase IgA). Treatment is largely empiric since there are few well-designed, controlled treatment trials. Antidiarrheal therapy with loperamide is the first-line treatment, providing symptom improvement in up to 70%. For patients who do not respond to loperamide, bismuth subsalicylate (three 262-mg tablets three times daily) leads to complete response in up to 50% patients in some series. The next option is delayed-release budesonide (Entocort), 9 mg/day for 6–8 weeks. Budesonide has been shown in three prospective controlled studies to induce clinical remission in greater than 80% of patients; however, relapse occurs in most patients after stopping therapy. Remission is maintained in 75% of patients treated long-term with low doses of budesonide. In clinical practice, budesonide is tapered to the lowest effective dose for suppressing symptoms (3 mg every other day to 6 mg daily). For patients who do not respond to budesonide, uncontrolled studies report that treatment with bile-salt binding agents (cholestyramine, colestipol) or 5-ASAs (sulfasalazine, mesalamine) may be effective in some patients. Less than 3% of patients have refractory or severe symptoms, which may be treated with immunosuppressive agents (azathioprine or methotrexate) or anti-TNF agents (infliximab, adalimumab).

Miehlke S et al. Microscopic colitis: pathophysiology and clinical management. *Lancet Gastroenterol Hepatol.* 2019;4:405. [PMID: 30860066]

Virine B et al. Biopsies from the ascending and descending colon are sufficient for diagnosis of microscopic colitis. *Clin Gastroenterol Hepatol.* 2020;18:2003. [PMID: 32109628]

several dozen. Almost all patients with diverticulosis have involvement in the sigmoid and descending colon; however, only 15% have proximal colonic disease.

For over 40 years, it has been believed that diverticulosis arises after many years of a diet deficient in fiber. Recent epidemiologic studies challenge this theory, finding no association between the prevalence of asymptomatic diverticulosis and low dietary fiber intake or constipation. Thus, the etiology of diverticulosis is uncertain. The extent to which abnormal motility and hereditary factors contribute to diverticular disease is unknown. Patients with abnormal connective tissue are also disposed to development of diverticulosis, including Ehlers-Danlos syndrome, Marfan syndrome, and systemic sclerosis.

1. Uncomplicated Diverticulosis

More than 90% of patients with diverticulosis have uncomplicated disease and no specific symptoms. In most, diverticulosis is an incidental finding detected during colonoscopic examination or barium enema examination. Some patients have nonspecific complaints of chronic constipation, abdominal pain, or fluctuating bowel habits. It is unclear whether these symptoms are due to alterations in the colonic motility, visceral hypersensitivity, gut microbiota, or low-grade inflammation. Physical examination is usually normal but may reveal mild left lower quadrant tenderness with a thickened, palpable sigmoid and descending colon. Screening laboratory studies should be normal in uncomplicated diverticulosis.

There is no reason to perform imaging studies for the purpose of diagnosing asymptomatic, uncomplicated disease. Diverticula are well seen on barium enema, colonoscopy, and CT imaging. Involved segments of colon may also be narrowed and deformed.

Patients in whom diverticulosis is discovered should be encouraged to increase dietary fiber either through diet (fruits, vegetables, whole grains) or fiber supplements (psyllium, methylcellulose), which is associated with a lower risk of diverticulitis in prospective cohort studies. Studies suggest that the risk of diverticulitis may be further reduced with exercise and avoidance of red meats and NSAIDs.

Ma W et al. Intake of dietary fiber, fruits, and vegetables and risk of diverticulitis. *Am J Gastroenterol.* 2019;114:1531. [PMID: 31397679]

Strate LL et al. Epidemiology, pathophysiology, and treatment of diverticulitis. *Gastroenterology.* 2019;156:1282. [PMID: 30660732]

DIVERTICULAR DISEASE OF THE COLON

Colonic diverticulosis increases with age, ranging from a prevalence of 5% in those under age 40 to over 50% by age 60 years in Western societies. Most are asymptomatic, discovered incidentally at endoscopy or on barium enema. Complications occur in less than 5%, including gastrointestinal bleeding and diverticulitis.

Colonic diverticula may vary in size from a few millimeters to several centimeters and in number from one to

2. Diverticulitis



- Acute abdominal pain and fever.
- Left lower abdominal tenderness and mass.
- Leukocytosis.

► Clinical Findings

A. Symptoms and Signs

Diverticulitis is defined as macroscopic inflammation of a diverticulum that may reflect a spectrum from inflammation alone, to microperforation with localized paracolic inflammation, to macroperforation with either abscess or generalized peritonitis. Thus, there is a range from mild to severe disease. Most patients with localized inflammation or infection report mild to moderate aching abdominal pain, usually in the left lower quadrant. Constipation or loose stools may be present. Nausea and vomiting are frequent. In many cases, symptoms are so mild that the patient may not seek medical attention until several days after onset. Physical findings include a low-grade fever, left lower quadrant tenderness, and a palpable mass. Stool occult blood is common, but hematochezia is rare. Leukocytosis is mild to moderate. Patients with free perforation present with a more dramatic picture of generalized abdominal pain and peritoneal signs.

B. Imaging

In most patients with suspected diverticulitis, a CT scan of the abdomen is obtained, especially in those with fever, leukocytosis, and signs of sepsis or peritonitis or with immunocompromise to look for evidence of complicated disease (abscess, phlegmon, perforation, fistula) and in those presenting for the first time with mild symptoms to look for evidence of diverticulitis (colonic diverticula, wall thickening, pericolic fat infiltration) and to exclude other causes of abdominal pain. Patients who respond to acute medical management should undergo complete colonic evaluation with colonoscopy or radiologic imaging (CT colonography) 4–8 weeks after resolution of clinical symptoms to exclude colorectal cancer (which may mimic diverticulitis), which is identified in 1.3% and 7.9% of patients following a diagnosis of uncomplicated or complicated diverticulitis, respectively. Endoscopy and colonography are contraindicated during the initial stages of an acute attack because of the risk of free perforation.

► Differential Diagnosis

Diverticulitis must be distinguished from other causes of lower abdominal pain, including perforated colonic carcinoma, Crohn disease, appendicitis, ischemic colitis, *C difficile*-associated colitis, and gynecologic disorders (ectopic pregnancy, ovarian cyst or torsion), by abdominal CT scan, pelvic ultrasonography, or radiographic studies of the distal colon that use water-soluble contrast enemas.

► Complications

Complications, such as phlegmon, abscess, perforation, peritonitis, or sepsis, develop in approximately 12% of patients with acute diverticulitis. Chronic inflammation or an untreated abscess may lead to smoldering disease (ongoing pain, leukocytosis), fistula formation that may involve the bladder, ureter, vagina, uterus, bowel, and abdominal wall or stricturing of the colon with partial or complete obstruction.

► Treatment

A. Medical Management

Most patients with uncomplicated disease can be managed with conservative measures. Patients with mild symptoms and no peritoneal signs may be managed initially as outpatients on a clear liquid diet for 2–3 days. Although broad-spectrum oral antibiotics with anaerobic activity commonly are prescribed, large clinical trials confirm that antibiotics are not beneficial in uncomplicated disease. A 2015 AGA guideline suggests that antibiotics should be used selectively for uncomplicated disease, including patients who are immunocompromised, have significant comorbid disease, or have small pericolonic abscesses (less than 3–4 cm). Reasonable regimens include amoxicillin and clavulanate potassium (875 mg/125 mg) twice daily; or metronidazole, 500 mg three times daily plus either ciprofloxacin, 500 mg twice daily, or trimethoprim-sulfamethoxazole, 160/800 mg twice daily orally, for 7–10 days or until the patient is afebrile for 3–5 days. Symptomatic improvement usually occurs within 3 days, at which time the diet may be advanced. Once the acute episode has resolved, a high-fiber diet is recommended.

Patients with increasing pain, fever, or inability to tolerate oral fluids require hospitalization. Hospitalization is required in patients who are immunocompromised, have significant comorbid illness, have abscesses greater than 3–4 cm, or have signs of severe diverticulitis (high fevers, leukocytosis, or peritoneal signs). Patients should be given nothing by mouth and should receive intravenous fluids. If ileus is present, a nasogastric tube should be placed. Intravenous antibiotics should be given to cover anaerobic and gram-negative bacteria. Single-agent therapy with either a second-generation cephalosporin (eg, cefotixin), piperacilllin-tazobactam, or ticarcillin clavulanate appears to be as effective as combination therapy (eg, metronidazole or clindamycin plus an aminoglycoside or third-generation cephalosporin [eg, ceftazidime, cefotaxime]). Symptomatic improvement should be evident within 2–3 days. Intravenous antibiotics should be continued for 5–7 days, before changing to oral antibiotics.

B. Surgical Management

Surgical consultation and repeat abdominal CT imaging should be obtained on all patients with severe disease or those who do not improve after 72 hours of medical management. Patients with a localized abdominal abscess 4 cm in size or larger are usually treated urgently with a percutaneous catheter drain placed by an interventional radiologist. This permits control of the infection and resolution of the immediate infectious inflammatory process. Indications for emergent surgical management include generalized peritonitis, large undrainable abscesses, and clinical deterioration despite medical management and percutaneous drainage. Following recovery from complicated diverticulitis, a subsequent elective one-stage surgical resection is generally recommended to reduce recurrent episodes of complicated disease. Patients with chronic disease resulting in fistulas or colonic obstruction will require elective surgical resection.

► Prognosis

Diverticulitis recurs in 15–20% of patients treated with medical management over 10–20 years. However, less than 5% have more than two recurrences. Among patients who have an episode of uncomplicated diverticulitis, less than 5% later develop complicated disease. Therefore, elective surgical resection is no longer routinely recommended in patients with recurrent bouts of uncomplicated disease but is individualized based on patient preference, age, comorbid disease, and frequency and severity of attacks. Diverticulosis is not associated with an increased risk of colorectal cancer.

► When to Refer

- Failure to improve within 72 hours of medical management.
- Presence of significant peridiverticular abscesses (4 cm or larger) requiring possible percutaneous or surgical drainage.
- Generalized peritonitis or sepsis.
- Recurrent attacks.
- Chronic complications, including colonic strictures or fistulas.

► When to Admit

- Severe pain or inability to tolerate oral intake.
- Signs of sepsis or peritonitis.
- CT scan showing signs of complicated disease (abscess, perforation, obstruction).
- Failure to improve with outpatient management.
- Immunocompromised or frail, elderly patient.

Ahmed AM et al. Surgical treatment of diverticulitis and its complications: a systematic review and meta-analysis of randomized control trials. *Surgeon*. 2018;16:372. [PMID: 30033140]

Huston JM et al. Antibiotics versus no antibiotics for the treatment of acute uncomplicated diverticulitis: review of the evidence and future directions. *Surg Infect (Larchmt)*. 2018;19:648. [PMID: 30204549]

Knott L et al. Medical management of diverticular disease. *Clin Colon Rectal Surg*. 2018;31:214. [PMID: 29942209]

Tehranian S et al. Prevalence of colorectal cancer and advanced adenoma in patients with acute diverticulitis: implications for follow up colonoscopy. *Gastrointest Endosc*. 2020;91:634. [PMID: 31521778]

3. Diverticular Bleeding

Half of all cases of acute lower gastrointestinal bleeding are attributable to diverticulosis. For a full discussion, see the section on Acute Lower Gastrointestinal Bleeding, above.

POLYPS OF THE COLON

Polyps are discrete mass lesions that protrude into the intestinal lumen. Although most commonly sporadic, they may be inherited as part of a familial polyposis syndrome. Polyps may be divided into four major pathologic groups:

mucosal adenomatous polyps (tubular, tubulovillous, and villous), mucosal serrated polyps (hyperplastic, sessile serrated polyps, and traditional serrated adenoma), mucosal nonneoplastic polyps (juvenile polyps, hamartomas, inflammatory polyps), and submucosal lesions (lipomas, lymphoid aggregates, carcinoids, pneumatosis cystoides intestinalis). Of polyps removed at colonoscopy, over 70% are adenomatous; most of the remainder are serrated. Adenomatous polyps and serrated polyps have significant clinical implications and will be considered further below.

NONFAMILIAL ADENOMATOUS & SERRATED POLYPs

Adenomas and serrated polyps may be non-polypoid (flat, slightly elevated, or depressed), sessile, or pedunculated (containing a stalk). Their significance is that over 95% of cases of adenocarcinoma of the colon are believed to arise from these lesions. Early detection and removal of these precancerous lesions through screening programs has resulted in a 34% reduction in deaths from colorectal cancer since 2000. It is proposed that there is a polyp → carcinoma sequence whereby nonfamilial colorectal cancer develops through a continuous process from normal mucosa to adenomatous or serrated polyp and later to carcinoma. An estimated 75% of cancers arise in adenomas after inactivation of the *APC* gene leads to chromosomal instability and inactivation or loss of other tumor suppressor genes. The remaining 25% of cancers arise through the serrated pathway in which hyperplastic polyps develop *Kras* mutations (forming traditional serrated adenomas) or *BRAF* oncogene activation (forming sessile serrated lesions) with widespread methylation of CpG-rich promoter regions that leads to inactivation of tumor suppressor genes or mismatch repair genes (*MLH1*) with microsatellite instability.

A. Adenomas

Adenomas are present in more than 30% of men and 20% of women over the age of 50. Most adenomas are smaller than 5 mm and have a low risk of becoming malignant. Adenomas are classified as “advanced” if they are 1 cm or larger or contain villous features or high-grade dysplasia. In the general population, the prevalence of advanced adenomas is 6%. Advanced lesions are believed to have a higher risk of harboring or progressing to malignancy. It has been estimated from longitudinal studies that it takes an average of 5 years for a medium-sized polyp to develop from normal-appearing mucosa and 10 years for a gross cancer to arise.

B. Serrated Polyps

There are three types of serrated polyps: hyperplastic polyps, sessile serrated lesions, and traditional serrated adenomas. It is believed that sessile serrated lesions (prevalence 5–12%) and traditional serrated adenomas (prevalence less than 1%) harbor an increased risk of colorectal cancer similar or greater to that of adenomas and account for up to 20–30% of colorectal cancers. Many pathologists cannot reliably distinguish between hyperplastic polyps and sessile serrated lesions. Diminutive hyperplastic polyps (less than 5 mm) are extremely common (prevalence 20–30%),

especially in the rectum, and believed to be without significant risk.

► Clinical Findings

A. Symptoms and Signs

Most patients with adenomatous and serrated polyps are completely asymptomatic. Chronic occult blood loss may lead to iron deficiency anemia. Large polyps may ulcerate, resulting in intermittent hematochezia.

B. Fecal Occult Blood or Multitarget DNA Tests

FOBT, FIT, and fecal DNA tests are available as part of colorectal cancer screening programs (see Chapter 39). FIT is a fecal immunochemical test for hemoglobin with a single specimen having a sensitivity of approximately 80% for colorectal cancer and 20–30% for advanced adenomas but a much lower sensitivity for serrated lesions. FIT is more sensitive than guaiac-based tests for the detection of colorectal cancer and advanced adenomas. In 2014, a test combining a fecal DNA test with a fecal immunochemical test for stool hemoglobin (under the proprietary name “Cologuard”) was approved by the FDA. In a prospective comparative trial conducted in persons at average risk for colorectal cancer undergoing colonoscopy, the sensitivity for colorectal cancer for Cologuard was 92.3% compared to 73.8% for FIT and the sensitivity for large (greater than 1 cm) adenomas or serrated polyps for Cologuard was 42.4% compared to 23.8% for FIT.

C. Radiologic Tests

CT colonography (“virtual colonoscopy”) uses data from helical CT imaging with computer-enabled luminal image reconstruction to generate two-dimensional and three-dimensional images of the colon. Using optimal imaging software with multidetector helical CT scanners, several studies report a sensitivity of 90% or more for the detection of polyps larger than 10 mm in size. However, the accuracy for detection of polyps 5–9 mm in size is significantly lower (sensitivity 50%). A small proportion of these diminutive polyps harbor advanced histology (up to 1.2%) or carcinoma (less than 1%). Abdominal CT imaging also results in a radiation exposure that may lead to a small risk of cancer. Barium enema is no longer recommended due to its poor diagnostic accuracy.

D. Endoscopic Tests

Colonoscopy allows evaluation of the entire colon and is the best means of detecting and removing adenomatous and serrated polyps. It should be performed in all patients who have positive FOBT, FIT, or fecal DNA tests or iron deficiency anemia (see Occult Gastrointestinal Bleeding above), as the prevalence of colonic neoplasms is increased in these patients. Colonoscopy should also be performed in patients with polyps detected on radiologic imaging studies (CT colonography or barium enema) or adenomas detected on flexible sigmoidoscopy to remove these polyps and to fully evaluate the entire colon. The newest

generation of capsule endoscopy of the colon has an 86% sensitivity and 88% specificity for detection of adenomas greater than 6 mm compared with colonoscopy, but only 29% sensitivity and 33% specificity for sessile serrated polyps. Capsule endoscopy may be considered in patients who are unsuitable or unwilling to undergo colonoscopy or who have an incomplete colonoscopy.

► Treatment

A. Colonoscopic Polypectomy

Most adenomatous and serrated polyps are less than 2 cm in size and are readily amenable to colonoscopic removal; this can be done with biopsy forceps (for those less than 3 mm), with cold snare excision (for those less than 10 mm), or with cold snare or hot snare cautery (for those 10–20 mm). Sessile polyps larger than 2 cm may be removed by appropriately trained physicians using a variety of endoscopic techniques (eg, saline-lift mucosal resection or dissection) or infrequently may require surgical resection. Patients with large sessile polyps removed in piecemeal fashion should undergo repeated colonoscopy in 6 months to verify complete polyp removal. Complications after colonoscopic polypectomy include perforation in 0.2% and clinically significant bleeding in 0.3–1.0% of all patients, but 4–8% following mucosal resection of large lesions.

B. Postpolypectomy Surveillance

Adenomas and serrated polyps can be found in 30–40% of patients when another colonoscopy is performed within 3–5 years after the initial examination and polyp removal. Periodic colonoscopic surveillance is therefore recommended to detect these “metachronous” lesions, which either may be new or may have been overlooked during the initial examination. Most of these polyps are small, without high-risk features, and of little immediate clinical significance. The probability of detecting advanced neoplasms at surveillance colonoscopy depends on the number, size, and histologic features of the polyps removed on initial (index) colonoscopy. The US Multi-Society Task Force Guideline provides the following recommendations for repeat colonoscopy that depend on the findings at baseline colonoscopy: (1) **10 years:** normal colonoscopy or fewer than 20 hyperplastic polyps less than 10 mm in the distal colon or rectum; (2) **7–10 years:** 1–2 adenomas less than 10 mm; (3) **5–10 years:** 1–2 sessile serrated polyps less than 10 mm; (4) **3–5 years:** 3–4 adenomas or sessile serrated polyps less than 10 mm; (5) **3 years:** 5–10 adenomas or sessile serrated polyps less than 10 mm; or 1 or more adenomas or sessile serrated polyp 10 mm or larger or an adenoma containing villous features or high-grade dysplasia or a sessile serrated polyp with dysplasia. Patients with more than 10 adenomas should have a repeat colonoscopy at 1 year and may be considered for evaluation for a familial polyposis syndrome.

Gupta S et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus updated by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2020;158:1131. [PMID: 32039982]

Kaltenbach T et al. Endoscopic removal of colorectal lesions—recommendations of the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2020;158:1095. [PMID: 32058340]

Meester RG et al. Prevalence and clinical features of sessile serrated polyps: a systematic review. *Gastroenterology*. 2020;159:105. [PMID: 32199884]

HEREDITARY COLORECTAL CANCER & POLYPOSIS SYNDROMES

Up to 4% of all colorectal cancers are caused by germline genetic mutations that impose on carriers a high lifetime risk of developing colorectal cancer (see Chapter 39). Because the diagnosis of these disorders has important implications for treatment of affected patients and for screening of family members, it is important to consider these disorders in patients with a family history of colorectal cancer that has affected more than one family member, those with a personal or family history of colorectal cancer developing at an early age (50 years or younger), those with a personal or family history of multiple polyps (more than 10), and those with a personal or family history of multiple extracolonic malignancies.

1. Familial Adenomatous Polyposis

ESSENTIALS OF DIAGNOSIS

- ▶ Inherited condition characterized by early development of hundreds to thousands of colonic adenomatous polyps.
- ▶ Variety of extracolonic manifestations (eg, duodenal adenomas, desmoid tumors, and osteomas) and extracolonic cancers (stomach, duodenum, thyroid).
- ▶ Attenuated variant with < 100 (average 25) colonic adenomas.
- ▶ Genetic testing confirms mutation of *APC* gene (90%) or *MUTYH* gene (8%).
- ▶ Prophylactic colectomy recommended to prevent otherwise inevitable colorectal cancer (adenocarcinoma).

► General Considerations

Familial adenomatous polyposis (FAP) is a syndrome affecting 1:10,000 people and accounts for approximately 0.5% of colorectal cancers. The classic form of FAP is characterized by the development of hundreds to thousands of colonic adenomatous polyps and a variety of extracolonic manifestations. Of patients with classic FAP, approximately 90% have a mutation in the *APC* gene that is inherited in an autosomal dominant fashion and 8% have mutations in the *MUTYH* gene that are inherited in an autosomal recessive fashion. FAP arises de novo in 25% of patients in the absence of genetic mutations in the parents. An attenuated variant of FAP also has been recognized in which an average of only 25 polyps (range of 1–100) develop.

► Clinical Findings

A. Symptoms and Signs

In classic FAP, colorectal polyps develop by a mean age of 15 years and cancer often by age 40 years. Unless prophylactic colectomy is performed, colorectal cancer is inevitable by age 50 years. In attenuated FAP, the mean age for development of cancer is about 56 years.

Adenomatous polyps of the duodenum and periampullary area develop in over 90% of patients, resulting in a 5–8% lifetime risk of adenocarcinoma. Adenomas occur less frequently in the gastric antrum and small bowel and, in those locations, have a lower risk of malignant transformation. Gastric fundus gland polyps occur in over 50% but have an extremely low (0.6%) malignant potential.

A variety of other benign extraintestinal manifestations, including soft tissue tumors of the skin, desmoid tumors, osteomas, and congenital hypertrophy of the retinal pigment, develop in some patients with FAP. These extraintestinal manifestations vary among families, depending in part on the type or site of mutation in the *APC* gene. Desmoid tumors are locally invasive fibromas, most commonly intra-abdominal, that may cause bowel obstruction, ischemia, or hemorrhage. They occur in 15% of patients and are the second leading cause of death in FAP. Malignancies of the central nervous system (Turcot syndrome) and tumors of the thyroid and liver (hepatoblastomas) may also develop in patients with FAP.

B. Genetic Testing

Genetic counseling and testing should be offered to patients found to have multiple adenomatous polyps at endoscopy and to first-degree family members of patients with FAP. Most centers now perform genetic testing using a multi-gene panel of 14–67 hereditary cancer genes, including *APC* and *MUTYH*. *APC* gene mutations are identified in 80% of patients with more than 1000, and 56% with 100–1000 polyps (ie, the classic phenotype of FAP). Current guidelines recommend that genetic testing be considered in individuals with as few as 10 adenomas to exclude a diagnosis of attenuated disease, most especially in patients less than age 50–60 years.

► Treatment

Once the diagnosis has been established, complete proctocolectomy with ileoanal anastomosis or colectomy with ileorectal anastomosis is recommended in most patients, usually before age 20 years. Colonoscopy every 1–2 years with polypectomy may be considered for patients with attenuated FAP and a low number of polyps. Upper endoscopic evaluation of the stomach, duodenum, and periampullary area should be performed every 1–3 years to look for adenomas or carcinoma with resection of duodenal or ampullary polyps greater than 10 mm, increasing in size, or suspicious for high-grade dysplasia or cancer. Sulindac and celecoxib have been shown to decrease the number and size of polyps in the rectal stump but not the duodenum.

Kupfer SS et al. Patients in whom to consider genetic evaluation and testing for hereditary colorectal cancer syndromes. *Am J Gastroenterol.* 2020;115:1. [PMID: 31634263]

Stanich PP et al. Prevalence of germline mutations in polyposis and colorectal cancer-associated genes in patients with multiple colorectal polyps. *Clin Gastroenterol Hepatol.* 2019;17:2008. [PMID: 30557735]

Yang J et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes. *Gastrointest Endosc.* 2020;91:963. [PMID: 32169282]

- Evaluation warranted in patients with personal history of early-onset colorectal cancer or family history of colorectal, endometrial, or other Lynch syndrome-related cancers at young age or in multiple family members.
- Diagnosis suspected by tumor tissue immunohistochemical staining for mismatch repair proteins or by testing for microsatellite instability.
- Diagnosis confirmed by genetic testing.

2. Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes are rare and account for less than 0.1% of colorectal cancers.

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by hamartomatous polyps throughout the gastrointestinal tract (most notably in the small intestine) as well as mucocutaneous pigmented macules on the lips, buccal mucosa, and skin. The hamartomas may become large, leading to bleeding, intussusception, or obstruction. Although hamartomas are not malignant, gastrointestinal malignancies (stomach, small bowel, and colon) develop in 40–60%, breast cancer in 30–50%, and a host of other malignancies of nonintestinal organs (gonads, pancreas). The defect has been localized to the serine threonine kinase 11 gene, and genetic testing is available.

Familial juvenile polyposis is also autosomal dominant and is characterized by multiple (more than ten) juvenile hamartomatous polyps located most commonly in the colon. There is an increased risk (up to 50%) of adenocarcinoma due to synchronous adenomatous polyps or mixed hamartomatous-adenomatous polyps. Genetic defects have been identified to loci on 18q and 10q (*MADH4* and *BMPRIA*). Genetic testing is available.

PTEN multiple hamartoma syndrome (Cowden disease) is characterized by hamartomatous polyps and lipomas throughout the gastrointestinal tract, trichilemmomas, and cerebellar lesions. An increased rate of malignancy is demonstrated in the thyroid, breast, and urogenital tract.

Byrne RM et al. Colorectal polyposis and inherited colorectal cancer syndromes. *Ann Gastroenterol.* 2018;31:24. [PMID: 29333064]

Daniell J et al. An exploration of genotype-phenotype link between Peutz-Jeghers syndrome and *STK11*: a review. *Fam Cancer.* 2018;17:421. [PMID: 28900777]

► General Considerations

Lynch syndrome (also known as hereditary nonpolyposis colon cancer [HNPCC]) is an autosomal dominant condition in which there is a markedly increased risk of developing colorectal cancer as well as a host of other cancers, including endometrial, ovarian, renal or bladder, hepatobiliary, gastric, and small intestinal cancers. It is estimated to account for up to 3% of all colorectal cancers. Affected individuals have a 22–75% lifetime risk of developing colorectal carcinoma and a 30–60% lifetime risk of endometrial cancer, depending on the affected gene. Unlike individuals with familial adenomatous polyposis, patients with Lynch syndrome develop only a few adenomas, which may be flat and more often contain villous features or high-grade dysplasia. In contrast to the traditional polyp → cancer progression (which may take over 10 years), these polyps are believed to undergo rapid transformation over 1–2 years from normal tissue → adenoma → cancer. Colon and endometrial cancer tend to develop at an earlier age than sporadic, nonhereditary cancers (mean age 45–50 years). A germline mutation is identified in 20% of patients in whom colon cancer was diagnosed before age 50. Compared with patients with sporadic tumors of similar pathologic stage, those with Lynch syndrome tumors have improved survival. Synchronous or metachronous cancers occur within 10 years in up to 45% of patients.

Lynch syndrome is caused by a defect in one of several genes that are important in the detection and repair of DNA base-pair mismatches: *MLH1*, *MSH2*, *MSH6*, and *PMS2* or *EPCAM*, a promoter for *MSH2*. Germline mutations in *MLH1* and *MSH2* account for almost 90% of the known mutations in families with Lynch syndrome. Mutations in any of these mismatch repair genes result in a characteristic phenotypic DNA abnormality known as microsatellite instability.

3. Lynch Syndrome

ESSENTIALS OF DIAGNOSIS

- Autosomal dominant inherited condition.
- Caused by mutations in a gene that detects and repairs DNA base-pair mismatches, resulting in DNA microsatellite instability and inactivation of tumor suppressor genes.
- Increased lifetime risk of colorectal cancer (22–75%), endometrial cancer (30–60%), and other cancers that may develop at young age.

► Clinical Findings

A thorough family cancer history is essential to identify families that may be affected by the Lynch syndrome so that appropriate genetic and colonoscopic screening can be offered. The National Colorectal Cancer Roundtable recommends a simple three-question tool for identifying increased risk and meriting more detailed assessment: (1) Have you had colorectal cancer or polyps diagnosed before age 50? (2) Do you have three or more relatives with colorectal cancer? and (3) Do you have a first-degree relative with colorectal cancer or another Lynch syndrome-related cancer diagnosed before age 50? The PREMM5 probability model is available for calculating the likelihood of Lynch syndrome

based on family and personal history (<https://premm.dfci.harvard.edu/>). Genetic evaluation is recommended for those with a personal or family history of colorectal cancer under age 50, a history of multiple family members with cancer, or a greater than 5% PREMM5 model-predicted chance of Lynch syndrome. Genetic testing can be performed with multigene panels that test for germline cancer genes (ie, Lynch, familial adenomatous polyposis, and hamartomatous syndromes) as well as others of uncertain significance for approximately \$250. Referral to a genetic counselor therefore is recommended.

Personal and family history alone are insufficient to identify a significant proportion of patients with Lynch syndrome. For this reason, the National Comprehensive Cancer Network recommend that *all* colorectal cancers should undergo testing for Lynch syndrome with either immunohistochemistry or microsatellite instability. Universal testing has the greatest sensitivity for the diagnosis of Lynch syndrome and is cost-effective. Individuals whose tumors have normal immunohistochemical staining or do not have microsatellite instability are unlikely to have germline mutations in mismatch repair genes, do not require further genetic testing, and do not require intensive cancer surveillance. Up to 15% of sporadic (noninherited) tumors have microsatellite instability or absent *MLH1* staining due to somatic (noninherited) methylation of the *MLH1* gene promoter and somatic *BRAF* mutations, which must be excluded before further genetic testing is considered. Germline testing for gene mutations is positive in more than 90% of individuals whose tumors show absent histochemical staining of one of the mismatch repair genes or high level of microsatellite instability without a *BRAF* mutation.

► Screening & Treatment

If a mutation is detected in a patient with cancer in one of the known mismatch genes, genetic testing of other first-degree family members is indicated. If genetic testing documents a Lynch syndrome gene mutation, affected relatives should be screened with colonoscopy every 1–2 years beginning at age 25 (or at age 5 years younger than the age at diagnosis of the youngest affected family member). If cancer is found, subtotal colectomy with ileorectal anastomosis (followed by annual surveillance of the rectal stump) should be performed. Women should undergo screening for endometrial and ovarian cancer beginning at age 30–35 years with pelvic examination, transvaginal ultrasound, and endometrial sampling. Prophylactic hysterectomy and oophorectomy are recommended to women at age 40 or once they have finished childbearing. Screening for gastric cancer with upper endoscopy should be considered every 2–3 years beginning at age 30–35 years.

Ballester V et al. How and when to consider genetic testing for colon cancer? *Gastroenterology*. 2018;155:955. [PMID: 30148981]

Burn J et al; CAP2 Investigators. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet*. 2020;395:1855. [PMID: 32534647]

Ladabaum U. What is Lynch-like syndrome and how should we manage it? *Clin Gastroenterol Hepatol*. 2020;18:294. [PMID: 31408703]

Pan JY et al. Worldwide practice patterns in Lynch syndrome diagnosis and management, based on data from the International Mismatch Repair Consortium. *Clin Gastroenterol Hepatol*. 2018;16:1901. [PMID: 29702294]

► ANORECTAL DISEASES

(See Chapter 39 for Carcinoma of the Anus.)

HEMORRHOIDS



ESSENTIALS OF DIAGNOSIS

- ▶ Bright red blood per rectum.
- ▶ Protrusion, discomfort.
- ▶ Characteristic findings on external anal inspection and anoscopy.

► General Considerations

Internal hemorrhoids are subepithelial vascular cushions consisting of connective tissue, smooth muscle fibers, and arteriovenous communications between terminal branches of the superior rectal artery and rectal veins. They are a normal anatomic entity, occurring in all adults, that contribute to normal anal pressures and ensure a water-tight closure of the anal canal. They commonly occur in three primary locations—right anterior, right posterior, and left lateral. External hemorrhoids arise from the inferior hemorrhoidal veins located below the dentate line and are covered with squamous epithelium of the anal canal or perianal region.

Hemorrhoids may become symptomatic as a result of activities that increase venous pressure, resulting in distention and engorgement. Straining at stool, diarrhea, constipation, prolonged sitting, pregnancy, obesity, and low-fiber diets all may contribute. With time, redundancy and enlargement of the venous cushions may develop and result in bleeding or protrusion.

► Clinical Findings

A. Symptoms and Signs

Patients often attribute a variety of perianal complaints to “hemorrhoids.” However, the principal problems attributable to internal hemorrhoids are bleeding, prolapse, and mucoid discharge. Bleeding is manifested by bright red blood that may range from streaks of blood visible on toilet paper or stool to bright red blood that drips into the toilet bowl after a bowel movement. Uncommonly, bleeding is severe and prolonged enough to result in anemia. Initially, internal hemorrhoids are confined to the anal canal (stage I). Over time, the internal hemorrhoids may gradually enlarge and protrude from the anal opening. At first, this

mucosal prolapse occurs during straining and reduces spontaneously (stage II). With progression over time, the prolapsed hemorrhoids may require manual reduction after bowel movements (stage III) or may remain chronically protruding (stage IV). Chronically prolapsed hemorrhoids may result in a sense of fullness or discomfort and mucoi discharge, resulting in irritation of perianal skin and soiling of underclothes. Pain is unusual with internal hemorrhoids, occurring only when there is extensive inflammation and thrombosis of irreducible tissue or with thrombosis of an external hemorrhoid.

B. Examination

External hemorrhoids are readily visible on perianal inspection. Nonprolapsed internal hemorrhoids are not visible but may protrude through the anus with gentle straining while the clinician spreads the buttocks. Prolapsed hemorrhoids are visible as protuberant purple nodules covered by mucosa. The perianal region should also be examined for other signs of disease such as fistulas, fissures, skin tags, condyloma, anal cancer, or dermatitis. On digital examination, uncomplicated internal hemorrhoids are neither palpable nor painful. Anoscopic evaluation, best performed in the prone jackknife position, provides optimal visualization of internal hemorrhoids.

► Differential Diagnosis

Small volume rectal bleeding may be caused by an anal fissure or fistula, neoplasms of the distal colon or rectum, ulcerative colitis or Crohn colitis, infectious proctitis, or rectal ulcers. Rectal prolapse, in which a full thickness of rectum protrudes concentrically from the anus, is readily distinguished from mucosal hemorrhoidal prolapse. Proctosigmoidoscopy or colonoscopy should be performed in all patients with hematochezia to exclude disease in the rectum or sigmoid colon that could be misinterpreted in the presence of hemorrhoidal bleeding.

► Treatment

A. Conservative Measures

Most patients with early (stage I and stage II) disease can be managed with conservative treatment. To decrease straining with defecation, patients should be given instructions for a high-fiber diet and told to increase fluid intake with meals, avoid straining, and limit sitting time on the toilet to less than 5 minutes. Dietary fiber may be supplemented with bran powder (1–2 tbsp twice daily added to food or in 8 oz of liquid) or with commercial bulk laxatives (eg, Benefiber, Metamucil, Citrucel). Suppositories and rectal ointments have no demonstrated utility in the management of mild disease. Mucoi discharge may be treated effectively by the local application of a cotton ball tucked next to the anal opening after bowel movements.

B. Medical Treatment

Patients with stage I, stage II, and stage III hemorrhoids and recurrent bleeding despite conservative measures may be treated without anesthesia with injection sclerotherapy,

rubber band ligation, or application of electrocoagulation (bipolar cautery or infrared photocoagulation). The choice of therapy is dictated by operator preference, but rubber band ligation is preferred due to its ease of use and high rate of efficacy. Major complications occur in less than 2%, including pelvic sepsis, pelvic abscess, urinary retention, and bleeding. Recurrence is common unless patients alter their dietary habits. Edematous, prolapsed (stage IV) internal hemorrhoids, may be treated acutely with topical creams, foams, or suppositories containing various combinations of emollients, topical anesthetics, (eg, pramoxine, dibucaine), vasoconstrictors (eg, phenylephrine), astringents (witch hazel), and corticosteroids. Common preparations include Preparation H (several formulations), Anusol HC, Proctofoam, Nupercainal, Tucks, and Doloproct (not available in the United States).

C. Surgical Treatment

Surgical excision (hemorrhoidectomy) is reserved for less than 5–10% of patients with chronic severe bleeding due to stage III or stage IV hemorrhoids or patients with acute thrombosed stage IV hemorrhoids with necrosis. Complications of surgical hemorrhoidectomy include postoperative pain (which may persist for 2–4 weeks) and impaired continence.

► Thrombosed External Hemorrhoid

Thrombosis of the external hemorrhoidal plexus results in a perianal hematoma. It most commonly occurs in otherwise healthy young adults and may be precipitated by coughing, heavy lifting, or straining at stool. The condition is characterized by the relatively acute onset of an exquisitely painful, tense and bluish perianal nodule covered with skin that may be up to several centimeters in size. Pain is most severe within the first few hours but gradually eases over 2–3 days as edema subsides. Symptoms may be relieved with warm sitz baths, analgesics, and ointments. With symptom resolution, a perianal skin tag may persist, which can be a source of irritation. If the patient is evaluated in the first 24–48 hours, removal of the clot may hasten symptomatic relief. With the patient in the lateral position, the skin around and over the lump is injected subcutaneously with 1% lidocaine using a tuberculin syringe with a 30-gauge needle. An ellipse of skin is then excised and the clot evacuated. A dry gauze dressing is applied for 12–24 hours, and daily sitz baths are then begun.

► When to Refer

- Stage I, II, or III: When conservative measures fail and expertise in medical procedures is needed (injection, banding, thermocoagulation).
- Stage IV: When surgical excision is required.

Gardner IH et al. Benign anorectal disease: hemorrhoids, fissures, and fistulas. Ann Gastroenterol. 2020;33:9. [PMID: 31892792]

Qureshi WA. Office management of hemorrhoids. Am J Gastroenterol. 2018;113:795. [PMID: 29487411]

ANORECTAL INFECTIONS

A number of organisms can cause inflammation of the anal and rectal mucosa. Proctitis is characterized by anorectal discomfort, tenesmus, constipation, and mucus or bloody discharge. Most cases of proctitis are sexually transmitted, especially by anal-receptive intercourse. Infectious proctitis must be distinguished from noninfectious causes of anorectal symptoms, including anal fissures or fistulae, perirectal abscesses, anorectal carcinomas, and inflammatory bowel disease (ulcerative colitis or Crohn disease).

Etiology & Management

Several organisms may cause infectious proctitis.

A. *Neisseria gonorrhoeae*

Gonorrhea may cause itching, burning, tenesmus, and a mucopurulent discharge, although many anorectal infections are asymptomatic. Rectal swab specimens should be taken during anoscopy for culture; Gram staining is unreliable. Cultures should also be taken from the pharynx and urethra in men and from the pharynx and cervix in women. Complications of untreated infections include strictures, fissures, fistulas, and perirectal abscesses. (For treatment, see Chapter 33.)

B. *Treponema pallidum*

Anal syphilis may be asymptomatic or may lead to perianal pain and discharge. With primary syphilis, the chancre may be at the anal margin or within the anal canal and may mimic a fissure, fistula, or ulcer. Proctitis or inguinal lymphadenopathy may be present. With secondary syphilis, condylomata lata (pale-brown, flat verrucous lesions) may be seen, with secretion of foul-smelling mucus. Although the diagnosis may be established with dark-field microscopy or fluorescent antibody testing of scrapings from the chancre or condylomas, this requires proper equipment and trained personnel. The VDRL or RPR test is positive in 75% of primary cases and in 99% of secondary cases. (For treatment, see Chapter 34.)

C. *Chlamydia trachomatis*

Chlamydial infection may cause proctitis similar to gonococcal proctitis; however, some infections are asymptomatic. It also may cause lymphogranuloma venereum, characterized by proctocolitis with fever and bloody diarrhea, painful perianal ulcerations, anorectal strictures and fistulas, and inguinal adenopathy (bubo). Previously rare in developed countries, an increasing number of cases have been identified among men who have sex with men. The diagnosis is established by serology, culture, or PCR-based testing of rectal discharge or rectal biopsy. Recommended treatment is doxycycline 100 mg orally twice daily for 21 days.

D. Herpes Simplex Type 2

Herpes simplex type 2 virus is a common cause of anorectal infection. Symptoms occur 4–21 days after exposure and include severe pain, itching, constipation, tenesmus,

urinary retention, and radicular pain from involvement of lumbar or sacral nerve roots. Small vesicles or ulcers may be seen in the perianal area or anal canal. Sigmoidoscopy is not usually necessary but may reveal vesicular or ulcerative lesions in the distal rectum. Diagnosis is established by viral culture, PCR, or antigen detection assays of vesicular fluid. Symptoms resolve within 2 weeks, but viral shedding may continue for several weeks. Patients may remain asymptomatic with or without viral shedding or may have recurrent mild relapses. Treatment of acute infection for 7–10 days with acyclovir, 400 mg, or famciclovir, 250 mg orally three times daily, or valacyclovir, 1 g twice daily, has been shown to reduce the duration of symptoms and viral shedding. Patients with AIDS and recurrent relapses may benefit from long-term suppressive therapy (see Chapter 31).

E. Condylomata Acuminata

Condylomata acuminata (warts) are a significant cause of anorectal symptoms. Caused by the HPV, they may occur on the perianal area, in the anal canal, or on the genitals. Perianal or anal warts are seen in up to 25% of men who have sex with men. HIV-positive individuals with condylomas have a higher relapse rate after therapy and a higher rate of progression to high-grade dysplasia or anal cancer. The warts are located on the perianal skin and extend within the anal canal up to 2 cm above the dentate line. Patients may have no symptoms or may report itching, bleeding, and pain. The warts may be small and flat or verrucous, or may form a confluent mass that may obscure the anal opening. Warts must be distinguished from condyloma lata (secondary syphilis) or anal cancer. Biopsies should be obtained from large or suspicious lesions. Treatment can be difficult. Sexual partners should also be examined and treated. The treatment of anogenital warts is discussed in Chapter 30. The HPV vaccine, Gardasil-9 valent, has demonstrated efficacy in preventing anogenital warts and is now recommended for all persons aged 9–14 (two or three doses) and persons aged 15–45 (three doses), as well as all men of any age who have sex with men (see Chapters 1 and 30). HIV-positive individuals with condylomas who have detectable serum HIV RNA levels should have anoscopic surveillance for anal cancer every 3–6 months.

Murphy M et al. Non-HPV perianal and anorectal sexually transmitted viral infections. Clin Colon Rectal Surg 2019;32:340. [PMID: 31507343]

FECAL INCONTINENCE

In a 2018 survey, 4.7% of US adults reported fecal incontinence within the prior 30 days. There are five general requirements for bowel continence: (1) solid or semisolid stool (even healthy young adults have difficulty maintaining continence with liquid rectal contents); (2) a distensible rectal reservoir (as sigmoid contents empty into the rectum, the vault must expand to accommodate); (3) a sensation of rectal fullness (if the patient cannot sense this, overflow may occur before the patient can take appropriate action); (4) intact pelvic nerves and muscles; and (5) the ability to reach a toilet in a timely fashion.

► Minor Incontinence

Many patients complain of inability to control flatus or slight soiling of undergarments that tends to occur after bowel movements or with straining or coughing. This may be due to local anal problems such as prolapsed hemorrhoids that make it difficult to form a tight anal seal or isolated weakness of the internal anal sphincter, especially if stools are somewhat loose. Patients should be treated with fiber supplements to provide greater stool bulk. Coffee and other caffeinated beverages should be eliminated. The perianal skin should be cleansed with moist, lanolin-coated tissue (baby wipes) to reduce excoriation and infection. After wiping, loose application of a cotton ball near the anal opening may absorb small amounts of fecal leakage. Prolapsing hemorrhoids may be treated with band ligation or surgical hemorrhoidectomy. Control of flatus and seepage may be improved by Kegel perineal exercises. Conditions such as ulcerative proctitis that cause tenesmus and urgency, chronic diarrheal conditions, and IBS may result in difficulty in maintaining complete continence, especially if a toilet is not readily available. Loperamide may be helpful to reduce urge incontinence in patients with loose stools and may be taken in anticipation of situations in which a toilet may not be readily available. Older patients may require more time or assistance to reach a toilet, which may lead to incontinence. Scheduled toileting and the availability of a bedside commode are helpful. Elderly patients with chronic constipation may develop stool impaction leading to “overflow” incontinence.

► Major Incontinence

Complete uncontrolled loss of stool reflects a significant problem with central perception or neuromuscular function. Incontinence that occurs without awareness suggests a loss of central awareness (eg, dementia, cerebrovascular accident, multiple sclerosis) or peripheral nerve injury (eg, spinal cord injury, cauda equina syndrome, pudendal nerve damage due to obstetric trauma or pelvic floor prolapse, aging, or diabetes mellitus). Incontinence that occurs despite awareness and active efforts to retain stool suggests sphincteric damage, which may be caused by traumatic childbirth (especially forceps delivery), episiotomy, prolapse, prior anal surgery, and physical trauma.

Physical examination should include careful inspection of the perianal area for hemorrhoids, rectal prolapse, fissures, fistulas, and either gaping or a keyhole defect of the anal sphincter (indicating severe sphincteric injury or neurologic disorder). The perianal skin should be stimulated to confirm an intact anocutaneous reflex. Digital examination during relaxation gives valuable information about resting tone (due mainly to the internal sphincter) and contraction of the external sphincter and pelvic floor during squeezing. It also excludes fecal impaction. Anoscopy is required to evaluate for hemorrhoids, fissures, and fistulas. Proctosigmoidoscopy is useful to exclude rectal carcinoma or proctitis. Anal ultrasonography or pelvic MRI is the most reliable test for definition of anatomic defects in the external and internal anal sphincters. Anal manometry may also be useful to define the severity of

weakness, to assess sensation, and to predict response to biofeedback training. In special circumstances, surface electromyography is useful to document sphincteric denervation and proctography to document perineal descent or rectal intussusception.

Patients who are incontinent only of loose or liquid stools are treated with bulking agents and antidiarrheal drugs (eg, loperamide, 2 mg before meals and prophylactically before social engagements, shopping trips, etc). Patients with incontinence of solid stool benefit from scheduled toilet use after glycerin suppositories or tap water enemas. Biofeedback training with pelvic floor strengthening (Kegel) exercises (alternating 5-second squeeze and 10-second rest for 10 minutes twice daily) may be helpful in motivated patients to lower the threshold for awareness of rectal filling and improve incontinence. In a 2019 randomized controlled trial, global incontinence symptom improvement occurred in 38% of patients instructed on daily pelvic floor contraction exercises (three sets of 10 contractions sustained for up to 10 seconds and two sets of 3 contractions sustained for up to 30 seconds) compared with 18% who did not perform these exercises. Operative management is seldom needed, but should be considered in patients with major incontinence due to prior injury to the anal sphincter who have not responded to medical therapy.

► When to Refer

- Conservative measures fail.
- Anorectal tests are deemed necessary (manometry, ultrasonography, electromyography).
- A surgically correctable lesion is suspected.

Pasricha T et al. Fecal incontinence in the elderly. Clin Geriatr Med. 2021;37:71. [PMID: 33213775]

Ussing A et al. Efficacy of supervised pelvic floor muscle training and biofeedback vs attention-control treatment in adults with fecal incontinence. Clin Gastroenterol Hepatol. 2019;17:2253. [PMID: 30580089]

Whitehead WE et al. Fecal incontinence diagnosed by Rome IV criteria in the United States, Canada, and the United Kingdom. Clin Gastroenterol Hepatol. 2020;18:385. [PMID: 31154029]

OTHER ANAL CONDITIONS

► Anal Fissures

Anal fissures are linear or rocket-shaped ulcers that are usually less than 5 mm in length. Most fissures are believed to arise from trauma to the anal canal during defecation, perhaps caused by straining, constipation, or high internal sphincter tone. They occur most commonly in the posterior midline, but 10% occur anteriorly. Fissures that occur off the midline should raise suspicion for Crohn disease, HIV/AIDS, tuberculosis, syphilis, or anal carcinoma. Patients complain of severe, tearing pain during defecation followed by throbbing discomfort that may lead to constipation due to fear of recurrent pain. There may be mild associated hematochezia, with blood on the stool or toilet paper. Anal fissures are confirmed by visual inspection of

the anal verge while gently separating the buttocks. Acute fissures look like cracks in the epithelium. Chronic fissures result in fibrosis and the development of a skin tag at the outermost edge (sentinel pile). Digital and anoscopic examinations may cause severe pain and may not be possible. Medical management is directed at promoting effortless, painless bowel movements. Fiber supplements and sitz baths should be prescribed. Topical anesthetics (5% lidocaine; 2.5% lidocaine plus 2.5% prilocaine) may provide temporary relief. Healing occurs within 2 months in up to 45% of patients with conservative management. Chronic fissures may be treated with topical 0.125–0.4% nitroglycerin, diltiazem 2% ointment, or nifedipine 0.5% (1 cm of ointment) applied twice daily just inside the anus with the tip of a finger for 4–8 weeks, or injection of botulinum toxin (20 units) into the internal anal sphincter. All these treatments result in healing in 50–80% of patients with chronic anal fissure, but headaches occur in up to 40% of patients treated with nitroglycerin. Botulinum toxin may cause transient anal incontinence. Fissures recur in up to 40% of patients after treatment. Chronic or recurrent fissures benefit from lateral internal sphincterotomy; however, minor incontinence may complicate this procedure.

Kyriakakis R et al. What predicts successful nonoperative management with botulinum toxin for anal fissure? *Am J Surg.* 2020;219:442. [PMID: 31679653]

Newman M et al. Anal fissure: diagnosis, management, and referral in primary care. *Br J Gen Pract.* 2019;69:409. [PMID: 31345824]

Qureshi W. How I approach it: anal fissures. *Am J Gastroenterol.* 2020;115:315. [PMID: 31972621]

tenderness, and pain. The treatment of Crohn-related fistula is discussed elsewhere in this chapter. Treatment of simple idiopathic fistula in ano is by surgical incision or excision under anesthesia. Care must be taken to preserve the anal sphincters. Surgical fistulotomy for treatment of complex (high, transsphincteric) anal fissures carries a high risk of incontinence. Techniques for healing the fistula while preserving the sphincter include an endoanal advancement flap over the internal opening and insertion of a bioprosthetic plug into the fistula opening.

Jamshidi R. Anorectal complaints: hemorrhoids, fissures, abscesses, fistulae. *Clin Colon Rectal Surg.* 2018;31:117. [PMID: 29487494]

Schllichtemeier S et al. Treatment for complex anal fistula, are we any wiser? *Colorectal Dis.* 2018;20:1067. [PMID: 30506657]

Williams G et al. The treatment of anal fistula: second ACPGBI Position Statement—2018. *Colorectal Dis.* 2018;20:5. [PMID: 30178915]

► Perianal Pruritus

Perianal pruritus is characterized by perianal itching and discomfort. It may be caused by poor anal hygiene associated with fistulas, fissures, prolapsed hemorrhoids, skin tags, and minor incontinence. Conversely, overzealous cleansing with soaps may contribute to local irritation or contact dermatitis. Contact dermatitis, atopic dermatitis, bacterial infections (*Staphylococcus* or *Streptococcus*), parasites (pinworms, scabies), candidal infection (especially in diabetics), sexually transmitted disease (condylomata acuminata, herpes, syphilis, molluscum contagiosum), and other skin conditions (psoriasis, Paget disease, lichen sclerosis) must be excluded. In patients with idiopathic perianal pruritus, examination may reveal erythema, excoriations, or lichenified, eczematous skin. Education is vital to successful therapy. Spicy foods, coffee, chocolate, and tomatoes may cause irritation and should be eliminated. After bowel movements, the perianal area should be cleansed with nonscented wipes premoistened with lanolin followed by gentle drying. A piece of cotton ball should be tucked next to the anal opening to absorb perspiration or fecal seepage. Anal ointments and lotions may exacerbate the condition and should be avoided. A short course of high-potency topical corticosteroid may be tried, although efficacy has not been demonstrated. Diluted capsaicin cream (0.006%) led to symptomatic relief in 75% of patients in a double-blind crossover study.

Cohee MW et al. Benign anorectal conditions: evaluation and management. *Am Fam Physician.* 2020;101:24. [PMID: 31894930]

Ortega AE et al. Idiopathic pruritus ani and acute perianal dermatitis. *Clin Colon Rectal Surg.* 2019;32:327. [PMID: 31507341]

► Perianal Abscess & Fistula

The anal glands located at the base of the anal crypts at the dentate line may become infected, leading to abscess formation. Other causes of abscess include anal fissure and Crohn disease. Abscesses may extend upward or downward through the intersphincteric plane. Symptoms of perianal abscess are throbbing, continuous perianal pain. Erythema, fluctuance, and swelling may be found in the perianal region on external examination or in the ischioanal fossa on digital rectal examination. Perianal abscesses are treated with local incision and drainage, while ischioanal abscesses require drainage in the operating room. After drainage of an abscess, most patients are found to have a fistula in ano.

Fistula in ano most often arises in an anal crypt and is usually preceded by an anal abscess. In patients with fistulas that connect to the rectum, other disorders such as Crohn disease, lymphogranuloma venereum, rectal tuberculosis, and cancer should be considered. Fistulas are associated with purulent discharge that may lead to itching,

Liver, Biliary Tract, & Pancreas Disorders

Lawrence S. Friedman, MD

16

JAUNDICE & EVALUATION OF ABNORMAL LIVER BIOCHEMICAL TESTS



ESSENTIALS OF DIAGNOSIS

- ▶ Jaundice results from accumulation of bilirubin in body tissues; the cause may be hepatic or nonhepatic.
- ▶ Hyperbilirubinemia may be due to abnormalities in the formation, transport, metabolism, or excretion of bilirubin.
- ▶ Persistent mild elevations of the aminotransferase levels are common in clinical practice and caused most often by nonalcoholic fatty liver disease (NAFLD).
- ▶ Evaluation of obstructive jaundice begins with ultrasonography and is usually followed by cholangiography.

► General Considerations

Jaundice (icterus) results from the accumulation of bilirubin—a product of heme metabolism—in body tissues. Hyperbilirubinemia may be due to abnormalities in the formation, transport, metabolism, or excretion of bilirubin. Total serum bilirubin is normally 0.2–1.2 mg/dL (3.42–20.52 μmol/L). Mean levels are higher in men than women, higher in Whites and Hispanics than Blacks, and correlate with an increased risk of symptomatic gallstone disease and inversely with the risk of stroke, respiratory disease, cardiovascular disease, and mortality, presumably because of antioxidant and intestinal anti-inflammatory effects. Jaundice may not be recognizable until serum bilirubin levels are about 3 mg/dL (51.3 μmol/L).

Jaundice may be caused by predominantly unconjugated or conjugated bilirubin in the serum (Table 16–1). Unconjugated hyperbilirubinemia may result from overproduction of bilirubin because of hemolysis; impaired

hepatic uptake of bilirubin due to certain drugs; or impaired conjugation of bilirubin by glucuronide, as in Gilbert syndrome, due to mild decreases in uridine diphosphate (UDP) glucuronyl transferase, or Crigler-Najjar syndrome, caused by moderate decreases (type II) or absence (type I) of UDP glucuronyl transferase. Hemolysis alone rarely elevates the serum bilirubin level to more than 7 mg/dL (119.7 μmol/L). Predominantly conjugated hyperbilirubinemia may result from impaired excretion of bilirubin from the liver due to hepatocellular disease, drugs, sepsis, or hereditary hepatocanicular transport defects (such as Dubin-Johnson syndrome, progressive familial intrahepatic cholestasis syndromes, and intrahepatic cholestasis of pregnancy) or from extrahepatic biliary obstruction. Features of some hyperbilirubinemic syndromes are summarized in Table 16–2. The term “cholestasis” denotes retention of bile in the liver, and the term “cholestatic jaundice” is often used when conjugated hyperbilirubinemia results from impaired bile formation or flow. Mediators of pruritus due to cholestasis have been identified to be lysophosphatidic acid and autotaxin, the enzyme that forms lysophosphatidic acid.

► Clinical Findings

A. Unconjugated Hyperbilirubinemia

Stool and urine color are normal, and there is mild jaundice and indirect (unconjugated) hyperbilirubinemia with no bilirubin in the urine. Splenomegaly occurs in all hemolytic disorders except in sickle cell disease.

B. Conjugated Hyperbilirubinemia

Cholestasis is often accompanied by pruritus, light-colored stools, and jaundice, although the patient may be asymptomatic. Malaise, anorexia, low-grade fever, and right upper quadrant discomfort are frequent with hepatocellular disease. Dark urine, jaundice, and, in women, amenorrhea occur. An enlarged tender liver, spider telangiectasias, palmar erythema, ascites, gynecomastia, sparse body hair, fetor hepaticus, and asterixis may be present, depending on the cause, severity, and chronicity of liver dysfunction.

Table 16–1. Classification of jaundice.

Type of Hyperbilirubinemia	Location and Cause
Unconjugated hyperbilirubinemia (predominantly indirect bilirubin)	Increased bilirubin production (eg, hemolytic anemias, hemolytic reactions, hematoma, pulmonary infarction) Impaired bilirubin uptake and storage (eg, posthepatitis hyperbilirubinemia, Gilbert syndrome, Crigler-Najjar syndrome, drug reactions)
Conjugated hyperbilirubinemia (predominantly direct bilirubin)	Hereditary Cholestatic Syndromes (see also Table 16–2) Faulty excretion of bilirubin conjugates (eg, Dubin-Johnson syndrome, Rotor syndrome) or mutation in genes coding for bile salt transport proteins (eg, progressive familial intrahepatic cholestasis syndromes, benign recurrent intrahepatic cholestasis, and some cases of intrahepatic cholestasis of pregnancy) Hepatocellular Dysfunction Biliary epithelial and hepatocyte damage (eg, hepatitis, hepatic cirrhosis) Intrahepatic cholestasis (eg, certain drugs, biliary cirrhosis, sepsis, postoperative jaundice) Hepatocellular damage or intrahepatic cholestasis resulting from miscellaneous causes (eg, spirochetal infections, infectious mononucleosis, cholangitis, sarcoidosis, lymphomas, hyperthyroidism, industrial toxins) Biliary Obstruction Choledocholithiasis, biliary atresia, carcinoma of biliary duct, sclerosing cholangitis, IgG ₄ -related cholangitis, ischemic cholangiopathy, choledochal cyst, external pressure on bile duct, pancreatitis, pancreatic neoplasms

Ig, immunoglobulin.

C. Biliary Obstruction

There may be right upper quadrant pain, weight loss (suggesting carcinoma), jaundice, pruritus, dark urine, and light-colored stools. Symptoms and signs may be intermittent if caused by a stone, carcinoma of the ampulla, or cholangiocarcinoma. Pain may be absent early in pancreatic cancer. Occult blood in the stools suggests cancer of the ampulla. A palpable gallbladder (Courvoisier sign) is characteristic, but neither specific nor sensitive, of a pancreatic head tumor. Fever and chills are more common in benign obstruction with associated cholangitis.

► Diagnostic Studies

(See Tables 16–3 and 16–4.)

A. Laboratory Findings

Elevated serum alanine and aspartate aminotransferase (ALT and AST) levels reflect hepatocellular injury. Normal reference values for ALT and AST are lower than generally reported when persons with risk factors for fatty liver are excluded. The upper limit of normal for ALT is 29–33 units/L in men and 19–25 units/L in women. Levels decrease with age and correlate with body mass index and mortality from liver disease and inversely with caffeine consumption and physical activity. There is controversy about whether a persistently elevated ALT level is associated with a low or high vitamin D level and, in the general population, with mortality from coronary artery disease, cancer, diabetes mellitus, and all causes; elevated AST levels have been reported to be associated with shorter life

expectancy. Truncal fat and early-onset paternal obesity are risk factors for increased ALT levels. Levels are mildly elevated in more than 25% of persons with untreated celiac disease and in type 1 diabetic patients with so-called glycogenic hepatopathy and often rise transiently in healthy persons who begin taking 4 g of acetaminophen per day or experience rapid weight gain on a fast-food diet. Levels may rise strikingly but transiently in patients with acute biliary obstruction from choledocholithiasis. NAFLD is by far the most common cause of persistent mildly to moderately elevated aminotransferase levels. Elevated ALT and AST levels, often greater than 1000 units/L (20 mckat/L), are the hallmark of hepatocellular necrosis or inflammation. Modest elevations are frequent in systemic infections, including coronavirus disease 2019 (COVID-19). The differential diagnosis of any liver test elevation always includes toxicity caused by drugs, herbal and dietary supplements, and toxins.

Elevated alkaline phosphatase levels are seen in cholestasis or infiltrative liver disease (such as tumor, granulomatous disease, or amyloidosis). Isolated alkaline phosphatase elevations of hepatic rather than bone, intestinal, or placental origin are confirmed by concomitant elevation of gamma-glutamyl transpeptidase or 5'-nucleotidase levels. Serum gamma-glutamyl transpeptidase levels appear to correlate with the risk of mortality and disability in the general population.

B. Imaging

Demonstration of dilated bile ducts by ultrasonography or CT indicates biliary obstruction (90–95% sensitivity). Ultrasonography, CT, and MRI may also demonstrate

Table 16–2. Hyperbilirubinemic disorders.

	Nature of Defect	Type of Hyperbilirubinemia	Clinical and Pathologic Characteristics
Gilbert syndrome ¹	Reduced activity of uridine diphosphate glucuronyl transferase	Unconjugated (indirect) bilirubin	Benign, asymptomatic hereditary jaundice. Hyperbilirubinemia increased by 24- to 36-hour fast. No treatment required. Associated with reduced mortality from cardiovascular disease.
Dubin-Johnson syndrome ²	Reduced excretory function of hepatocytes	Conjugated (direct) bilirubin	Benign, asymptomatic hereditary jaundice. Gallbladder does not visualize on oral cholecystography. Liver darkly pigmented on gross examination. Biopsy shows centrilobular brown pigment. Prognosis excellent.
Rotor syndrome ³	Reduced hepatic reuptake of bilirubin conjugates	Conjugated (direct) bilirubin	Similar to Dubin-Johnson syndrome, but liver is not pigmented and the gallbladder is visualized on oral cholecystography. Prognosis excellent.
Recurrent or progressive intrahepatic cholestasis ⁴	Cholestasis, often on a familial basis	Predominantly conjugated (direct) bilirubin	Episodic attacks of or progressive jaundice, itching, and malaise. Onset in early life and may persist for a lifetime. Alkaline phosphatase increased. Cholestasis found on liver biopsy. (Biopsy may be normal during remission.) Prognosis is generally excellent for “benign” recurrent intrahepatic cholestasis but may not be for familial forms.
Intrahepatic cholestasis of pregnancy ⁵	Cholestasis	Predominantly conjugated (direct) bilirubin	Benign cholestatic jaundice, usually occurring in the third trimester of pregnancy. Itching, gastrointestinal symptoms, and abnormal liver excretory function tests. Cholestasis noted on liver biopsy. Prognosis excellent, but recurrence with subsequent pregnancies or use of oral contraceptives is characteristic.

¹Gilbert syndrome generally results from the addition of extra dinucleotide(s) TA sequences to the TATA promoter of the conjugating enzyme *UGT1A1*.

²Dubin-Johnson syndrome is caused by a mutation in the *ABCC2* gene coding for organic anion transporter multidrug resistance protein 2 in bile canaliculi on chromosome 10q24.

³Rotor syndrome is caused by mutations in the genes coding for organic anion transporting polypeptides OATP1B1 and OATP1B3 on chromosome 12p.

⁴Mutations in genes that control hepatocellular transport systems that are involved in the formation of bile and inherited as autosomal recessive traits are on chromosomes 18q21–22, 2q24, 7q21, and others in families with progressive familial intrahepatic cholestasis. Gene mutations on chromosome 18q21–22 alter a P-type ATPase expressed in the small intestine and liver and on chromosome 2q24 alter the bile acid export pump and also cause benign recurrent intrahepatic cholestasis. Mutations in the *ABCB4* gene on chromosome 7 that encodes multidrug resistance protein 3 account for progressive familial intrahepatic cholestasis type 3. Less common causes of progressive familial intrahepatic cholestasis are mutations in genes that encode TJP2, FXR, and MYO5B.

⁵Mutations in genes (especially *ABCB4* and *ABCB11*) that encode biliary canalicular transporters account for many cases of intrahepatic cholestasis of pregnancy.

Table 16–3. Liver biochemical tests: normal values and changes in hepatocellular and obstructive jaundice.

Tests	Normal Values	Hepatocellular Jaundice	Obstructive Jaundice
Bilirubin ¹			
Direct	0.1–0.3 mg/dL (1.71–5.13 μmol/L)	Increased	Increased
Indirect	0.2–0.7 mg/dL (3.42–11.97 μmol/L)	Increased	Increased
Urine bilirubin	None	Increased	Increased
Serum albumin	3.5–5.5 g/dL (35–55 g/L)	Decreased	Generally unchanged
Alkaline phosphatase	30–115 units/L (0.6–2.3 mkat/L)	Mildly increased (+)	Markedly increased (+++)
Prothrombin time	INR of 1.0–1.4. After vitamin K, 10% decrease in 24 hours	Prolonged if damage is severe; does not respond to parenteral vitamin K	Prolonged if obstruction is marked; generally responds to parenteral vitamin K
ALT, AST	ALT, ≤ 30 units/L (0.6 mkat/L) (men), ≤ 19 units/L (0.38 mkat/L) (women); AST, 5–40 units/L (0.1–0.8 mkat/L)	Increased, as in viral hepatitis	Minimally increased

¹Measured by the van den Bergh reaction, which overestimates direct bilirubin in normal persons. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

Table 16–4. Causes of serum aminotransferase elevations.¹

Mild Elevations (< 5 × normal)	Severe Elevations (> 15 × normal)
Hepatic: ALT-predominant	
Chronic hepatitis B, C, and D	
Acute viral hepatitis (A-E, EBV, CMV)	Acute viral hepatitis (A-E, herpes)
Steatosis/steatohepatitis	Medications/toxins
Hemochromatosis	Ischemic hepatitis
Medications/toxins	Autoimmune hepatitis
Autoimmune hepatitis	Wilson disease
Alpha-1-antitrypsin (alpha-1-antiprotease) deficiency	Acute bile duct obstruction
Wilson disease	Acute Budd-Chiari syndrome
Celiac disease	Hepatic artery ligation
Glycogenic hepatopathy	
Hepatic: AST-predominant	
Alcohol-related liver injury (AST:ALT > 2:1)	
Cirrhosis	
Nonhepatic	
Strenuous exercise	
Hemolysis	
Myopathy	
Thyroid disease	
Macro-AST	

¹Almost any liver disease can cause moderate aminotransferase elevations (5–15 × normal).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

Adapted, with permission, from Green RM et al. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology. 2002 Oct;123(4):1367–84. Copyright © Elsevier.

hepatomegaly, intrahepatic tumors, and portal hypertension. Use of color Doppler ultrasonography or contrast agents that produce microbubbles increases the sensitivity of transcutaneous ultrasonography for detecting small neoplasms. MRI is the most accurate technique for identifying isolated liver lesions such as hemangiomas, focal nodular hyperplasia, or focal fatty infiltration and for detecting hepatic iron overload. The most sensitive techniques for detection of individual small hepatic metastases in patients eligible for resection are multiphasic helical or multislice CT; MRI with use of gadolinium or ferumoxides as contrast agents; CT arterial portography, in which imaging follows intravenous contrast infusion via a catheter placed in the superior mesenteric artery; and intraoperative ultrasonography. Dynamic gadolinium-enhanced MRI and MRI following administration of superparamagnetic iron oxide show promise in visualizing hepatic fibrosis. Because of its much lower cost, ultrasonography is preferable to CT (~six times more expensive) or MRI (~seven times more expensive) as a screening test for hepatocellular carcinoma in persons with cirrhosis. Positron emission tomography (PET) can be used to detect small pancreatic tumors and metastases. Ultrasonography can detect gallstones with a sensitivity of 95%.

Magnetic resonance cholangiopancreatography (MRCP) is a sensitive, noninvasive method of detecting bile duct

stones, strictures, and dilatation; however, it is less reliable than endoscopic retrograde cholangiopancreatography (ERCP) for distinguishing malignant from benign strictures. ERCP requires a skilled endoscopist and may be used to demonstrate pancreatic or ampullary causes of jaundice, carry out sphincterotomy and stone extraction, insert a stent through an obstructing lesion, or facilitate direct cholangiopancreatoscopy. Complications of ERCP include pancreatitis (5% or less) and, less commonly, cholangitis, bleeding, or duodenal perforation after sphincterotomy. Risk factors for post-ERCP pancreatitis include female sex, pregnancy, prior post-ERCP pancreatitis, suspected sphincter of Oddi dysfunction, and a difficult or failed cannulation. Percutaneous transhepatic cholangiography (PTC) is an alternative approach to evaluating the anatomy of the biliary tract. Serious complications of PTC occur in 3% and include fever, bacteremia, bile peritonitis, and intraperitoneal hemorrhage. Endoscopic ultrasonography (EUS) is the most sensitive test for detecting small lesions of the ampulla or pancreatic head and for detecting portal vein invasion by pancreatic cancer. It is also accurate for detecting or excluding bile duct stones.

C. Liver Biopsy

Percutaneous liver biopsy is considered the definitive study for determining the cause and histologic severity of hepatocellular dysfunction or infiltrative liver disease, although it is subject to sampling error. It is generally performed under ultrasound or, in some patients with suspected metastatic disease or a hepatic mass, CT guidance. A transjugular route can be used in patients with coagulopathy or ascites, and in selected cases endoscopic ultrasound-guided liver biopsy has proved advantageous. The risk of bleeding after a percutaneous liver biopsy is approximately 0.6% and is increased in persons with a platelet count of 50,000/mcL ($50 \times 10^9/\text{mcL}$) or less. The risk of death is less than 0.1%. Panels of blood tests (eg, FibroSure, NAFLD fibrosis score, enhanced liver fibrosis score) and, more accurately, elastography (vibration-controlled transient, shear wave, acoustic radiation force impulse, or magnetic resonance elastography) to measure liver stiffness are used for estimating the stage of liver fibrosis and degree of portal hypertension without the need for liver biopsy; they are most useful for excluding advanced fibrosis.

► When to Refer

Patients with jaundice should be referred for diagnostic procedures.

► When to Admit

Patients with liver failure should be hospitalized.

Fix OK et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD Expert Panel Consensus Statement. Hepatology. 2020;72:287. [PMID: 32298473]

Loomba R et al. Advances in non-invasive assessment of hepatic fibrosis. Gut. 2020;69:1343. [PMID: 32066623]

Neuberger J et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. Gut. 2020;69:1382. [PMID: 32467090]

DISEASES OF THE LIVER

See Chapter 39 for Hepatocellular Carcinoma.

ACUTE HEPATITIS A



ESSENTIALS OF DIAGNOSIS

- ▶ Prodrome of anorexia, nausea, vomiting, malaise, aversion to smoking.
- ▶ Fever, enlarged and tender liver, jaundice.
- ▶ Normal to low white cell count; markedly elevated aminotransferases.

General Considerations

Hepatitis can be caused by viruses, including the five hepatotropic viruses—A, B, C, D, and E—and many drugs and toxic agents; the clinical manifestations may be similar regardless of cause. Hepatitis A virus (HAV) is a 27-nm RNA hepatovirus (in the picornavirus family) that causes epidemics or sporadic cases of hepatitis. HAV infection is hyperendemic in developing countries. Globally, 15 million people are infected with HAV annually. The virus is transmitted by the fecal-oral route by either person-to-person contact or ingestion of contaminated food or water, and its spread is favored by crowding and poor sanitation. Since introduction of the HAV vaccine in the United States in 1995, the incidence rate of HAV infection has declined from as much as 14 to 0.4 per 100,000 population, with a corresponding decline in the mortality rate from 0.1 to 0.02 death per 100,000 population and an increase in the mean age of infection and death. Nevertheless, over 80% of persons aged 20–60 years in the United States are still susceptible to HAV, and vulnerable populations are especially at risk. The highest incidence rate (2.1 per 100,000) is in adults aged 30–39. Common source outbreaks resulting from contaminated food, including inadequately cooked shellfish, or untreated ground water from wells continue to occur, although no drinking water-associated outbreaks have occurred in the United States since 2009. In 2017, an outbreak beginning in California and extending to 33 other states affected a large number of homeless persons and resulted in many deaths. Outbreaks among people who inject drugs or who are unvaccinated residents in institutions and cases among international adoptees and their contacts also occur. In the United States, international travel emerged as an important risk factor, accounting for over 40% of cases in the early 2000s but a lower percentage in the 2010s. Overall, however, reports of HAV infection increased by nearly 300% during 2016–2018 compared to 2013–2015.

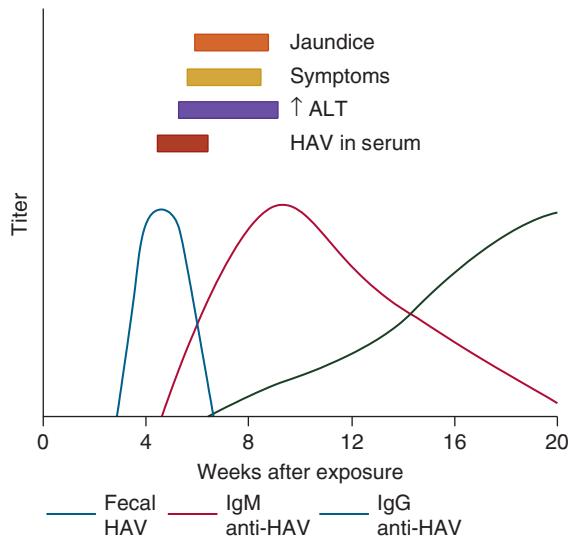
The incubation period averages 30 days. HAV is excreted in feces for up to 2 weeks before clinical illness but rarely after the first week of illness. The mortality rate for hepatitis A is low, and acute liver failure due to hepatitis A is uncommon except for rare instances in which it occurs in a patient with concomitant chronic hepatitis C. There is no chronic carrier state. In the United States, about 30% of the population have serologic evidence of previous HAV infection.

Clinical Findings

A. Symptoms and Signs

Figure 16–1 shows the typical course of acute hepatitis A. Clinical illness is more severe in adults than in children, in whom it is usually asymptomatic. The onset may be abrupt or insidious, with malaise, myalgia, arthralgia, easy fatigability, upper respiratory symptoms, and anorexia. A distaste for smoking, paralleling anorexia, may occur early. Nausea and vomiting are frequent, and diarrhea or constipation may occur. Fever is generally present but is low-grade except in occasional cases in which systemic toxicity may occur. Defervescence and a fall in pulse rate often coincide with the onset of jaundice.

Abdominal pain is usually mild and constant in the right upper quadrant or epigastrium, often aggravated by jarring or exertion, and rarely may be severe enough to simulate cholecystitis. Jaundice occurs after 5–10 days but may appear at the same time as the initial symptoms. In many patients, jaundice never develops. With the onset of jaundice, prodromal symptoms often worsen, followed by progressive clinical improvement. Stools may be acholic



▲ Figure 16-1. The typical course of acute type A hepatitis. (HAV, hepatitis A virus; anti-HAV, antibody to hepatitis A virus; ALT, alanine aminotransferase.) (Reprinted, with permission, from Koff RS. Acute viral hepatitis. In: Friedman LS, Keeffe EB [editors]. *Handbook of Liver Disease*, 4th ed. Philadelphia: Saunders Elsevier, 2018. Copyright © Elsevier.)

during this phase. Hepatomegaly—rarely marked—is present in over half of cases. Liver tenderness is usually present. Splenomegaly is reported in 15% of patients, and soft, enlarged lymph nodes—especially in the cervical or epitrochlear areas—may be noted.

The acute illness usually subsides over 2–3 weeks with complete clinical and laboratory recovery by 9 weeks. In some cases, clinical, biochemical, and serologic recovery may be followed by one or two relapses, but recovery is the rule. Acute cholecystitis occasionally complicates the course of acute hepatitis A. Other occasional extrahepatic complications include acute kidney injury, arthritis, vasculitis, acute pancreatitis, aplastic anemia, and a variety of neurologic manifestations.

B. Laboratory Findings

The white blood cell count is normal to low, especially in the preicteric phase. Large atypical lymphocytes may occasionally be seen. Mild proteinuria is common, and bilirubinuria often precedes the appearance of jaundice. Strikingly elevated ALT or AST levels occur early, followed by elevations of bilirubin and alkaline phosphatase; in a minority of patients, the latter persist after aminotransferase levels have normalized. Cholestasis is occasionally marked. Antibody to hepatitis A (anti-HAV) appears early in the course of the illness (Figure 16–1). Both IgM and IgG anti-HAV are detectable in serum soon after the onset. Peak titers of IgM anti-HAV occur during the first week of clinical disease and usually disappear within 3–6 months. Detection of IgM anti-HAV is an excellent test for diagnosing acute hepatitis A but is not recommended for the evaluation of asymptomatic persons with persistently elevated serum aminotransferase levels because false-positive results occur. False-negative results have been described in a patient receiving rituximab for rheumatoid arthritis. Titers of IgG anti-HAV rise after 1 month of the disease and may persist for years. IgG anti-HAV (in the absence of IgM anti-HAV) indicates previous exposure to HAV, noninfectivity, and immunity.

Differential Diagnosis

The differential diagnosis includes other viruses that cause hepatitis, particularly hepatitis B and C, and diseases such as infectious mononucleosis, cytomegalovirus infection, herpes simplex virus infection, Middle East respiratory syndrome, and infections caused by many other viruses, including influenza, Ebola virus, and SARS-CoV-2; spirochetal diseases such as leptospirosis and secondary syphilis; brucellosis; rickettsial diseases such as Q fever; drug-induced liver injury; and ischemic hepatitis (shock liver). Occasionally, autoimmune hepatitis may have an acute onset mimicking acute viral hepatitis. Rarely, metastatic cancer of the liver, lymphoma, or leukemia may present as a hepatitis-like picture.

The prodromal phase of viral hepatitis must be distinguished from other infectious disease such as influenza and COVID-19, upper respiratory infections, and the prodromal stages of the exanthematous diseases. Cholestasis may mimic obstructive jaundice.

Prevention

Strict isolation of patients is not necessary, but hand washing after bowel movements is required. Unvaccinated persons who are exposed to HAV are advised to receive postexposure prophylaxis with a single dose of HAV vaccine or immune globulin (0.01 mL/kg), or both, within 2 weeks of exposure. The vaccine is preferred in healthy persons aged 1 year to 40 years, whereas immune globulin and the vaccine is preferred in those who are younger than 1 year or older than 40 years, are immunocompromised, or have chronic liver disease.

Vaccination with one of two effective inactivated hepatitis A vaccines available in the United States provides long-term immunity and is recommended for persons living in or traveling to endemic areas (including military personnel), persons over age 40, patients with chronic liver disease upon diagnosis after prescreening for immunity (although the cost-effectiveness of vaccinating all patients with concomitant chronic hepatitis C has been questioned), men who have sex with men, persons with HIV infection, animal handlers, persons who use injection or noninjection drugs, persons experiencing homelessness, persons who are incarcerated, close personal contacts of international adoptees, persons living in group settings for those with developmental disabilities, and persons who request protection against HAV. For healthy travelers, a single dose of vaccine at any time before departure can provide adequate protection. Routine vaccination is advised by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) in all children aged 12–23 months in the United States, with catch-up vaccination for children and adolescents aged 2–18 years who have not previously received the HAV vaccine. HAV vaccine is also effective in the prevention of secondary spread to household contacts of primary cases. The recommended dose for adults is 1 mL (1440 ELISA units) of Havrix (GlaxoSmithKline) or 1 mL (50 units) of Vaqta (Merck) intramuscularly, followed by a booster dose at 6–18 months. A combined hepatitis A and B vaccine (Twinrix, GlaxoSmithKline) is available. HIV infection impairs the response to the HAV vaccine, especially in persons with a CD4 count less than 200/mcL ($0.2 \times 10^9/L$).

Treatment

Bed rest is recommended only if symptoms are marked. If nausea and vomiting are pronounced or if oral intake is substantially decreased, intravenous 10% glucose is indicated.

Dietary management consists of palatable meals as tolerated, without overfeeding; breakfast is usually tolerated best. Strenuous physical exertion, alcohol, and hepatotoxic agents should be avoided. Small doses of oxazepam are safe because metabolism is not hepatic; morphine sulfate should be avoided.

Corticosteroids have no benefit in patients with viral hepatitis, including those with acute liver failure.

Prognosis

In most patients, clinical recovery is generally complete within 3 months. Laboratory evidence of liver dysfunction

may persist for a longer period, but most patients recover completely. Hepatitis A does not cause chronic liver disease, although it may persist for up to 1 year, and clinical and biochemical relapses may occur before full recovery. The mortality rate is less than 1.0%, with a higher rate in older adults than in younger persons.

► When to Admit

- Encephalopathy is present.
- International normalized ratio (INR) greater than 1.6.
- The patient is unable to maintain hydration.

Desai AN et al. Management of hepatitis A in 2020–2021. *JAMA*. 2020;324:383. [PMID: 32628251]

Freedman M et al. Recommended adult immunization schedule, United States, 2020. *Ann Intern Med*. 2020;172:337. [PMID: 32016359]

Nelson NP et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR Recomm Rep*. 2020;69:1. [PMID: 32614811]

ACUTE HEPATITIS B



ESSENTIALS OF DIAGNOSIS

- ▶ Prodrome of anorexia, nausea, vomiting, malaise, aversion to smoking.
- ▶ Fever, enlarged and tender liver, jaundice.
- ▶ Normal to low white blood cell count; markedly elevated aminotransferases early in the course.
- ▶ Liver biopsy shows hepatocellular necrosis and mononuclear infiltrate but is rarely indicated.

► General Considerations

Hepatitis B virus (HBV) is a 42-nm hepadnavirus with a partially double-stranded DNA genome, inner core protein (hepatitis B core antigen, HBcAg), and outer surface coat (hepatitis B surface antigen, HBsAg). There are 10 different genotypes (A–J), which may influence the course of infection and responsiveness to antiviral therapy. HBV is usually transmitted by inoculation of infected blood or blood products or by sexual contact and it is present in saliva, semen, and vaginal secretions. HBsAg-positive mothers may transmit HBV at delivery; the risk of chronic infection in the infant is as high as 90%.

Since 1990, the incidence of HBV infection in the United States has decreased from 8.5 to 1.5 cases per 100,000 population. The prevalence is 0.27% in persons aged 6 or older. Because of universal vaccination since 1992, exposure to HBV is now very low among persons aged 18 or younger. HBV is prevalent in men who have sex with men and in people who inject drugs (about 7% of HIV-infected persons are coinfecte^d with HBV), but the greatest number of cases result from heterosexual

transmission. Other groups at risk include patients and staff at hemodialysis centers, physicians, dentists, nurses, and personnel working in clinical and pathology laboratories and blood banks. Half of all patients with acute hepatitis B in the United States have previously been incarcerated or treated for a sexually transmitted disease. The risk of HBV infection from a blood transfusion in the United States is no higher than 1 in 350,000 units transfused. Screening for HBV infection is recommended for high-risk groups by the US Preventive Services Task Force.

The incubation period of hepatitis B is 6 weeks to 6 months (average 12–14 weeks). The onset of hepatitis B is more insidious, and the aminotransferase levels are higher on average, than in HAV infection. Acute liver failure occurs in less than 1%, with a mortality rate of up to 60%. Following acute hepatitis B, HBV infection persists in 1–2% of immunocompetent adults, but in a higher percentage of children and immunocompromised adults. There are an estimated 1.59 (range, 1.25–2.49) million persons (including an estimated 1.32 million foreign-born persons from endemic areas) with chronic hepatitis B in the United States and 248 million worldwide. Compared with the general population, the prevalence of chronic HBV infection is increased 2- to 3-fold in non-Hispanic Blacks and 10-fold in Asians. Persons with chronic hepatitis B, particularly when HBV infection is acquired early in life and viral replication persists, are at substantial risk for cirrhosis and hepatocellular carcinoma (up to 25–40%); men are at greater risk than women.

► Clinical Findings

A. Symptoms and Signs

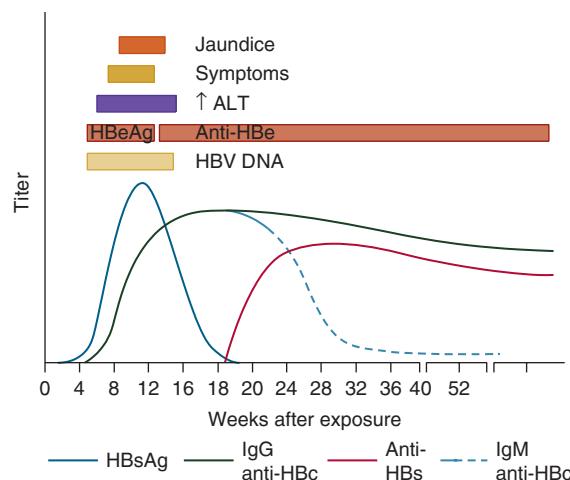
The clinical picture of viral hepatitis is extremely variable, ranging from asymptomatic infection without jaundice to acute liver failure and death in a few days to weeks. Figure 16–2 shows the typical course of acute HBV infection. The onset may be abrupt or insidious, and the clinical features are similar to those for acute hepatitis A. Serum sickness may be seen early in acute hepatitis B. Fever is generally present and is low-grade. Defervescence and a fall in pulse rate often coincide with the onset of jaundice. Infection caused by HBV may be associated with glomerulonephritis and polyarteritis nodosa.

The acute illness usually subsides over 2–3 weeks with complete clinical and laboratory recovery by 16 weeks. In 5–10% of cases, the course may be more protracted, but less than 1% will develop acute liver failure. Hepatitis B may become chronic.

B. Laboratory Findings

The laboratory features are similar to those for acute hepatitis A, although serum aminotransferase levels are higher on average in acute hepatitis B, and marked cholestasis is not a feature. Marked prolongation of the prothrombin time in severe hepatitis correlates with increased mortality.

There are several antigens and antibodies as well as HBV DNA that relate to HBV infection and that are useful



▲ Figure 16-2. The typical course of acute type B hepatitis. (anti-HBs, antibody to HBsAg; HBeAg, hepatitis Be antigen; HBsAg, hepatitis B surface antigen; anti-HBe, antibody to HBeAg; anti-HBc, antibody to hepatitis B core antigen; ALT, alanine aminotransferase.) (Reprinted, with permission, from Koff RS. Acute viral hepatitis. In: Friedman LS, Keeffe EB [editors]. *Handbook of Liver Disease*, 3rd ed. Philadelphia: Saunders Elsevier, 2012. Copyright © Elsevier.)

in diagnosis. Interpretation of common serologic patterns is shown in Table 16-5.

1. HBsAg—The appearance of HBsAg in serum is the first evidence of infection, appearing before biochemical evidence of liver disease, and persisting throughout the clinical illness. Persistence of HBsAg more than 6 months after the acute illness signifies chronic hepatitis B.

2. Anti-HBs—Specific antibody to HBsAg (anti-HBs) appears in most individuals after clearance of HBsAg and after successful vaccination against hepatitis B. Disappearance of HBsAg and the appearance of anti-HBs signal

recovery from HBV infection, noninfectivity, and immunity.

3. Anti-HBc—IgM anti-HBc appears shortly after HBsAg is detected. In the setting of acute hepatitis, IgM anti-HBc indicates a diagnosis of acute hepatitis B, and it fills the serologic gap in rare patients who have cleared HBsAg but do not yet have detectable anti-HBs. IgM anti-HBc can persist for 3–6 months, and sometimes longer. IgM anti-HBc may also reappear during flares of previously inactive chronic hepatitis B. IgG anti-HBc also appears during acute hepatitis B but persists indefinitely, whether the patient recovers (with the appearance of anti-HBs in serum) or chronic hepatitis B develops (with persistence of HBsAg). In asymptomatic blood donors, an isolated anti-HBc with no other positive HBV serologic results may represent a falsely positive result or latent infection in which HBV DNA is detectable in serum only by polymerase chain reaction (PCR) testing.

4. HBeAg—HBeAg is a secretory form of HBcAg that appears in serum during the incubation period shortly after the detection of HBsAg. HBeAg indicates viral replication and infectivity. Persistence of HBeAg beyond 3 months indicates an increased likelihood of chronic hepatitis B. Its disappearance is often followed by the appearance of anti-HBe, generally signifying diminished viral replication and decreased infectivity.

5. HBV DNA—The presence of HBV DNA in serum generally parallels the presence of HBeAg, although HBV DNA is a more sensitive and precise marker of viral replication and infectivity. In some patients with chronic hepatitis B, HBV DNA is present at high levels without HBeAg in serum because of development of a mutation in the core promoter or precore region of the gene that codes HBcAg; these mutations prevent synthesis of HBeAg in infected hepatocytes. When additional mutations in the core gene are also present, the severity of HBV infection is enhanced and the risk of cirrhosis is increased.

Table 16-5. Common serologic patterns in hepatitis B virus (HBV) infection and their interpretation.

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBc	Interpretation
+	-	IgM	+	-	Acute hepatitis B
+	-	IgG ¹	+	-	Chronic hepatitis B with active viral replication
+	-	IgG	-	+	Inactive HBV carrier state (low HBV DNA level) or HBeAg-negative chronic hepatitis B with active viral replication (high HBV DNA level)
+	+	IgG	+ or -	+ or -	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)
-	-	IgM	+ or -	-	Acute hepatitis B
-	+	IgG	-	+ or -	Recovery from hepatitis B (immunity)
-	+	-	-	-	Vaccination (immunity)
-	-	IgG	-	-	False-positive; less commonly, infection in remote past

¹Low levels of IgM anti-HBc may also be detected.

► Differential Diagnosis

The differential diagnosis includes hepatitis A and the same disorders listed for the differential diagnosis of acute hepatitis A. In addition, coinfection with HDV must be considered.

► Prevention

Strict isolation of patients is not necessary. Thorough hand washing by medical staff who may contact contaminated utensils, bedding, or clothing is essential. Medical staff should handle disposable needles carefully and not recap them. Screening of donated blood for HBsAg, anti-HBc, and anti-HCV has reduced the risk of transfusion-associated hepatitis markedly. All pregnant women should undergo testing for HBsAg. HBV-infected persons should practice safe sex. Immunoprophylaxis of the neonate reduces the risk of perinatal transmission of HBV infection; when the mother's serum HBV DNA level is 200,000 international units/mL or higher (or the mother's serum HBsAg level is above $4-4.5 \log_{10}$ international units/mL), antiviral treatment of the mother should also be initiated in the third trimester (see Chronic Hepatitis B & Chronic Hepatitis D). HBV-infected health care workers are not precluded from practicing medicine or dentistry if they follow CDC guidelines.

Hepatitis B immune globulin (HBIG) may be protective—or may attenuate the severity of illness—if given within 7 days after exposure (adult dose is 0.06 mL/kg body weight) followed by initiation of the HBV vaccine series. This approach is recommended for unvaccinated persons exposed to HBsAg-contaminated material via mucous membranes or through breaks in the skin and for individuals who have had sexual contact with a person with HBV infection (irrespective of the presence or absence of HBeAg in the source). HBIG is also indicated for newborn infants of HBsAg-positive mothers, with initiation of the vaccine series at the same time, both within 12 hours of birth (administered at different injection sites).

The CDC recommends HBV vaccination of all infants and children in the United States and all adults who are at risk for hepatitis B (including persons under age 60 with diabetes mellitus) or who request vaccination; the vaccine appears to be underutilized in adults for whom vaccination is recommended. Over 90% of recipients of the vaccine mount protective antibody to hepatitis B; immunocompromised persons, including patients receiving dialysis (especially those with diabetes mellitus), respond poorly (see Table 30–7). Reduced response to the vaccine may have a genetic basis in some cases and has also been associated with age over 40 years and celiac disease. The standard regimen for adults is 10–20 mcg (depending on the formulation) repeated again at 1 and 6 months, but alternative schedules have been approved, including accelerated schedules of 0, 1, 2, and 12 months and of 0, 7, and 21 days plus 12 months. For greatest reliability of absorption, the deltoid muscle is the preferred site of inoculation. Vaccine formulations free of the mercury-containing preservative thimerosal are given to infants under 6 months of age. A newer vaccine, Heplisav-B, which uses a novel immune system-stimulating ingredient, was approved by the FDA

for adults in 2017. Immunization requires only two injections, and Heplisav-B appears to be more effective than previous HBV vaccines. When documentation of seroconversion is considered desirable, postimmunization anti-HBs titers may be checked. Protection appears to be excellent even if the titer wanes—persisting for at least 20 years—and booster reimmunization is not routinely recommended but is advised for immunocompromised persons in whom anti-HBs titers fall below 10 milli-international units/mL. For vaccine nonresponders, three additional vaccine doses may elicit seroprotective anti-HBs levels in 30–50% of persons. Doubling of the standard dose may also be effective. Universal vaccination of neonates in countries endemic for HBV has reduced the incidence of hepatocellular carcinoma. Incomplete immunization is the most important predictor of liver disease among vaccinees. Unfortunately, approximately 64 million high-risk adults in the United States remain susceptible to HBV.

► Treatment

Treatment of acute hepatitis B is the same as that for acute hepatitis A. Encephalopathy or severe coagulopathy indicates acute liver failure, and hospitalization at a liver transplant center is mandatory. Antiviral therapy is generally unnecessary in patients with acute hepatitis B but is usually prescribed in cases of acute liver failure caused by HBV as well as in spontaneous reactivation of chronic hepatitis B presenting as acute-on-chronic liver failure (see Acute Liver Failure).

► Prognosis

In most patients, clinical recovery is complete in 3–6 months. Laboratory evidence of liver dysfunction may persist for a longer period, but most patients recover completely. The mortality rate for acute hepatitis B is 0.1–1% but is higher with superimposed hepatitis D.

Chronic hepatitis, characterized by elevated aminotransferase levels for more than 3–6 months, develops in 1–2% of immunocompetent adults with acute hepatitis B, but in as many as 90% of infected neonates and infants and a substantial proportion of immunocompromised adults. Ultimately, cirrhosis develops in up to 40% of those with chronic hepatitis B; the risk of cirrhosis is even higher in HBV-infected patients coinfecting with hepatitis C or HIV. Patients with cirrhosis are at risk for hepatocellular carcinoma at a rate of 3–5% per year. Even in the absence of cirrhosis, patients with chronic hepatitis B—particularly those with active viral replication—are at increased risk for hepatocellular carcinoma.

► When to Refer

Refer patients with acute hepatitis who require liver biopsy for diagnosis.

► When to Admit

- Encephalopathy is present.
- INR greater than 1.6.
- The patient is unable to maintain hydration.

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- Hwang JP et al. USPSTF 2020 Hepatitis B Screening Recommendation: evidence to broaden screening and strengthen linkage to care. *JAMA*. 2020;324:2380. [PMID: 33320206]
- Lim JK et al. Prevalence of chronic hepatitis B virus infection in the United States. *Am J Gastroenterol*. 2020;115:1429. [PMID: 32483003]
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- US Preventive Services Task Force; Owens DK et al. Screening for hepatitis B virus infection in pregnant women: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2019;322:349. [PMID: 31334800]

ACUTE HEPATITIS C & OTHER CAUSES OF ACUTE VIRAL HEPATITIS

Viruses other than HAV and HBV that can cause hepatitis are hepatitis C virus (HCV), hepatitis D virus (HDV) (delta agent), and hepatitis E virus (HEV) (an enterically transmitted hepatitis seen in epidemic form in Asia, the Middle East, and North Africa and sporadically in Western countries). Human pegivirus (formerly hepatitis G virus [HGV]) rarely, if ever, causes frank hepatitis. A related virus has been named human hepegivirus-1. A DNA virus designated the TT virus (TTV) has been identified in up to 7.5% of blood donors and found to be transmitted readily by blood transfusions, but an association between this virus and liver disease has not been established. A related virus known as SEN-V has been found in 2% of US blood donors, is transmitted by transfusion, and may account for some cases of transfusion-associated non-ABCDE hepatitis. In immunocompromised and rare immunocompetent persons, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus should be considered in the differential diagnosis of hepatitis. Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), SARS coronavirus infection (SARS-CoV-2), Ebola virus infection, and influenza may be associated with elevated serum aminotransferase levels (occasionally marked). Unidentified pathogens account for a small percentage of cases of acute viral hepatitis.

1. Hepatitis C

HCV is a single-stranded RNA virus (hepacivirus) with properties similar to those of flaviviruses. Seven major genotypes of HCV have been identified. In the past, HCV was responsible for over 90% of cases of posttransfusion hepatitis, yet only 4% of cases of hepatitis C were attributable to blood transfusions. Over 50% of cases are transmitted by injection drug use, and both reinfection and superinfection of HCV are common in people who actively inject drugs. Body piercing, tattoos, and hemodialysis are risk factors. The risk of sexual and maternal-neonatal transmission is low and may be greatest in a subset of patients with high circulating levels of HCV RNA. Having multiple sexual partners may increase the risk of HCV

infection, and HIV coinfection, unprotected receptive anal intercourse with ejaculation, and sex while high on methamphetamine increase the risk of HCV transmission in men who have sex with men. Transmission via breastfeeding has not been documented. An outbreak of hepatitis C in patients with immune deficiencies has occurred in some recipients of intravenous immune globulin. Hospital- and outpatient facility-acquired transmission has occurred via multidose vials of saline used to flush Portacaths; through reuse of disposable syringes; through drug “diversion” and tampering with injectable opioids by an infected health care worker; through contamination of shared saline, radiopharmaceutical, and sclerosant vials; via inadequately disinfected endoscopy equipment; and between hospitalized patients on a liver unit. In the developing world, unsafe medical practices lead to a substantial number of cases of HCV infection. Covert transmission during bloody fisticuffs has even been reported, and incarceration in prison is a risk factor, with a seroprevalence of 26% in the United States and rates as high as 90% in some states. In many patients, the source of infection is unknown. Coinfection with HCV is found in at least 30% of HIV-infected persons. HIV infection leads to an increased risk of acute liver failure and more rapid progression of chronic hepatitis C to cirrhosis; in addition, HCV increases the hepatotoxicity of antiretroviral therapy. The number of cases of chronic HCV infections in the United States is reported to have decreased from 3.2 million in 2001 to 2.3 million in 2013 with a small increase to 2.4 million between 2013 and 2016, although estimates of at least 4.6 million exposed and 3.5 million currently infected have also been reported. The incidence of new cases of acute, symptomatic hepatitis C declined from 1992 to 2005, but an increase was observed in persons aged 15 to 24 after 2002, as a result of injection drug use, with a 3.8-fold increase in overall incidence since 2010. An increase has also been observed in women of reproductive age. Worldwide, 71 million people are infected with HCV, with the highest rates in Central and East Asia, North Africa, and the Middle East.

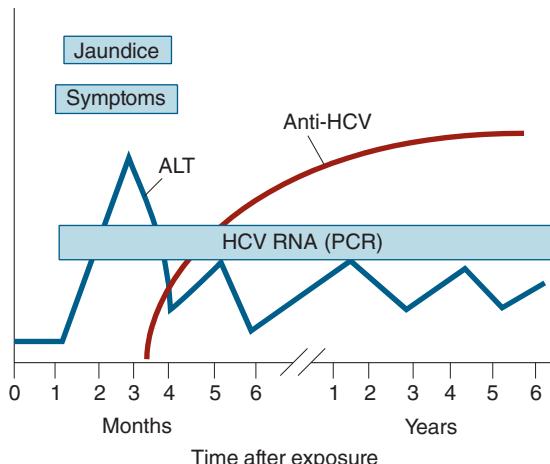
Clinical Findings

A. Symptoms and Signs

Figure 16–3 shows the typical course of HCV infection. The incubation period for hepatitis C averages 6–7 weeks, and clinical illness is often mild, usually asymptomatic, and characterized by waxing and waning aminotransferase elevations and a high rate (greater than 80%) of chronic hepatitis. Spontaneous clearance of HCV following acute infection is more common (64%) in persons with the CC genotype of the *IFNL3* (*IL28B*) gene than in those with the CT or TT genotype (24% and 6%, respectively). In persons with the CC genotype, jaundice is more likely to develop during the course of acute hepatitis C. In pregnant patients with chronic hepatitis C, serum aminotransferase levels frequently normalize despite persistence of viremia, only to increase again after delivery.

B. Laboratory Findings

Diagnosis of hepatitis C is based on an enzyme immunoassay (EIA) that detects antibodies to HCV. Anti-HCV is not



▲ Figure 16-3. The typical course of acute and chronic hepatitis C. (ALT, alanine aminotransferase; Anti-HCV, antibody to hepatitis C virus by enzyme immunoassay; HCV RNA [PCR], hepatitis C viral RNA by polymerase chain reaction.)

protective, and in patients with acute or chronic hepatitis, its presence in serum generally signifies that HCV is the cause. Limitations of the EIA include moderate sensitivity (false-negatives) for the diagnosis of acute hepatitis C early in the course and low specificity (false-positives) in some persons with elevated gamma-globulin levels. A diagnosis of hepatitis C may be confirmed by using an assay for HCV RNA. Occasional persons are found to have anti-HCV without HCV RNA in the serum, suggesting recovery from HCV infection in the past.

► Complications

HCV is a pathogenic factor in mixed cryoglobulinemia and membranoproliferative glomerulonephritis and may be related to lichen planus, autoimmune thyroiditis, lymphocytic sialadenitis, idiopathic pulmonary fibrosis, sporadic porphyria cutanea tarda, and monoclonal gammopathies. HCV infection confers a 20–30% or more increased risk of non-Hodgkin lymphoma, and chronic HCV infection (especially genotype 1) is associated with an increased risk of end-stage renal disease. Hepatic steatosis is a particular feature of infection with HCV genotype 3 and may also occur in patients infected with other HCV genotypes who have risk factors for fatty liver. On the other hand, chronic HCV infection is associated with a decrease in serum cholesterol and low-density lipoprotein levels.

► Prevention

Testing donated blood for HCV has helped reduce the risk of transfusion-associated hepatitis C from 10% in 1990 to about 1 case per 2 million units in 2011. The US Preventive Services Task Force recommends that asymptomatic adults ages 18–79 be screened for HCV infection. The CDC recommends HCV screening for all persons over age 18 at least once in a lifetime and all pregnant women (in both cases except in settings where the prevalence of HCV infection is

less than 0.1% [very rare]). Screening of all pregnant women for HCV infection has also been recommended by professional societies. HCV-infected persons should practice safe sex, but there is little evidence that HCV is spread easily by sexual contact or perinatally, and no specific preventive measures are recommended for persons in a monogamous relationship or for pregnant women. Because a majority of cases of HCV infection are acquired by injection drug use, public health officials have recommended avoidance of shared needles and access to needle exchange programs for injection drug users. As yet, there is no vaccine for HCV. Vaccination against HAV (after prescreening for prior immunity) and HBV is recommended for patients with chronic hepatitis C, just as vaccination against HAV is recommended for patients with chronic hepatitis B.

► Treatment

In the past, treatment of patients with acute hepatitis C with a peginterferon-based regimen for 6–24 weeks was shown to appreciably decrease the risk of chronic hepatitis in patients in whom serum HCV RNA levels had failed to clear spontaneously after 3 months. Oral direct-acting agents have supplanted interferon-based therapy (see Chronic Viral Hepatitis), and a 6-week course of ledipasvir and sofosbuvir has been shown to prevent chronic hepatitis in patients with acute genotype-1 hepatitis C. Treatment of acute hepatitis C may be cost effective.

► Prognosis

In most patients, clinical recovery is complete in 3–6 months. Laboratory evidence of liver dysfunction may persist for a longer period. The overall mortality rate is less than 1%, but the rate is reportedly higher in older people. Acute liver failure due to HCV is rare in the United States.

Chronic hepatitis, which progresses very slowly in many cases, develops in as many as 85% of all persons with acute hepatitis C. Ultimately, cirrhosis develops in up to 30% of those with chronic hepatitis C; the risk of cirrhosis and hepatic decompensation is higher in patients coinfected with both HCV and HBV or HIV. Patients with cirrhosis are at risk for hepatocellular carcinoma at a rate of 3–5% per year. Long-term morbidity and mortality in patients with chronic hepatitis C is lower in Black than in White patients and lowest in those infected with HCV genotype 2 and highest in those with HCV genotype 3.

Awan AA et al. Hepatitis C in chronic kidney disease: an overview of the KDIGO Guideline. *Clin Gastroenterol Hepatol.* 2020;18:2158. [PMID: 31376491]

Schillie S et al. CDC recommendations for hepatitis C screening among adults—United States, 2020. *MMWR Recomm Rep.* 2020;69:1. [PMID: 32271723]

Spearman CW et al. Hepatitis C. *Lancet.* 2019;394:1451. [PMID: 31631857]

2. Hepatitis D (Delta Agent)

HDV is a defective RNA virus that causes hepatitis only in association with HBV infection and specifically only in the presence of HBsAg; it is cleared when the latter is cleared.

HDV may coinfect with HBV or may superinfect a person with chronic hepatitis B, usually by percutaneous exposure. When acute hepatitis D is coincident with acute HBV infection, the infection is generally similar in severity to acute hepatitis B alone. In chronic hepatitis B, superinfection by HDV appears to carry a worse short-term prognosis, often resulting in acute liver failure or severe chronic hepatitis that progresses rapidly to cirrhosis.

New cases of hepatitis D are infrequent in the United States primarily because of the control of HBV infection (although rates of testing HBV carriers for HDV are inappropriately low), and cases seen today are usually from cohorts infected years ago who survived the initial impact of hepatitis D and now have cirrhosis. These patients are at risk for decompensation and have a threefold increased risk of hepatocellular carcinoma. HDV is estimated to cause 18% of cases of cirrhosis and 20% of cases of hepatocellular carcinoma associated with HBV infection. New cases are seen primarily in immigrants from endemic areas, including Africa, Central Asia, Eastern Europe, and the Amazon region of Brazil. As many as 13% of HBV carriers are infected with HDV worldwide; principal risk factors are injecting drug use, high-risk sexual behavior, and HIV and HCV coinfections. The diagnosis of hepatitis D is made by detection of antibody to hepatitis D antigen (anti-HDV) and, where available, hepatitis D antigen (HDAg) or HDV RNA in serum.

3. Hepatitis E

HEV is a 27- to 34-nm RNA hepevirus (in the Hepeviridae family) that is a major cause of acute hepatitis throughout Central and Southeast Asia (about 16% of the population there have antibodies to the virus), and it should be considered in patients with acute hepatitis after a trip to an endemic area. In rare cases, hepatitis E can be mistaken for drug-induced liver injury. In industrialized countries, it may be spread by swine, and having a pet in the home and consuming undercooked organ meats or infected cow's milk are risk factors. The risk appears to be increased in patients undergoing hemodialysis.

Illness generally is self-limited (no carrier state), but instances of chronic hepatitis with rapid progression to cirrhosis attributed to HEV genotype 3 have been reported in transplant recipients (particularly when tacrolimus rather than cyclosporine is used as the main immunosuppressant) and, rarely, in persons with HIV infection, preexisting liver disease, or cancer undergoing chemotherapy. The diagnosis of acute hepatitis E is made most readily by testing for IgM anti-HEV in serum, although available tests may not be reliable.

Reported extrahepatic manifestations include arthritis; pancreatitis; thyroiditis; myocarditis; glomerulonephritis; monoclonal gammopathy; thrombocytopenia; aplastic anemia; a variety of neurologic complications, including Guillain-Barré syndrome and neuralgic amyotrophy (which involves the brachial plexuses bilaterally); and hemophagocytic lymphohistiocytosis. In endemic regions, the mortality rate is high (15–25%) in pregnant women and correlates with high levels of HEV RNA in serum and gene mutations that lead to reduced expression of

progesterone receptors. The risk of hepatic decompensation and death is increased in patients with underlying chronic liver disease.

A 3-month course of treatment with oral ribavirin has been reported to induce sustained clearance of HEV RNA from the serum in 78% of patients with persistent HEV infection and may be considered in patients with severe acute hepatitis E. Improved public hygiene reduces the risk of HEV infection in endemic areas. Recombinant vaccines against HEV have shown promise in clinical trials, and one (Hecolin) is approved in China.

Whitsett M et al. Hepatitis E virus infection in the United States: current understanding of the prevalence and significance in the liver transplant patient population and proposed diagnostic and treatment strategies. *Liver Transpl*. 2020;26:709. [PMID: 32061053]

ACUTE LIVER FAILURE

ESSENTIALS OF DIAGNOSIS

- ▶ May be fulminant or subfulminant; both forms carry a poor prognosis.
- ▶ Acetaminophen and idiosyncratic drug reactions are the most common causes.

► General Considerations

Acute liver failure may be fulminant or subfulminant. Fulminant hepatic failure is characterized by the development of hepatic encephalopathy within 8 weeks after the onset of acute liver injury. Coagulopathy (INR 1.5 or higher) is invariably present. Subfulminant hepatic failure occurs when these findings appear between 8 weeks and 6 months after the onset of acute liver injury and carries an equally poor prognosis. Acute-on-chronic liver failure refers to acute deterioration in liver function (often caused by infection) and associated failure of other organs in a person with preexisting chronic liver disease.

An estimated 1600 cases of acute liver failure occur each year in the United States. Toxicity caused by acetaminophen (a direct hepatotoxin) is the most common cause, accounting for at least 45% of cases. Suicide attempts account for 44% of cases of acetaminophen-induced hepatic failure, and unintentional overdoses ("therapeutic misadventures"), which are often a result of a decrease in the threshold toxic dose because of chronic alcohol use or fasting and have been reported after weight loss surgery, account for at least 48%. Other causes include idiosyncratic (in some cases, immune-mediated) drug reactions (the second most common cause, with antibiotics, antituberculosis drugs, and antiepileptics implicated most commonly), viral hepatitis, poisonous mushrooms (*Amanita phalloides*), shock, heat stroke, Budd-Chiari syndrome, malignancy (most commonly lymphomas), Wilson disease, Reye syndrome, fatty liver of pregnancy and other disorders of fatty acid oxidation, autoimmune hepatitis, parvovirus B19

infection, and rarely grand mal seizures. The cause is indeterminate in approximately 5.5% of cases. The risk of acute liver failure is increased in patients with diabetes mellitus, and outcome is worsened by obesity. Herbal and dietary supplements are thought to be contributory to acute liver failure in a substantial portion of cases, regardless of cause, and may be associated with lower rates of transplant-free survival. Acute-on-chronic liver failure is often precipitated by a bacterial infection or an alcohol binge and alcohol-associated hepatitis.

Viral hepatitis now accounts for only 12% of all cases of acute liver failure. The decline of viral hepatitis as the principal cause of acute liver failure is due to universal vaccination of infants and children against hepatitis B and the availability of the hepatitis A vaccine. Acute liver failure may occur after reactivation of hepatitis B in carriers who receive immunosuppressive therapy. In endemic areas, hepatitis E is an important cause of acute liver failure, particularly in pregnant women. Hepatitis C is a rare cause of acute liver failure in the United States, but acute hepatitis A or B superimposed on chronic hepatitis C may cause acute liver failure.

► Clinical Findings

Gastrointestinal symptoms, systemic inflammatory response, and kidney dysfunction are common. Clinically significant bleeding is uncommon and reflects severe systemic inflammation rather than coagulopathy. Adrenal insufficiency and subclinical myocardial injury (manifesting as an elevated serum troponin I level) often complicate acute liver failure. Jaundice may be absent or minimal early in the course, but laboratory tests show severe hepatocellular damage. In acetaminophen toxicity, serum aminotransferase elevations are often towering (greater than 5000 units/L), and acetaminophen is undetectable in plasma in 50% of cases. In acute liver failure due to microvesicular steatosis (eg, fatty liver of pregnancy), serum aminotransferase elevations may be modest (less than 300 units/L). Over 10% of patients have an elevated serum amylase level at least three times the upper limit of normal, often as a result of renal dysfunction. The blood ammonia level is typically elevated and correlates (along with the Model for End-Stage Liver Disease [MELD] score) with the development of encephalopathy and intracranial hypertension. Intracranial hypertension rarely develops when the blood ammonia level is less than 75 $\mu\text{mol}/\text{L}$ and is invariable when it is greater than 200 $\mu\text{mol}/\text{L}$. The severity of extrahepatic organ dysfunction (as assessed by the Sequential Organ Failure Assessment [SOFA]) also correlates with the likelihood of intracranial hypertension. Acute kidney injury frequently complicates acute-on-chronic liver failure.

► Treatment

The treatment of acute liver failure is directed toward achieving metabolic and hemodynamic stability. Intravascular volume should be preserved, but large-volume infusions of hypotonic fluids should be avoided. Norepinephrine is the preferred vasopressor; vasopressin may be added for persistent hypotension. Hypoglycemia should be

prevented. Intermittent renal replacement therapy may be required. To preserve muscle mass and immune function, enteral administration of protein, 1–1.5 g/kg/day, is advised, with careful monitoring of the ammonia level.

Cerebral edema and sepsis are the leading causes of death. Prophylactic antibiotic therapy decreases the risk of infection, observed in up to 90%, but has no effect on survival and is not routinely recommended. Microbiological screening cultures should be obtained for patients admitted to hospital. For suspected sepsis, broad coverage is indicated. Despite a high rate of adrenal insufficiency, corticosteroids do not reduce mortality and may lower overall survival in patients with a high MELD score, although they may reduce vasopressor requirements. Stress gastropathy prophylaxis with an H₂-receptor blocker or proton pump inhibitor is recommended. Administration of acetylcysteine (140 mg/kg orally followed by 70 mg/kg orally every 4 hours for an additional 17 doses or 150 mg/kg in 5% dextrose intravenously over 15 minutes followed by 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours) prevents acetaminophen toxicity if administered within 12 hours of ingestion and may be beneficial when given up to 72 hours after ingestion. For massive acetaminophen overdoses, treatment with intravenous acetylcysteine may need to be extended in duration until the serum aminotransferase levels are declining and serum acetaminophen levels are undetectable. Treatment with acetylcysteine improves cerebral blood flow and oxygenation as well as transplant-free survival in patients with stage 1 or 2 encephalopathy due to acute liver failure of any cause. (Acetylcysteine treatment can prolong the prothrombin time, leading to the erroneous assumption that liver failure is worsening; it can also cause nausea, vomiting, and an anaphylactoid reaction [especially in persons with a history of asthma].) Penicillin G (300,000 to 1 million units/kg/day) or silibinin (silymarin or milk thistle), which is not licensed in the United States, is administered to patients with mushroom poisoning. Nucleoside analogs are recommended for patients with acute liver failure caused by HBV (see Chronic Viral Hepatitis), and intravenous acyclovir has shown benefit in those with herpes simplex virus hepatitis. Plasmapheresis combined with D-penicillamine has been used in acute liver failure due to Wilson disease. Subclinical seizure activity is common in patients with acute liver failure, but the value of prophylactic phenytoin is uncertain.

Early transfer to a liver transplantation center is essential. The head of the patient's bed should be elevated to 30 degrees, and patients with stage 3 or 4 encephalopathy should be intubated. In some centers, extradural sensors are placed in patients at high risk for intracranial hypertension to monitor intracranial pressure for impending cerebral edema with the goal of maintaining the intracranial pressure below 20 mm Hg and the cerebral perfusion pressure above 70 mm Hg but may be associated with complications. Lactulose is of uncertain value. Mannitol, 0.5 g/kg, or 100–200 mL of a 20% solution by intravenous infusion over 10 minutes, may decrease cerebral edema but should be used with caution in patients with advanced chronic kidney disease. Intravenously administered hypertonic

saline to induce hypernatremia (serum sodium concentration of 145–155 mEq/L [145–155 mmol/L]) also may reduce intracranial hypertension. Hypothermia to a temperature of 32–34°C may reduce intracranial pressure when other measures have failed and may improve survival long enough to permit liver transplantation, although a controlled trial showed no benefit and some authorities recommend a target core temperature of 35–36°C. The value of hyperventilation is uncertain. A short-acting barbiturate, propofol, or intravenous boluses of indomethacin, 25 mg, are considered for refractory intracranial hypertension. Hemodialysis raises intracranial pressure and should be avoided, but continuous renal replacement therapy may be used, if necessary, in patients with acute kidney injury.

► Prognosis

With earlier recognition of acute liver failure, the frequency of cerebral edema has declined, and overall survival has improved steadily since the 1970s and is now as high as 75%. However, the survival rate in acute liver failure with severe encephalopathy is as low as 20%. The cause of liver injury is the most important determinant of transplant-free survival. In acetaminophen hepatotoxicity, the transplant-free survival is 75%, and no more than 8% of patients undergo liver transplantation. Survival rates are also favorable for hepatitis A, ischemic hepatitis, and pregnancy-related liver disease. For patients with acute liver failure not due to acetaminophen, the outlook is poor in patients younger than 10 and older than 40 years of age and in those with an idiosyncratic drug reaction but appears to be improved when acetylcysteine is administered to patients with stage 1 or 2 encephalopathy. Other adverse prognostic factors are a serum bilirubin level greater than 18 mg/dL (307.8 μmol/L), INR higher than 6.5, onset of encephalopathy more than 7 days after the onset of jaundice, and a low factor V level (less than 20% of normal in patients younger than 30 years and 30% or less in those 30 years of age or older). For acetaminophen-induced acute liver failure, indicators of a poor outcome are acidosis ($\text{pH} < 7.3$), INR greater than 6.5, and azotemia (serum creatinine 3.4 mg/dL [283.22 μmol/L] or higher), whereas a rising serum alpha-fetoprotein level predicts a favorable outcome. Other predictors of poor survival in patients with acute liver failure are an elevated blood lactate level (greater than 3.5 mEq/L [3.5 mmol/L]), elevated blood ammonia level (greater than 211 mcg/dL [124 μmol/L]), and possibly hyperphosphatemia (greater than 3.7 mg/dL [1.2 mmol/L]). The development of thrombocytopenia in the first week is associated with the development of multi-organ system failure and a poor outcome. A number of prognostic indices have been proposed: the “BiLE” score, based on the serum bilirubin, serum lactate, and etiology; the Acute Liver Failure Early Dynamic (ALFED) model, based on the arterial ammonia level, serum bilirubin, INR, and hepatic encephalopathy; and the Acute Liver Failure Study Group (ALFSG) index, based on coma grade, INR, serum bilirubin and phosphorous levels, and serum levels of M30, a cleavage product of cytokeratin-18 caspase. The likelihood of transplant-free survival on admission has been reported to be predicted by a regression model that

incorporates the grade of hepatic encephalopathy, etiology, vasopressor use, and log transformations of the serum bilirubin and INR. For acetaminophen-induced acute liver failure, a model that incorporates hepatic encephalopathy grade equal to or greater than 3, Glasgow coma score, cardiovascular failure, mean arterial pressure, INR, serum bilirubin, serum AST, serum creatinine, arterial pH, and arterial lactate has shown good discrimination. In general, emergency liver transplantation is considered for patients with stage 2 to stage 3 encephalopathy or a MELD score of 30.5 or higher (see Cirrhosis) and is associated with a 70% survival rate at 5 years. For mushroom poisoning, liver transplantation should be considered when the interval between ingestion and the onset of diarrhea is less than 8 hours or the INR is 6.0 or higher, even in the absence of encephalopathy. Acute-on-chronic liver failure has a poor prognosis, particularly when associated with kidney dysfunction; some patients may be candidates for liver transplantation.

► When to Admit

All patients with acute liver failure should be hospitalized.

Liukkonen V et al. Role of autoimmunity in patients transplanted for acute liver failure of unknown origin: a clinical and graft biopsy analysis. *Liver Transpl*. 2020;26:764. [PMID: 32034878]

Stravitz RT et al. Acute liver failure. *Lancet*. 2019;394:869. [PMID: 31498101]

CHRONIC VIRAL HEPATITIS

ESSENTIALS OF DIAGNOSIS

- ▶ Defined by chronic infection (HBV, HCV, HDV) for longer than 3–6 months.
- ▶ Diagnosis is usually made by antibody tests and viral nucleic acid in serum.

► General Considerations

Chronic hepatitis is defined as chronic necroinflammation of the liver of more than 3–6 months' duration, demonstrated by persistently elevated serum aminotransferase levels or characteristic histologic findings, often in the absence of symptoms. In many cases, the diagnosis of chronic hepatitis may be made on initial presentation. The causes of chronic hepatitis include HBV, HCV, and HDV as well as autoimmune hepatitis; alcohol-associated and nonalcoholic steatohepatitis; certain medications, such as isoniazid and nitrofurantoin; Wilson disease; alpha-1-anti-protease deficiency; and, rarely, celiac disease. Mortality from chronic HBV and HCV infection has been rising in the United States, and HCV has surpassed HIV as a cause of death. Chronic hepatitis is categorized on the basis of etiology; the grade of portal, periportal, and lobular inflammation (minimal, mild, moderate, or severe); and

the stage of fibrosis (none, mild, moderate, severe, cirrhosis). In the absence of advanced cirrhosis, patients are often asymptomatic or have mild nonspecific symptoms. The World Health Organization has outlined a strategy for eliminating chronic viral hepatitis by 2030 (by measures such as vaccinating against hepatitis B, ensuring blood safety and injection safety, timely birth dosing of hepatitis B vaccine, harm reduction from injecting drug use, and testing and treating persons coinfecte^d with hepatitis viruses and HIV).

1. Chronic Hepatitis B & Chronic Hepatitis D

► Clinical Findings & Diagnosis

Chronic hepatitis B afflicts 248 million people worldwide (2 billion overall have been infected; endemic areas include Asia and sub-Saharan Africa) and an estimated 1.59 (range, 1.25–2.49) million (predominantly males) in the United States. It may be noted as a continuum of acute hepatitis B or diagnosed because of repeated detection of HBsAg in serum, often with elevated aminotransferase levels.

Five phases of chronic HBV infection are recognized: immune tolerant phase, immune active (or immune clearance) phase, inactive HBsAg carrier state, reactivated chronic hepatitis B phase, and the HBsAg-negative phase. In the immune tolerant phase (**HBeAg-positive chronic HBV infection**), HBeAg and HBV DNA are present in serum and are indicative of active viral replication, and serum aminotransferase levels are normal, with little necroinflammation in the liver. This phase is common in infants and young children whose immature immune system fails to mount an immune response to HBV.

Persons in the immune tolerant phase and those who acquire HBV infection later in life may enter an immune active phase (**HBeAg-positive chronic hepatitis B**), in which aminotransferase and HBV DNA levels are elevated and necroinflammation is present in the liver, with a risk of progression to cirrhosis (at a rate of 2–5.5% per year) and of hepatocellular carcinoma (at a rate of more than 2% per year in those with cirrhosis); low-level IgM anti-HBc is present in serum in about 70%.

Patients enter the inactive HBsAg carrier state (**HBeAg-negative chronic HBV infection**) when biochemical improvement follows immune clearance. This improvement coincides with disappearance of HBeAg and reduced HBV DNA levels (less than 10^5 copies/mL, or less than 20,000 international units/mL) in serum, appearance of anti-HBe, and integration of the HBV genome into the host genome in infected hepatocytes. Patients in this phase are at a low risk for cirrhosis (if it has not already developed) and hepatocellular carcinoma, and those with persistently normal serum aminotransferase levels infrequently have histologically significant liver disease, especially if the HBsAg level is low.

The reactivated chronic hepatitis B phase (**HBeAg-negative chronic hepatitis B**) may result from infection by a pre-core mutant of HBV or spontaneous mutation of the pre-core or core promoter region of the HBV genome during the course of chronic hepatitis caused by wild-type

HBV. HBeAg-negative chronic hepatitis B accounts for less than 10% of cases of chronic hepatitis B in the United States, up to 50% in Southeast Asia, and up to 90% in Mediterranean countries, reflecting in part differences in the frequencies of HBV genotypes. In reactivated chronic hepatitis B, there is a rise in serum HBV DNA levels and possible progression to cirrhosis (at a rate of 8–10% per year), particularly when additional mutations in the core gene of HBV are present. Risk factors for reactivation include male sex and HBV genotype C as well as immunosuppression. Treatment of HCV infection with direct-acting antiviral agents has been reported to lead to instances of HBV reactivation.

In patients with either HBeAg-positive or HBeAg-negative chronic hepatitis B, the risk of cirrhosis and of hepatocellular carcinoma correlates with the serum HBV DNA level. Other risk factors include advanced age, male sex, alcohol use, cigarette smoking, HBV genotype C, and coinfection with HCV or HDV. HIV coinfection is also associated with an increased frequency of cirrhosis when the CD4 count is low.

Only 1% of treated and untreated patients per year reach the **HBsAg-negative phase**, in which anti-HBe may remain, serum ALT levels are normal, and HBV DNA is undetectable in serum but remains present in the liver. This phase is also referred to as a “functional cure.” In some cases, anti-HBs appears in serum.

Acute **hepatitis D** infection superimposed on chronic HBV infection may result in severe chronic hepatitis, which may progress rapidly to cirrhosis and may be fatal. Patients with long-standing chronic hepatitis D and B often have inactive cirrhosis and are at risk for decompensation and hepatocellular carcinoma. The diagnosis is confirmed by detection of anti-HDV or HDAg (or HDV RNA) in serum.

► Treatment

Patients with active viral replication (HBeAg and HBV DNA [10^5 copies/mL or more, or 20,000 international units/mL or more] in serum and elevated aminotransferase levels) may be treated with a nucleoside or nucleotide analog or with pegylated interferon. Nucleoside and nucleotide analogs are preferred because they are better tolerated and can be taken orally. For patients who are HBeAg-negative, the threshold for treatment is a serum HBV DNA level of 10^4 copies/mL, or 2000 international units/mL. If the threshold HBV DNA level for treatment is met but the serum ALT level is normal, treatment may still be considered in patients over age 35–40 if liver biopsy or a noninvasive assessment of liver fibrosis demonstrates a fibrosis stage of 2 of 4 (moderate) or higher. Therapy is aimed at reducing and maintaining the serum HBV DNA level to the lowest possible levels, thereby leading to normalization of the ALT level and histologic improvement. An additional goal in HBeAg-positive patients is seroconversion to anti-HBe, and some responders eventually clear HBsAg. Although nucleoside and nucleotide analogs generally have been discontinued 6–12 months after HBeAg-to-anti-HBc seroconversion, some patients (especially Asian patients) serorevert to HBeAg after discontinuation, have a rise in

HBV DNA levels and recurrence of hepatitis activity, and require long-term therapy, which also is required when seroconversion does not occur and in patients with cirrhosis (at least until HBsAg clears and possibly indefinitely). HBeAg-negative patients with chronic hepatitis B also generally require long-term therapy because relapse is frequent when therapy is stopped. The ultimate goal of therapy is “functional cure,” characterized by loss of HBsAg, with or without appearance of anti-HBs, and undetectable HBV DNA in serum.

The available nucleoside and nucleotide analogs—entecavir, tenofovir, lamivudine, adefovir, and telbivudine—differ in efficacy and rates of resistance; however, in HBeAg-positive patients, they all achieve an HBeAg-to-anti-HBe seroconversion rate of about 20% at 1 year, with higher rates after more prolonged therapy. The preferred first-line oral agents are entecavir and tenofovir. Entecavir is rarely associated with resistance unless a patient is already resistant to lamivudine. The daily dose is 0.5 mg orally for patients not resistant to lamivudine and 1 mg for patients who previously became resistant to lamivudine. Suppression of HBV DNA in serum occurs in nearly all treated patients, and histologic improvement is observed in 70% of patients. Entecavir has been reported to cause lactic acidosis when used in patients with decompensated cirrhosis. Tenofovir disoproxil fumarate, 300 mg orally daily, is equally effective and is used as a first-line agent or when resistance to a nucleoside analog has developed. Like entecavir, tenofovir has a low rate of resistance when used as initial therapy. Long-term use may lead to an elevated serum creatinine level and reduced serum phosphate level (Fanconi-like syndrome) that is reversible with discontinuation of the drug. Tenofovir alafenamide, 25 mg orally daily, is an alternative formulation of tenofovir that was approved by the FDA in 2016; it is associated with a lower rate of renal and bone toxicity than tenofovir disoproxil fumarate.

The first available nucleoside analog was lamivudine, 100 mg orally daily. No longer considered first-line therapy in the United States, it still may be used in countries in which cost is a deciding factor. Adefovir dipivoxil has activity against wild-type and lamivudine-resistant HBV but in a standard dose of 10 mg daily is the least potent of the oral antiviral agents for HBV and is now rarely if ever used. Telbivudine, given in a daily dose of 600 mg orally, is more potent than either lamivudine or adefovir but like them is associated with resistance. Elevated creatine kinase levels are common in patients treated with telbivudine.

Nucleoside and nucleotide analogs are well tolerated even in patients with decompensated cirrhosis (for whom the treatment threshold may be an HBV DNA level less than 10^4 copies/mL and therapy should be continued indefinitely) and may be effective in patients with rapidly progressive hepatitis B (“fibrosing cholestatic hepatitis”) following organ transplantation. Combined use of a nucleoside and nucleotide analog or of peginterferon and a nucleoside or nucleotide analog has not been shown convincingly to have a substantial advantage over the use of one drug alone.

Nucleoside analogs are also recommended to prevent reactivation in both inactive HBV carriers and

those positive only for anti-HBc prior to the initiation of immunosuppressive therapy (including rituximab or anti-tumor necrosis factor antibody therapy) or cancer chemotherapy. In patients infected with both HBV and HIV, antiretroviral therapy, including two drugs active against both viruses (eg, tenofovir plus lamivudine or emtricitabine), has been recommended when treatment of HIV infection is indicated. Telbivudine, tenofovir, and lamivudine have been shown to be safe in pregnant women. Antiviral therapy has been recommended, beginning in the third trimester, when the mother’s serum HBV DNA level is 200,000 international units/mL or higher to reduce levels at the time of delivery.

Peginterferon alfa-2a is still an alternative to the oral agents in selected cases. A dose of 180 mcg subcutaneously once weekly for 48 weeks leads to sustained normalization of aminotransferase levels, disappearance of HBeAg and HBV DNA from serum, and appearance of anti-HBe in up to 40% of treated patients and results in improved survival. A response is most likely in patients with a low baseline HBV DNA level and high aminotransferase levels and is more likely in those who are infected with HBV genotype A than with other genotypes (especially genotype D). Moreover, many complete responders eventually clear HBsAg and develop anti-HBs in serum, and are thus cured. Relapses are uncommon in complete responders who seroconvert from HBeAg to anti-HBe. Peginterferon may be considered in order to avoid long-term therapy with an oral agent, as in young women who may want to become pregnant in the future. Patients with HBeAg-negative chronic hepatitis B have a response rate of 60% after 48 weeks of therapy with peginterferon, but the response may not be durable once peginterferon is stopped. The response to peginterferon is poor in patients with HIV coinfection.

In **chronic hepatitis D**, peginterferon alfa-2b (1.5 mcg/kg/wk for 48 weeks) may lead to normalization of serum aminotransferase levels, histologic improvement, and elimination of HDV RNA from serum in 20–50% of patients, but relapse may occur and tolerance is poor. Nucleoside and nucleotide analogs are generally not effective in treating chronic hepatitis D.

► Prognosis

The sequelae of chronic hepatitis secondary to hepatitis B include cirrhosis, liver failure, and hepatocellular carcinoma. The 5-year mortality rate is 0–2% in those without cirrhosis, 14–20% in those with compensated cirrhosis, and 70–86% following decompensation. The risk of cirrhosis and hepatocellular carcinoma correlates with serum HBV DNA levels, and a focus of therapy is to suppress HBV DNA levels below 300 copies/mL (60 international units/mL). In patients with cirrhosis, even low levels of HBV DNA in serum increase the risk of hepatocellular carcinoma compared with undetectable levels. HBV genotype C is associated with a higher risk of cirrhosis and hepatocellular carcinoma than other genotypes. Antiviral treatment improves the prognosis in responders, prevents (or leads to regression of) cirrhosis, and decreases the

frequency of liver-related complications (although the risk of hepatocellular carcinoma does not become as low as that in inactive HBV carriers and hepatocellular carcinoma may even occur after clearance of HBsAg). A risk score (PAGE-B) based on a patient's age, sex, and platelet count has been reported to predict the 5-year risk of hepatocellular carcinoma in White patients taking entecavir or tenofovir.

2. Chronic Hepatitis C

► Clinical Findings & Diagnosis

Chronic hepatitis C develops in up to 85% of patients with acute hepatitis C. It is clinically indistinguishable from chronic hepatitis due to other causes and may be the most common. Worldwide, 71 million people are infected with HCV, with 1.8% of the US population infected. Peak prevalence in the United States (about 4%) is in persons born between 1945 and 1964. In approximately 40% of cases, serum aminotransferase levels are persistently normal. The diagnosis is confirmed by detection of anti-HCV by EIA. In rare cases of suspected chronic hepatitis C but a negative EIA, HCV RNA is detected by PCR testing. Progression to cirrhosis occurs in 20% of affected patients after 20 years, with an increased risk in men, those who drink more than 50 g of alcohol daily, and those who acquire HCV infection after age 40 years. The rate of fibrosis progression accelerates after age 50. Blacks have a higher rate of chronic hepatitis C but lower rates of fibrosis progression and response to therapy than Whites. Immunosuppressed persons—including patients with hypogammaglobulinemia or HIV infection with a low CD4 count or those receiving immunosuppressants—appear to progress more rapidly to cirrhosis than immunocompetent persons with chronic hepatitis C. Tobacco and cannabis smoking and hepatic steatosis also appear to promote progression of fibrosis, whereas coffee consumption appears to slow progression. Persons with chronic hepatitis C and persistently normal serum aminotransferase levels usually have mild chronic hepatitis with slow or absent progression to cirrhosis; however, cirrhosis is present in 10% of these patients. Serum fibrosis testing (eg, FibroSure) or elastography may be used to identify the absence of fibrosis or presence of cirrhosis.

► Treatment

The introduction of direct-acting and host-targeting antiviral agents has rapidly expanded the therapeutic armamentarium against HCV (Table 16–6). Standard therapy for HCV infection from the late 1990s to the early 2010s was a combination of peginterferon plus ribavirin, and ribavirin continues to be used in some all-oral regimens. Sustained virologic response rates (negative HCV RNA in serum at 24 weeks after completion of therapy) for peginterferon plus ribavirin were 45% in patients with HCV genotype 1 infection and 70–80% in those with genotype 2 or 3 infection. Treatment with peginterferon-based therapy is associated with frequent, often distressing, side effects, and discontinuation rates are as high as 15–30%.

After the introduction of all-oral regimens, the criterion for a sustained virologic response was shortened from 24 weeks to 12 weeks following the completion of treatment. The definition of clearance of HCV RNA requires use of a sensitive real-time reverse transcriptase-PCR assay to monitor HCV RNA during treatment (the lower limit of quantification should be 25 international units/mL or less, and the limit of detection should be 10–15 international units/mL).

Several types of direct-acting antiviral agents have been developed (Tables 16–6 and 16–7). HCV protease inhibitors (“...previrs”) generally have high antiviral potency but differ with respect to the development of resistance (although resistance-associated substitutions in the HCV genome tend not to persist after therapy with these agents is stopped). Examples include glecaprevir and voxilaprevir. Medications in this class are contraindicated in patients with decompensated cirrhosis.

NS5A inhibitors (“...asavirs”), such as ledipasvir and velpatasvir, are characterized by high antiviral potency at picomolar doses. The cross-genotype efficacy of these agents varies.

HCV polymerase inhibitors (“...buvir”) are categorized as nucleoside or nucleotide analog and non-nucleoside polymerase inhibitors. Nucleos(t)ide analogs are active against all HCV genotypes and have a high barrier to resistance. Sofosbuvir has been the sole available agent in this category. Non-nucleos(t)ide polymerase inhibitors, such as dasabuvir, are the weakest class of compounds against HCV because of a low barrier to resistance. Drugs in this class are generally more active against HCV genotype 1b than HCV genotype 1a. They have been developed to be used only in combination with the other direct-acting antiviral agents, mainly protease inhibitors and NS5A inhibitors.

In late 2019, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommended two preferred combination regimens: glecaprevir plus pibrentasvir for 8 weeks for genotypes 1–6 and sofosbuvir plus velpatasvir for 12 weeks for genotypes 1, 2, 4, 5, or 6 (see Table 16–7). The combination of glecaprevir and pibrentasvir is approved for 8 weeks in treatment-naïve, noncirrhotic or compensated cirrhotic and treatment-experienced noncirrhotic patients, including those coinfected with HIV, and for 12 weeks in treatment-experienced, compensated cirrhotic patients. Sofosbuvir and velpatasvir should also be administered for 12 weeks in treatment-experienced compensated cirrhotic patients. Additional modifications may be required in patients with genotype-3 treatment-experienced compensated or decompensated cirrhosis. The combination of glecaprevir and pibrentasvir is also a pangenotypic option for patients with chronic kidney disease, including those receiving dialysis. The combination of sofosbuvir, velpatasvir, and voxilaprevir is recommended as “rescue” therapy in patients with nonresponse or relapse following treatment with an NS5A-containing regimen. Where available, testing for resistance-associated substitutions may be helpful in some cases before re-treatment. Use of any regimen containing a protease inhibitor is contraindicated in patients with decompensated cirrhosis.

Table 16–6. Direct-acting antiviral agents for HCV infection (in alphabetic order within class).¹

Agent	Genotype(s)	Dose ²	Comment
NS3/4A Protease Inhibitors			
Glecaprevir	1–6	300 mg orally once daily	Used in combination with pibrentasvir ³ with or without ribavirin
Grazoprevir	1 and 4	100 mg orally once daily	Used in combination with elbasvir ⁴
Paritaprevir	1 and 4	150 mg orally once daily	Used in combination with ombitasvir and dasabuvir; ritonavir (100 mg) boosted ⁵ ; for genotype 1b with cirrhosis and genotype 1a, used with ribavirin. Used in combination with ombitasvir, ritonavir boosting, and ribavirin for genotype 4 ⁶
Simeprevir	1 and 4	150 mg orally once daily	Used in combination with sofosbuvir
Voxilaprevir	1–6	100 mg orally once daily	Used in combination with sofosbuvir and velpatasvir ⁷
NS5A Inhibitors			
Daclatasvir ⁸	1–6	60 mg orally once daily	Used in combination with sofosbuvir (genotypes 1–6, with or without ribavirin depending on presence of cirrhosis) or with asunaprevir (not available in the United States)
Elbasvir	1 and 4	50 mg orally once daily	Used in combination with grazoprevir (see above)
Ledipasvir	1, 4–6	90 mg orally once daily	Used in combination with sofosbuvir ⁹
Ombitasvir	1 and 4	25 mg orally once daily	Used in combination with paritaprevir (ritonavir boosted) with or without dasabuvir and with or without ribavirin as per paritaprevir above
Pibrentasvir	1–6	120 mg orally once daily	Used in combination with glecaprevir with or without ribavirin
Velpatasvir	1–6	100 mg orally once daily	Used in combination with sofosbuvir, ¹⁰ may be used with sofosbuvir and voxilaprevir
NS5B Nucleos(t)ide Polymerase Inhibitor			
Sofosbuvir	1–6	400 mg orally once daily	Used in combination with ribavirin (genotypes 2 and 3) or with simeprevir (genotypes 1 and 4) or with daclatasvir (all genotypes) or with ledipasvir (genotypes 1, 3, and 4) or with velpatasvir (all genotypes) or with velpatasvir and voxilaprevir (all genotypes)
NS5B Non-Nucleos(t)ide Polymerase Inhibitor			
Dasabuvir	1 and 4	250 mg orally twice daily	Used in combination with paritaprevir (ritonavir boosted) and ombitasvir with or without ribavirin as per paritaprevir above

¹Regimens approved by the FDA as of early 2021.²The preferred regimen and duration of treatment may vary depending on HCV genotype, presence or absence of cirrhosis or chronic kidney disease, or nonresponse to prior therapy for HCV infection. In selected cases, testing for resistance-associated substitutions may be considered.³Marketed as Mavyret (AbbVie).⁴Marketed as Zepatier (Merck) for HCV genotypes 1 and 4 infection.⁵Marketed as Viekira Pak and Viekira XR (AbbVie).⁶Marketed as Technivie (AbbVie).⁷Marketed as Vosevi (Gilead Sciences).⁸Approved by the FDA for use with sofosbuvir in HCV genotypes 1 and 3 infection but taken off the market in the United States in 2019.⁹Marketed as Harvoni (Gilead Sciences).¹⁰Marketed as Epclusa (Gilead Sciences).

Overall treatment rates are still less than 20% and lowest among Hispanics and persons with Medicaid or indigent care insurance. The cost of direct-acting antiviral agents has been high (although declining), and lack of insurance coverage has often been a barrier to their use. Additional factors to consider in the selection of a regimen are the presence of cirrhosis or kidney dysfunction, prior treatment, potential drug interactions (of which there are many), and the likelihood that a patient may require liver transplantation in the future. Certain cytochrome P450/P-glycoprotein inducing

medications, such as carbamazepine, phenytoin, and phenobarbital, contraindicate the use of all HCV direct-acting antiviral regimens. HCV genotype 1 is now easy to cure with oral direct-acting agents, with expected sustained virologic response rates well above 90%, and virtually all HCV genotype 2 infection is curable with all-oral regimens. HCV genotype 3 infection, particularly in association with cirrhosis, has been the most challenging to treat, but the newest regimens achieve a high rate of cure. Interferon is now rarely required, and the need for ribavirin has also decreased.

Table 16–7. Preferred FDA-approved oral direct-acting antiviral (DAA) treatment regimens for HCV infection.¹

Regimen	Indication	Duration of Treatment in Noncirrhotic Treatment-Naïve Patients (weeks)
Glecaprevir and pibrentasvir	Genotypes 1–6 and DAA-experienced genotype 1	8
Sofosbuvir and velpatasvir	Genotypes 1–6, and DAA-experienced genotypes 1b and 2	12
Sofosbuvir, velpatasvir, and voxilaprevir	DAA-experienced genotypes 1–6	—

¹Based on the American Association for the Study of Liver Diseases/Infectious Diseases Society of America 2018 Guidance. In late 2019, two preferred regimens were proposed: glecaprevir and pibrentasvir for 8 weeks (genotypes 1–6) and sofosbuvir and velpatasvir for 12 weeks (genotypes 1, 2, 4, 5, 6). See HCV Guidance: Recommendation for testing, managing, and treating hepatitis C. <http://www.hcvguidelines.org>, accessed December 18, 2020.

Other agents that have been studied include NS3/4A protease inhibitors (eg, danoprevir); polymerase inhibitors (eg, mericitabine); virus entry, assembly, and secretion inhibitors; microRNA-122 antisense oligonucleotides (eg, miravirsen); cyclophilin A inhibitors (eg, alisporivir); interferon lambda-3; and therapeutic vaccines.

Antiviral therapy has been shown to be beneficial in the treatment of cryoglobulinemia associated with chronic hepatitis C; an acute flare of cryoglobulinemia may first require treatment with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange. As noted above, patients with HCV and HIV coinfection have been shown to respond well to treatment of HCV infection. Moreover, in persons coinfecte with HCV and HIV, long-term liver disease-related mortality increases as HIV infection-related mortality is reduced by antiretroviral therapy. Occasional instances of reactivation of HBV infection, as well as herpesvirus, have occurred with direct-acting antiviral agents for HCV infection, and all candidates should be prescreened for HBV infection, with the initiation of antiviral prophylactic therapy in those who are HBsAg positive before treatment of HCV infection is begun.

► Prognosis

Chronic hepatitis C is an indolent, often subclinical disease that may lead to cirrhosis and hepatocellular carcinoma after decades. The overall mortality rate in patients with transfusion-associated hepatitis C may be no different from that of an age-matched control population. Nevertheless, mortality or transplantation rates clearly rise to 5% per year once cirrhosis develops. A risk score combining age, sex, platelet count, and AST-to-ALT ratio has been proposed. There is some evidence that HCV genotype 1b is associated with a higher risk of hepatocellular carcinoma than other genotypes. Antiviral therapy has a beneficial effect on mortality, cardiovascular events, type 2 diabetes mellitus, and quality of life, is cost-effective, appears to retard and even reverse fibrosis, and reduces (but does not eliminate) the risk of decompensated cirrhosis and hepatocellular carcinoma in responders with advanced fibrosis. Even patients who achieve a sustained virologic response remain at an increased risk for mortality compared with the general population. An increased risk of death from extrahepatic cancers has been described in this group, as

well as in patients who achieve suppression of HBV infection. Although mortality from cirrhosis and hepatocellular carcinoma due to hepatitis C is still substantial, the need for liver transplantation for chronic hepatitis C has declined, and survival after transplantation has improved. The risk of mortality from drug addiction is higher than that for liver disease in patients with chronic hepatitis C. HCV infection appears to be associated with increased cardiovascular mortality, especially in persons with diabetes mellitus and hypertension. Statin use has been reported to be associated with improved virologic response to antiviral therapy and decreased progression of liver fibrosis and frequency of hepatocellular carcinoma.

► When to Refer

- For liver biopsy.
- For antiviral therapy.

► When to Admit

For complications of decompensated cirrhosis.

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AUTOIMMUNE HEPATITIS

► ESSENTIALS OF DIAGNOSIS

- Usually young to middle-aged women.
- Chronic hepatitis with high serum globulins and characteristic liver histology.
- Positive antinuclear antibody (ANA) and/or smooth muscle antibody in most cases in the United States.
- Responds to corticosteroids.

► General Considerations

Although autoimmune hepatitis is usually seen in young women, it can occur in either sex at any age. The incidence, which has been rising, and prevalence are estimated to be 8.5 and 107 per million population, respectively. The risk of autoimmune hepatitis is increased in first-degree relatives of affected patients.

► Clinical Findings

A. Symptoms and Signs

The onset is usually insidious. About 25% of cases present with acute severe hepatitis (and occasionally acute liver failure), and some cases follow a viral illness (such as hepatitis A, Epstein-Barr infection, or measles) or exposure to a drug or toxin (such as nitrofurantoin, minocycline, hydralazine, methyldopa, infliximab, or an immune checkpoint inhibitor). Exacerbations may occur postpartum. Amenorrhea may be a presenting feature, and the frequency of depression appears to be increased. Thirty-four percent of patients, and particularly elderly patients, are asymptomatic. Examination may reveal a healthy-appearing young woman with multiple spider telangiectasias, cutaneous striae, acne, hirsutism, and hepatomegaly. Extrahepatic features include arthritis, Sjögren syndrome, thyroiditis, nephritis, ulcerative colitis, and Coombs-positive hemolytic anemia. Patients, especially elderly patients, with autoimmune hepatitis are at increased risk for cirrhosis, which, in turn, increases the risk of hepatocellular carcinoma (at a rate of about 1% per year).

B. Laboratory Findings

Serum aminotransferase levels may be greater than 1000 units/L, and the total bilirubin is usually increased. Autoimmune hepatitis has been classified as type I or type II, although the clinical features and response to treatment are similar between the two types. In type I (classic) autoimmune hepatitis, ANA or smooth muscle antibodies (either or both) are usually detected in serum. Serum gamma-globulin levels are typically elevated (up to 5–6 g/dL [0.05–0.06 g/L]); in such patients, the EIA for antibody to HCV may be falsely positive. Other antibodies, including atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) and antibodies to histones, F-actin, and alpha-actinin may be found. In acute severe autoimmune hepatitis, ANAs are absent and serum IgG is normal each in up to 39% of cases. Antibodies to soluble liver antigen (anti-SLA) characterize a variant of type I that is marked by severe disease, a high relapse rate after treatment, and absence of the usual antibodies (ANA and smooth muscle antibodies). Type II, seen more often in girls under age 14 in Europe, is characterized by circulating antibodies to liver-kidney microsome type 1 (anti-LKM1) without smooth muscle antibodies or ANA. In some cases, antibodies to liver cytosol type 1 are detected. Type II autoimmune hepatitis can be seen in patients with autoimmune polyglandular syndrome type 1. Concurrent primary biliary cholangitis (PBC) or primary sclerosing cholangitis (“overlap syndrome”) has been recognized in 7–13% and

6–11% of patients with autoimmune hepatitis, respectively. Liver biopsy is indicated to help establish the diagnosis (interface hepatitis is the hallmark), evaluate disease severity and stage of fibrosis, and determine the need for treatment. Histologic features of NAFLD are found in 17–30% of patients with autoimmune hepatitis. Cirrhosis is present in 28–33% of adults at presentation.

Simplified diagnostic criteria based on the detection of autoantibodies (1 point for a titer of > 1:40 or 2 points for a titer of > 1:80), elevated IgG levels (1 point for IgG level \geq upper limit of normal or 2 points for level \geq 1.1 times upper limit of normal), characteristic histologic features (1 or 2 points depending on how typical the features are), and exclusion of viral hepatitis (2 points) can be useful for diagnosis; a score of 6 indicates probable and a score of 7 indicates definite autoimmune hepatitis with a high degree of specificity but moderate sensitivity. Diagnostic criteria for an overlap of autoimmune hepatitis and PBC (“Paris criteria”) have been proposed.

► Treatment

Prednisone with or without azathioprine (often started 2 weeks after prednisone) improves symptoms; decreases the serum bilirubin, aminotransferase, and gamma-globulin levels; and reduces hepatic inflammation. Symptomatic patients with aminotransferase levels elevated 10-fold (or 5-fold if the serum globulins are elevated at least 2-fold) are optimal candidates for therapy, and asymptomatic patients with modest enzyme elevations may be considered for therapy depending on the clinical circumstances and histologic severity; however, asymptomatic patients usually remain asymptomatic, have either mild hepatitis or inactive cirrhosis on liver biopsy specimens, and have a good long-term prognosis without therapy.

Prednisone is given initially in a dose of 30 mg orally daily with azathioprine, 50 mg orally daily, which is generally well tolerated and permits the use of lower corticosteroid doses than a regimen beginning with prednisone 60 mg orally daily alone. A decrease in serum AST levels by 80% after 8 weeks predicts normalization of AST levels at 1 year. Intravenous corticosteroids or prednisone, 60 mg orally daily, is recommended for patients with acute severe autoimmune hepatitis; azathioprine is often started 2 weeks later. In patients with noncirrhotic autoimmune hepatitis, budesonide, 3 mg orally two or three times daily, may be at least as effective as prednisone as first-line treatment and associated with fewer side effects. Whether patients should undergo testing for the genotype or level of thiopurine methyltransferase prior to treatment with azathioprine to predict toxicity is debated. Adjusting the dose of azathioprine based on metabolite levels, as in inflammatory bowel disease, has been suggested. Blood counts are monitored weekly for the first 2 months of therapy and monthly thereafter because of the small risk of bone marrow suppression. The dose of prednisone is lowered from 30 mg/day after 1 week to 20 mg/day and again after 2 or 3 weeks to 15 mg/day. Treatment is response guided, and ultimately, a maintenance dose of 10 mg/day should be achieved. While symptomatic improvement is often prompt, biochemical

improvement is more gradual, with normalization of serum aminotransferase levels after an average of 22 months. Histologic resolution of inflammation lags biochemical remission by 3–6 months, and repeat liver biopsy should be considered in persons with at least 2 years of biochemical remission. Failure of aminotransferase levels to return to normal invariably predicts lack of histologic resolution.

The response rate to therapy with prednisone and azathioprine is 80%, with remission in 65% by 3 years. Older patients and those with HLA genotype *DRB1*04* are more likely to respond than younger patients and those with HLA *DRB1*03*, hyperbilirubinemia, or a high MELD score (12 or higher, see Cirrhosis). Fibrosis may reverse with therapy and rarely progresses after apparent biochemical and histologic remission. Once complete remission is achieved, therapy may be withdrawn, but the subsequent relapse rate is 90% by 3 years. Relapses may again be treated in the same manner as the initial episode, with the same remission rate. After successful treatment of a relapse, the patient may continue taking azathioprine (up to 2 mg/kg) or the lowest dose of prednisone with or without azathioprine (50 mg/day) needed to maintain aminotransferase levels as close to normal as possible; another attempt at withdrawing therapy may be considered in patients remaining in remission long term (eg, 4 years or longer). During pregnancy, flares can be treated with prednisone, and maintenance azathioprine does not have to be discontinued.

Nonresponders to corticosteroids and azathioprine (failure of serum aminotransferase levels to decrease by 50% after 6 months) may be considered for a trial of cyclosporine, tacrolimus, sirolimus, everolimus, methotrexate, rituximab, or infliximab. Mycophenolate mofetil, 500 mg increased to 1 g twice daily, is an effective alternative to azathioprine in patients who cannot tolerate it but is less effective in nonresponders to azathioprine and is a known teratogen that must be withdrawn prior to conception. It may be effective in up to 60% of patients refractory to or intolerant of corticosteroids. Occasionally, 6-mercaptopurine may be tolerated in patients who do not tolerate azathioprine. Bone density should be monitored—particularly in patients receiving maintenance corticosteroid therapy—and measures undertaken to prevent or treat osteoporosis (see Chapter 26). Liver transplantation may be required for treatment failures and patients with a severe acute presentation (immediately in those with acute liver failure and after 2 weeks in those with acute severe autoimmune hepatitis and a lack of improvement with corticosteroids), but the outcome may be worse than that for PBC because of an increased rate of infectious complications. As immunosuppression is reduced, the disease has been recognized to recur in up to 70% of transplanted livers at 5 years (and rarely to develop de novo); sirolimus can be effective in such cases.

Overall long-term mortality of patients with autoimmune hepatitis and cirrhosis appears to be twofold higher than that of the general population despite response to immunosuppressive therapy. Factors that predict the need for liver transplantation or that predict liver-related death include the following: (1) age 20 years or younger or age 60 years or older at presentation, (2) low serum albumin

level at diagnosis, (3) cirrhosis at diagnosis, (4) the presence of anti-SLA, and (5) incomplete normalization of the serum ALT level after 6 months of treatment. The disease appears to be more aggressive in Black patients than in White patients.

► When to Refer

- For liver biopsy.
- For immunosuppressive therapy.

► When to Admit

- Hepatic encephalopathy.
- INR greater than 1.6.

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ALCOHOL-ASSOCIATED LIVER DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Chronic alcohol intake usually exceeds 80 g/day in men and 30–40 g/day in women with alcohol-associated hepatitis or cirrhosis.
- ▶ Fatty liver is often asymptomatic.
- ▶ Fever, right upper quadrant pain, tender hepatomegaly, and jaundice characterize alcohol-associated hepatitis, but the patient may be asymptomatic.
- ▶ AST is usually elevated but infrequently > 300 units/L (6 mckat/L); AST is > ALT, usually by a factor of 2 or more.
- ▶ Alcohol-associated hepatitis is often reversible, but it is the most common precursor of cirrhosis in the United States.

► General Considerations

Excessive alcohol intake can lead to fatty liver, hepatitis, and cirrhosis. Validated tools, such as the Alcohol Use Disorders Inventory Test (AUDIT), can be used to identify persons with alcohol abuse and dependence (see Table 1–6). Alcohol-associated hepatitis is characterized by acute or chronic inflammation and parenchymal necrosis of the liver induced by alcohol. Alcohol-associated hepatitis is often a reversible disease, but it is the most common precursor of cirrhosis in the United States. It is associated with four to five times the number of hospitalizations and

deaths as hepatitis C. Mortality from alcohol-associated liver disease has been increasing since 1999.

The frequency of alcohol-associated cirrhosis is estimated to be 10–15% among persons who consume over 50 g of alcohol (4 oz of 100-proof whiskey, 15 oz of wine, or four 12-oz cans of beer) daily for over 10 years (although the risk of cirrhosis may be lower for wine than for a comparable intake of beer or spirits). The risk of cirrhosis is lower (5%) in the absence of other cofactors such as chronic viral hepatitis and obesity. Genetic factors may also account for differences in susceptibility to and severity of liver disease. Women appear to be more susceptible than men, in part because of lower gastric mucosal alcohol dehydrogenase levels, but young men who drink excessively are at increased risk for liver disease later in life when they are no longer drinking as much.

► Clinical Findings

A. Symptoms and Signs

The clinical presentation of alcohol-associated liver disease can vary from asymptomatic hepatomegaly to a rapidly fatal acute illness (acute-on-chronic liver failure) or end-stage cirrhosis. A recent period of heavy drinking, complaints of anorexia and nausea, and the demonstration of hepatomegaly and jaundice strongly suggest the diagnosis. Abdominal pain and tenderness, splenomegaly, ascites, fever, and encephalopathy may be present. Infection, including invasive aspergillosis, is common in patients with severe alcohol-associated hepatitis.

B. Laboratory Findings

In patients with steatosis, mild liver enzyme elevations may be the only laboratory abnormality. Anemia (usually macrocytic) may be present. Leukocytosis with a shift to the left is common in patients with severe alcohol-associated hepatitis. Leukopenia is occasionally seen and resolves after cessation of drinking. About 10% of patients have thrombocytopenia related to a direct toxic effect of alcohol on megakaryocyte production or to hypersplenism.

AST is usually elevated but infrequently above 300 units/L (6 mckat/L). AST is greater than ALT, usually by a factor of 2 or more. Serum alkaline phosphatase is generally elevated, but seldom more than three times the normal value. Serum bilirubin is increased in 60–90% of patients with alcohol-associated hepatitis.

Serum bilirubin levels greater than 10 mg/dL (171 mcmmol/L) and marked prolongation of the prothrombin time (6 seconds or more above control) indicate severe alcohol-associated hepatitis with a mortality rate as high as 50%. The serum albumin is depressed, and the gamma-globulin level (especially IgA) is elevated in 50–75% of individuals, even in the absence of cirrhosis. Increased transferrin saturation, hepatic iron stores, and sideroblastic anemia are found in many alcoholic patients. Folic acid deficiency may coexist.

C. Imaging

Imaging studies can detect moderate to severe hepatic steatosis reliably but not inflammation or fibrosis.

Ultrasonography helps exclude biliary obstruction and identifies subclinical ascites. CT with intravenous contrast or MRI may be indicated in selected cases to evaluate patients for collateral vessels, space-occupying lesions of the liver, or concomitant disease of the pancreas.

D. Liver Biopsy

Liver biopsy, if done, demonstrates macrovesicular fat and, in patients with alcohol-associated hepatitis, polymorpho-nuclear infiltration with hepatic necrosis, Mallory (or Mallory-Denk) bodies (alcoholic hyaline), and perivenular and perisinusoidal fibrosis. Micronodular cirrhosis may be present as well. The findings are similar to those of nonalcoholic steatohepatitis.

► Differential Diagnosis

Alcohol-associated hepatitis may be closely mimicked by cholecystitis and cholelithiasis and by drug toxicity. Other causes of hepatitis or chronic liver disease may be excluded by serologic or biochemical testing, imaging studies, or liver biopsy. A formula based on the AST/ALT ratio, body mass index, mean corpuscular volume, and sex has been reported to reliably distinguish alcohol-associated liver disease from NAFLD.

► Treatment

A. General Measures

Abstinence from alcohol is essential. Hospitalized patients should be monitored for alcohol withdrawal; the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) is often used in practice (see Figure 25–3). Acamprosate, naltrexone, or baclofen may be considered in combination with counseling to reduce the likelihood of relapse. Baclofen appears to be safe in persons with end-stage alcohol-associated liver disease but can worsen hepatic encephalopathy. Fatty liver is quickly reversible with abstinence. Every effort should be made to provide sufficient amounts of carbohydrates and calories in anorectic patients to reduce endogenous protein catabolism, promote gluconeogenesis, and prevent hypoglycemia. Nutritional support (30–40 [and no less than 21.5] kcal/kg with 1.0–1.5 g/kg as protein) improves liver disease, but not necessarily survival, in patients with malnutrition. Intensive enteral nutrition is difficult to implement, however. The administration of micronutrients, particularly folic acid, thiamine, and zinc, is indicated, especially when deficiencies are noted; glucose administration increases the thiamine requirement and can precipitate Wernicke-Korsakoff syndrome if thiamine is not coadministered. Nephrotoxic drugs should be avoided in patients with severe alcohol-associated hepatitis.

B. Pharmacologic Measures

Methylprednisolone, 32 mg/day orally, or the equivalent, for 1 month, may reduce short-term (1-month but not 6-month) mortality in patients with alcohol-associated hepatitis and encephalopathy or a Maddrey discriminant function index (defined by the patient's prothrombin time

minus the control prothrombin time times 4.6 plus the total bilirubin in mg/dL) of 32 or more, or a MELD score of 20 or more (see Cirrhosis). Concomitant gastrointestinal bleeding or infection may not preclude treatment with corticosteroids if otherwise indicated, but treatment with prednisolone increases the risk of serious infections during and after treatment is completed. The combination of corticosteroids and N-acetylcysteine has been reported to further improve 1-month but not 6-month survival and reduce the risk of hepatorenal syndrome and infections; the combination may be superior to corticosteroids alone, but more data are needed.

Pentoxifylline, 400 mg orally three times daily for 4 weeks, decreases the risk of hepatorenal syndrome. It does not appear to reduce short-term mortality. Its use is not recommended in some guidelines, but it has been used when corticosteroids are contraindicated. The addition of pentoxifylline to prednisolone does not appear to improve survival but may reduce the frequency of hepatorenal syndrome compared with prednisolone alone. Other experimental therapies include propylthiouracil; oxandrolone; S-adenosyl-l-methionine; infliximab; antioxidants; granulocyte colony-stimulating factor; interleukin-2 agonists; interleukin-22; the combination of anakinra, zinc, and pentoxifylline; modulation of intestinal flora; and extracorporeal liver support.

► Prognosis

A. Short-Term

The overall mortality rate for alcohol-associated hepatitis is 34% (20% within 1 month) without corticosteroid therapy. Individuals in whom the prothrombin time prohibits liver biopsy have a 42% mortality rate at 1 year. Other unfavorable prognostic factors are older age, a serum bilirubin greater than 10 mg/dL (171 μmol/L), hepatic encephalopathy, coagulopathy, azotemia, leukocytosis, sepsis and other infections, systematic inflammatory response syndrome (which is associated with multiorgan failure), lack of response to corticosteroid therapy, a low serum transferrin level, and possibly a paucity of steatosis on a liver biopsy specimen and reversal of portal blood flow by Doppler ultrasonography. Concomitant gastrointestinal bleeding does not appear to worsen survival. Failure of the serum bilirubin level to decline after 7 days of treatment with corticosteroids predicts nonresponse and poor long-term survival, as does the Lille model (which includes age, serum creatinine, serum albumin, prothrombin time [or INR], serum bilirubin on admission, and serum bilirubin on day 7). The MELD score used for cirrhosis and the Glasgow alcohol-associated hepatitis score (based on age, white blood cell count, blood urea nitrogen, prothrombin time ratio, and bilirubin level) also correlate with mortality from alcohol-associated hepatitis and have higher specificities than the discriminant function and Lille score. A scoring system based on age, serum bilirubin, INR, and serum creatinine (ABIC) has been proposed, and at least one study has shown that the development of acute kidney injury is the most accurate predictor of 90-day mortality. Another scoring system based on hepatic encephalopathy,

systemic inflammatory response syndrome, and MELD score has also been reported to predict acute kidney injury and mortality. The combination of the MELD score and Lille model has been reported to be the best predictor of short-term mortality among the scoring systems. Histologic features associated with 90-day mortality include the degree of fibrosis and neutrophil infiltration, presence of megamitochondria, and bilirubinostasis.

B. Long-Term

Overall mortality from alcohol-associated liver disease has declined slightly in the United States since 1980. Nevertheless, the 3-year mortality rate of persons who recover from acute alcohol-associated hepatitis is 10 times greater than that of control individuals of comparable age; the 5-year mortality rate is as high as 85%. Histologically severe disease is associated with continued excessive mortality rates after 3 years, whereas the death rate is not increased after the same period in those whose liver biopsy specimens show only mild alcohol-associated hepatitis. Complications of portal hypertension (ascites, variceal bleeding, hepatorenal syndrome), coagulopathy, and severe jaundice following recovery from acute alcohol-associated hepatitis also suggest a poor long-term prognosis.

The most important long-term prognostic factor is continued excessive drinking. There is no safe level of drinking in persons with alcohol-associated liver disease or other liver diseases. The risk of alcohol-associated cirrhosis is greater in women than in men and associated with obesity, cigarette smoking, chronic hepatitis C, and low vitamin D levels; the risk is inversely associated with coffee drinking. Alcohol-associated cirrhosis is a risk factor for hepatocellular carcinoma, and the risk is highest in carriers of the C282Y mutation for hemochromatosis or those with increased hepatic iron. A 6-month period of abstinence is generally required before liver transplantation is considered, although this requirement has been questioned and early liver transplantation has been performed in selected patients with alcohol-associated hepatitis, with good outcomes. Optimal candidates have adequate social support, do not smoke, have no psychosis or personality disorder, are adherent to therapy, and have regular appointments with a psychiatrist or psychologist who specializes in addiction treatment. Patients with alcohol-associated liver disease are at higher risk for posttransplant malignancy than those with other types of liver disease because of alcohol and tobacco use.

► When to Refer

Refer patients with alcohol-associated hepatitis who require liver biopsy for diagnosis.

► When to Admit

- Hepatic encephalopathy.
- INR greater than 1.6.
- Total bilirubin 10 mg/dL or more.
- Inability to maintain hydration.

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DRUG- & TOXIN-INDUCED LIVER INJURY



ESSENTIALS OF DIAGNOSIS

- ▶ Drug-induced liver injury can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease.
- ▶ Clinicians must inquire about the use of many widely used therapeutic agents, including over-the-counter "natural" and herbal and dietary supplements, in any patient with liver disease.

General Considerations

Many therapeutic agents may cause drug-induced liver injury, with jaundice occurring in 30% of cases and up to 10% of patients with drug-induced liver injury dying or undergoing liver transplantation within 6 months of onset. In any patient with liver disease, the clinician must inquire carefully about the use of potentially hepatotoxic drugs or exposure to hepatotoxins, including over-the-counter herbal and dietary supplements. Khat chewing has been associated with an increased risk of chronic liver disease. The medications most commonly implicated are antibiotics because of their widespread use. In some cases, coadministration of a second agent may increase the toxicity of the first (eg, isoniazid and rifampin, acetaminophen and alcohol, combinations of immune checkpoint inhibitors). For some drugs, HLA and other genetic associations have been identified (eg, HLA-B57:01 in flucloxacillin hepatotoxicity in Asians, HLA-DRB1*15:01 in amoxicillin-clavulanic acid hepatotoxicity, and HLA-B*35:01 in toxicity caused by green tea extract). The diagnosis often depends on exclusion of other causes of liver disease. A relationship between increased serum ALT levels in premarketing clinical trials and postmarketing reports of hepatotoxicity has been identified. Except for drugs used to treat tuberculosis and HIV infection, obeticholic acid, and possibly azithromycin, the risk of hepatotoxicity is not increased in patients with preexisting cirrhosis, but hepatotoxicity may be more severe and the outcome worse when it does occur. Older persons may be at higher risk for hepatotoxicity from certain agents, such as amoxicillin-clavulanic acid, isoniazid, and nitrofurantoin, and more likely to have persistent and cholestatic, rather than hepatocellular, injury compared with younger persons. Drug toxicity may be categorized on the basis of pathogenesis or predominant

histologic appearance. Drug-induced liver injury can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease (and vice versa). The development of jaundice in a patient with serum aminotransferase levels at least three times the upper limit of normal predicts a mortality rate of at least 10% ("Hy's Law"). A model based on the presence of comorbidities, the MELD score, and serum albumin has been reported to predict 6-month mortality.

► Categorization by Pathogenesis

A. Direct Hepatotoxicity

Liver toxicity caused by this group of drugs is characterized by dose-related severity, a latent period following exposure, and susceptibility in all individuals. One example is acetaminophen (the toxicity of which is enhanced by fasting because of depletion of glutathione and by long-term alcohol use both because of depletion of glutathione and because of induction of cytochrome P450 2E1; and the toxicity of which is possibly reduced by statins, fibrates, and nonsteroidal anti-inflammatory drugs [NSAIDs] and acetylcysteine treatment). Other examples include alcohol, *Amanita phalloides* mushrooms, carbon tetrachloride, chloroform, heavy metals, mercaptopurine, niacin, obeticholic acid, plant alkaloids, phosphorus, pyrazinamide, tetracyclines, tipranavir, valproic acid, and vitamin A.

B. Idiosyncratic Reactions

Except for acetaminophen, most severe hepatotoxicity is idiosyncratic. Reactions of this type are (1) sporadic, (2) not related to dose above a general threshold of 100 mg/day, and (3) occasionally associated with features suggesting an allergic reaction, such as fever and eosinophilia (including drug rash with eosinophilia and systemic symptoms [DRESS] syndrome), which may be associated with a favorable outcome. In many instances, the drug is lipophilic, and toxicity results directly from a reactive metabolite that is produced only in certain individuals on a genetic basis. Illness tends to be more severe in Blacks than in Whites. Drug-induced liver injury may be observed only during post-marketing surveillance and not during pre-clinical trials. Examples include abacavir, amiodarone, aspirin, carbamazepine, chloramphenicol, dapsone, diclofenac, disulfiram, duloxetine, ezetimibe, flavocoxid (a "medical food"), fluoroquinolones (levofloxacin and moxifloxacin, in particular), flutamide, halothane, isoniazid, ketoconazole, lamotrigine, methyldopa, natalizumab, nevirapine, oxacillin, phenytoin, pyrazinamide, quinidine, rivaroxaban, streptomycin, temozolomide, thiazolidinediones, tolvaptan, and perhaps tacrine. Statins, like all cholesterol-lowering agents, may cause serum aminotransferase elevations but rarely cause true hepatitis, and even more rarely cause acute liver failure, and are no longer considered contraindicated in patients with liver disease. Most acute idiosyncratic drug-induced liver injury is reversible with discontinuation of the offending agent. Risk factors for chronicity (longer than 1 year) are older age, dyslipidemia, and severe acute injury.

C. Indirect Hepatotoxicity

Indirect hepatotoxicity refers to liver injury that results when use of a drug leads to exacerbation of preexisting liver disease. An example is a flare of HBV infection in the setting of immunosuppressive therapy for a nonhepatitis autoimmune disease.

► Categorization by Histopathology

A. Cholestasis

1. Noninflammatory—Drug-induced cholestasis results from inhibition or genetic deficiency of various hepatobiliary transporter systems. The following drugs cause cholestasis: anabolic steroids containing an alkyl or ethinyl group at carbon 17, azathioprine, cetirizine, cyclosporine, diclofenac, estrogens, febuxostat, indinavir (increased risk of indirect hyperbilirubinemia in patients with Gilbert syndrome), mercaptopurine, methyltestosterone, tamoxifen, temozolomide, and ticlopidine.

2. Inflammatory—The following drugs cause inflammation of portal areas with bile duct injury (cholangitis [and, in some cases, bile duct loss]), often with allergic features such as eosinophilia: amoxicillin-clavulanic acid (among the most common causes of drug-induced liver injury), azathioprine, azithromycin, captopril, celecoxib, cephalosporins, chlorothiazide, chlorpromazine, chlorpropamide, erythromycin, mercaptopurine, pazopanib, penicillamine, prochlorperazine, semisynthetic penicillins (eg, cloxacillin), sulfadiazine, and temozolomide. Ketamine abuse may cause secondary biliary cirrhosis. Cholestatic and mixed cholestatic-hepatocellular toxicity is more likely than pure hepatocellular toxicity to lead to chronic liver disease.

B. Acute or Chronic Hepatitis

Medications that may result in acute or chronic hepatitis that is histologically and, in some cases, clinically similar to autoimmune hepatitis include minocycline and nitrofurantoin, most commonly, as well as aspirin, isoniazid (increased risk in HBV and HCV carriers), methyldopa, NSAIDs, propylthiouracil, terbinafine, tumor necrosis factor inhibitors, and varenicline. Histologic features that favor a drug cause include portal tract neutrophils and hepatocellular cholestasis. Hepatitis also can occur in patients taking cocaine, diclofenac, dimethyl fumarate, efavirenz, imatinib mesylate, ipilimumab, nivolumab, and other checkpoint inhibitors (hepatotoxicity occurs in up to 16% of patients; the rate is higher with combination therapy than with monotherapy), methylenedioxymethamphetamine (MDMA; Ecstasy), nefazodone (has a black box warning for a potential to cause liver failure), nevirapine (like other HIV protease inhibitors, increased risk in HBV and HCV carriers), pioglitazone, ritonavir (greater rate than other HIV protease inhibitors), rosiglitazone, saquinavir, sulfonamides, telithromycin, tocilizumab, and zafirlukast, as well as a variety of alternative remedies (eg, black cohosh, chaparral, garcinia cambogia, germander, green tea extract, Herbalife products, Hydroxycut, jin bu huan, kava, saw palmetto, skullcap, usnic acid, and other traditional Chinese herbal preparations), in addition to dietary

supplements (eg, 1,3-dimethylamylamine in OxyELITE Pro, a weight-loss supplement withdrawn from the US market).

C. Other Reactions

1. Fatty liver—

A. MACROVESICULAR—This type of liver injury may be produced by alcohol, amiodarone, corticosteroids, haloperidol, irinotecan, lomitapide, methotrexate, mipomersen, tamoxifen, vinyl chloride (in exposed workers), zalcitabine, and possibly oxaliplatin.

B. MICROVESICULAR—Often resulting from mitochondrial injury, microvesicular steatosis is associated with aspirin (Reye syndrome), didanosine, linezolid, stavudine, tetracyclines, valproic acid, and zidovudine.

2. Granulomas—Allopurinol, hydralazine, pembrolizumab and other immune checkpoint inhibitors, phenytoin, pyrazinamide, quinidine, quinine, sulfasalazine, and vemurafenib can lead to granulomas and, in some cases, granulomatous hepatitis.

3. Fibrosis and cirrhosis—Methotrexate and vitamin A are associated with fibrosis and cirrhosis.

4. Sinusoidal obstruction syndrome (veno-occlusive disease)—This disorder may result from treatment with antineoplastic agents (eg, pre–bone marrow transplant, busulfan, gemtuzumab ozogamicin, inotuzumab ozogamicin, oxaliplatin), mycophenolate mofetil, and pyrrolizidine alkaloids (eg, comfrey).

5. Peliosis hepatitis (blood-filled cavities)—Peliosis hepatitis may be caused by anabolic steroids and oral contraceptive steroids as well as azathioprine and mercaptopurine, which may also cause nodular regenerative hyperplasia and other forms of liver injury.

6. Nodular regenerative hyperplasia—Nodular regenerative hyperplasia may be caused by azathioprine, 5-fluorouracil, oxaliplatin, and thioguanine.

7. Neoplasms—Neoplasms may result from therapy with oral contraceptive steroids, including estrogens (hepatocellular adenoma but not focal nodular hyperplasia) and vinyl chloride (angiosarcoma).

► When to Refer

Refer patients with drug- and toxin-induced hepatitis who require liver biopsy for diagnosis.

► When to Admit

Patients with liver failure should be hospitalized.

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NONALCOHOLIC FATTY LIVER DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Often asymptomatic.
- ▶ Elevated aminotransferase levels, hepatomegaly, or steatosis on ultrasonography.
- ▶ Predominantly macrovesicular steatosis with or without inflammation and fibrosis on liver biopsy.

► General Considerations

NAFLD is estimated to affect 20–45% of the US population and has increased in incidence at least fivefold since the late 1990s. Even adolescents and young adults may be affected. The principal causes of NAFLD are obesity (present in 40% or more of affected patients), diabetes mellitus (in 20% or more), and hypertriglyceridemia (in 20% or more) in association with insulin resistance as part of the metabolic syndrome. In fact, the alternative designation “metabolic-associated (or metabolic dysfunction-associated) fatty liver disease” (MAFLD) has been proposed. The risk of NAFLD in persons with metabolic syndrome is 4 to 11 times higher than that of persons without insulin resistance. Nonobese persons (more frequently Asians) account for 3–30% of persons with NAFLD and have metabolic profiles characteristic of insulin resistance. Other causes of fatty liver include corticosteroids, amiodarone, diltiazem, tamoxifen, irinotecan, oxaliplatin, antiretroviral therapy, toxins (vinyl chloride, carbon tetrachloride, yellow phosphorus), endocrinopathies such as Cushing syndrome and hypopituitarism, polycystic ovary syndrome, hypothyroidism, hypobetalipoproteinemia and other metabolic disorders, obstructive sleep apnea (with chronic intermittent hypoxia), excessive dietary fructose consumption, starvation and refeeding syndrome, and total parenteral nutrition. NAFLD may be a predisposing factor in liver injury caused by some drugs. Gut dysbiosis, altered bile acid metabolism, and genetic factors play a role in NAFLD (and likely account for NAFLD in lean persons), and polymorphisms of the patatin-like phospholipase domain containing 3 (*PNPLA3*) gene modify the natural history of NAFLD and may account in part for an increased risk in Hispanics. The risk of NAFLD is increased in persons with psoriasis and appears to correlate with the activity of psoriasis. Soft drink consumption and cholecystectomy have been reported to be associated with NAFLD. Physical activity protects against the development of NAFLD.

In addition to macrovesicular steatosis, histologic features may include focal infiltration by polymorphonuclear neutrophils and Mallory hyalin, a picture indistinguishable from that of alcohol-associated hepatitis and referred to as nonalcoholic steatohepatitis (NASH), which affects 3–6% of the US population and leads to cirrhosis in approximately 20% of affected persons. In patients with NAFLD, older age, obesity, and diabetes mellitus are risk factors for advanced hepatic fibrosis and cirrhosis, whereas coffee

consumption reduces the risk. The frequency and severity of NAFLD is greater in men than in women during reproductive age, but after menopause the frequency is higher in women than men, suggesting that estrogen is protective. However, in women, synthetic hormone use (oral contraceptives and hormone replacement therapy) increases the histologic severity of NASH. Cirrhosis caused by NASH appears to be uncommon in Blacks. Persons with NAFLD are at increased risk for cardiovascular disease, chronic kidney disease, and colorectal cancer.

Microvesicular steatosis is seen with Reye syndrome, with toxicity caused by didanosine, stavudine, linezolid, valproic acid, or high-dose tetracycline, and with acute fatty liver of pregnancy and may result in acute liver failure. Women in whom fatty liver of pregnancy develops often have a defect in fatty acid oxidation due to reduced long-chain 3-hydroxyacyl-CoA dehydrogenase activity.

► Clinical Findings

A. Symptoms and Signs

Most patients with NAFLD are asymptomatic or have mild right upper quadrant discomfort. Hepatomegaly is present in up to 75% of patients, but stigmata of chronic liver disease are uncommon. Rare instances of subacute liver failure caused by previously unrecognized NASH have been described. Signs of portal hypertension generally signify advanced liver fibrosis or cirrhosis, but occasionally occur in patients with mild or no fibrosis and severe steatosis.

B. Laboratory Findings

Laboratory studies may show mildly elevated aminotransferase and alkaline phosphatase levels; however, laboratory values may be normal in up to 80% of persons with hepatic steatosis. In contrast to alcohol-associated liver disease, the ratio of ALT to AST is almost always greater than 1 in NAFLD, but it decreases, often to less than 1, as advanced fibrosis and cirrhosis develop. Antinuclear or smooth muscle antibodies and an elevated serum ferritin level may each be detected in 30% of patients with NASH. Iron deficiency is also common and associated with female sex, obesity, increased waist circumference, diabetes mellitus, and Black or Native American race.

C. Imaging

Macrovascular steatosis may be demonstrated on ultrasonography, CT, or MRI. However, imaging does not distinguish steatosis from steatohepatitis or detect fibrosis.

D. Liver Biopsy

Percutaneous liver biopsy is diagnostic and is the standard approach to assessing the degree of inflammation and fibrosis. The risks of the procedure must be balanced against the impact of the added information on management decisions and assessment of prognosis. Liver biopsy is generally not recommended in asymptomatic persons with unsuspected hepatic steatosis detected on imaging but normal liver biochemistry test results. The histologic spectrum of NAFLD includes fatty liver, isolated portal fibrosis,

steatohepatitis, and cirrhosis. A risk score for predicting advanced fibrosis, known as BARD, is based on body mass index more than 28, AST/ALT ratio 0.8 or more, and diabetes mellitus; it has a high negative predictive value (ie, a low score reliably excludes advanced fibrosis). Another risk score for advanced fibrosis, the NAFLD Fibrosis Score (<http://nafldscore.com>) based on age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio, has a positive predictive value of over 80% and identifies patients at increased risk for liver-related complications and death. Another index for predicting fibrosis that has also performed well is FIB-4, which is based on age, platelet count, and serum AST and ALT levels. A clinical scoring system to predict the likelihood of NASH in morbidly obese persons includes six predictive factors: hypertension, type 2 diabetes mellitus, sleep apnea, AST greater than 27 units/L (0.54 mkat/L), ALT greater than 27 units/L (0.54 mkat/L), and non-Black race. The role of liver stiffness measurement by elastography to assess the fibrosis stage continues to evolve; in general, results are less accurate in obese than in nonobese persons.

Treatment

Treatment consists of lifestyle changes to remove or modify the offending factors. Weight loss, dietary fat restriction, and moderate exercise (through reduction of abdominal obesity) often lead to improvement in liver biochemical tests and steatosis in obese patients with NAFLD. A Mediterranean diet can reduce liver fat without weight loss and is often recommended. Loss of 3–5% of body weight appears necessary to improve steatosis, but loss of at least 10% may be needed to improve necroinflammation and fibrosis. Exercise may reduce liver fat with minimal or no weight loss and no reduction in ALT levels. Resistance training and aerobic exercise are equally effective in reducing hepatic fat content in patients with NAFLD and type 2 diabetes mellitus. Although avoidance of alcohol is recommended, modest wine consumption may not be detrimental in nonsmokers. Various drugs for the treatment of NASH are under study. Vitamin E 800 international units/day (to reduce oxidative stress) appears to be of benefit in patients with NASH who do not have diabetes mellitus; there is controversy as to whether vitamin E increases the risk of prostate cancer in men. Thiazolidinediones reverse insulin resistance and, in most relevant studies, have improved both serum aminotransferase levels and histologic features of steatohepatitis but lead to weight gain. Metformin, which reduces insulin resistance, improves abnormal liver chemistries but may not reliably improve liver histology. Pentoxifylline improves liver biochemical test levels but is associated with a high rate of side effects, particularly nausea. Ursodeoxycholic acid, 12–15 mg/kg/day, has not consistently resulted in biochemical and histologic improvement in patients with NASH but may be effective when given in combination with vitamin E. Hepatic steatosis due to total parenteral nutrition may be ameliorated—and perhaps prevented—with supplemental choline. Obeticholic acid, a farnesoid X receptor agonist that has been approved for the treatment of PBC, has been shown to improve liver fibrosis in patients with NASH.

Statins are not contraindicated in persons with NAFLD and may protect against histologic progression in some patients. Bariatric surgery may be considered in patients with a body mass index greater than 35 and leads to histologic regression of NASH in most patients (but worsening in a few). Liver transplantation is indicated in appropriate candidates with advanced cirrhosis caused by NASH, now the third most common (and most rapidly increasing) indication for liver transplantation in the United States. Liver transplantation for NASH with advanced cirrhosis may be associated with increased mortality from cardiovascular disease and sepsis compared with liver transplantation for other indications.

Prognosis

Fatty liver often has a benign course and is readily reversible with discontinuation of alcohol (or no more than one glass of wine per day, which has been reported in some, but not other, studies to reduce the frequency of NASH in persons with NAFLD), or treatment of other underlying conditions; if untreated, fibrosis progresses at an average rate of 1 stage every 14 years, with 20% of patients progressing more rapidly. In patients with NAFLD, the likelihood of NASH is increased by the following factors: obesity, older age, non-Black ethnicity, female sex, diabetes mellitus, hypertension, higher ALT or AST level, higher AST/ALT ratio, low platelet count, elevated fasting C-peptide level, and a high ultrasound steatosis score. NASH may be associated with hepatic fibrosis in 40% of cases with progression at a rate of 1 stage every 7 years; cirrhosis develops in 9–25%; and decompensated cirrhosis occurs in 30–50% of cirrhotic patients over 10 years. The course may be more aggressive in diabetic persons than in nondiabetic persons. In the United States, NAFLD is associated with 8% of all-cause mortality and more than one-third of deaths associated with liver disease and with diabetes mellitus. Risk factors for fibrosis in patients with fatty liver without NASH are severe steatosis and the I148M variant of the *PNPLA3* gene. Heterozygous alpha-1-antitrypsin deficiency also appears to be a risk factor for fibrosis in patients with NASH. Mortality is increased in patients with NAFLD, correlates with fibrosis stage, and is more likely to be the result of cardiovascular disease and malignancy (including hepatocellular carcinoma, colorectal cancer, and breast cancer) than of liver disease. Risk factors for mortality are older age, male sex, White race, the I148M variant of the *PNPLA3* gene, smoking, higher body mass index, hypertension, diabetes mellitus, and cirrhosis. In the general population, in fact, both excess adiposity and reduced activity are significant predictors of liver-related mortality. Steatosis is a cofactor for the progression of fibrosis in patients with other causes of chronic liver disease, such as hepatitis C, and NAFLD appears to be a risk factor for chronic kidney disease. Hepatocellular carcinoma is a complication of cirrhosis caused by NASH, as it is for other causes of cirrhosis, and has been reported even in the absence of cirrhosis. NASH accounts for a substantial percentage of cases labeled as cryptogenic cirrhosis and can recur following liver transplantation. Central obesity is an independent risk factor for death from cirrhosis of any cause.

► When to Refer

Refer patients with NAFLD who require liver biopsy for diagnosis.

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CIRRHOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Result of injury that leads to both fibrosis and regenerative nodules.
- ▶ May be reversible if cause is removed.
- ▶ The clinical features result from hepatic cell dysfunction, portosystemic shunting, and portal hypertension.

► General Considerations

Cirrhosis is the result of hepatocellular injury that leads to both fibrosis and regenerative nodules throughout the liver. It is the eleventh leading cause of death globally and eighth leading cause of death in the United States. The prevalence rate is 0.27%, with an estimated 1.5 billion persons having chronic liver disease and 2.14 million liver-related deaths worldwide. Hospitalization rates for cirrhosis and portal hypertension are rising in the United States, and patients with chronic liver disease have longer hospital stays, more readmissions, and less access to post-acute care than patients with other chronic diseases. Causes include chronic viral hepatitis; alcohol; drug toxicity; autoimmune and metabolic liver diseases, including NAFLD; and miscellaneous disorders. Celiac disease appears to be associated with an increased risk of cirrhosis. Many patients have more than one risk factor (eg, chronic hepatitis and alcohol use) and likely genetic predisposition. Mexican Americans and Blacks have a higher frequency of cirrhosis than Whites because of a higher rate of risk factors. In persons at increased risk for liver injury (eg, heavy alcohol use, obesity, iron overload), higher coffee and tea consumption and statin use reduce the risk of cirrhosis.

Clinically, cirrhosis is considered to progress through three stages that correlate with the thickness of fibrous septa: compensated, compensated with varices, and decompensated (ascites, variceal bleeding, encephalopathy, or jaundice).

A diagnosis of acute-on-chronic liver failure should be made in a patient with cirrhosis and acute decompensation (new or worsening ascites, gastrointestinal hemorrhage,

overt encephalopathy, worsening nonobstructive jaundice, or bacterial infection associated with other organ failure). Various definitions have been proposed. The pathophysiology is largely unknown but is thought to involve intense systemic inflammation and oxidative stress. Precipitating factors include infections, hemodynamic instability, heavy alcohol use, and drug hepatotoxicity.

► Clinical Findings

A. Symptoms and Signs

The clinical features of cirrhosis result from hepatocyte dysfunction, portosystemic shunting, and portal hypertension. Patients may have no symptoms for long periods. The onset of symptoms may be insidious or, less often, abrupt. Fatigue, disturbed sleep, muscle cramps, and weight loss are common. In advanced cirrhosis, anorexia is usually present and may be extreme, with associated nausea and occasional vomiting, as well as reduced muscle strength and exercise capacity. Abdominal pain may be present and is related either to hepatic enlargement and stretching of Glisson capsule or to the presence of ascites. Menstrual abnormalities (usually amenorrhea), erectile dysfunction, loss of libido, sterility, and gynecomastia may occur. Hematemesis is the presenting symptom in 15–25%. The risk of falls is increased in hospitalized patients with cirrhosis who are taking psychoactive medications.

Skin manifestations consist of spider telangiectasias (invariably on the upper half of the body), palmar erythema (mottled redness of the thenar and hypothenar eminences), and Dupuytren contractures. Evidence of vitamin deficiencies (glossitis and cheilosis) is common. Weight loss, wasting (due to sarcopenia), and the appearance of chronic illness are present in advanced cirrhosis. Jaundice—usually not an initial sign—is mild at first, increasing in severity during the later stages of the disease. In 70% of cases, the liver is enlarged, palpable, and firm if not hard and has a sharp or nodular edge; the left lobe may predominate. Splenomegaly is present in 35–50% of cases and is associated with an increased risk of complications of portal hypertension. The superficial veins of the abdomen and thorax are dilated, reflecting the intrahepatic obstruction to portal blood flow, as do rectal varices. The abdominal wall veins fill from below when compressed. Ascites, pleural effusions, peripheral edema, and ecchymoses are late findings. Ascites is classified as grade 1, or mild, when it is detectable only by ultrasound; grade 2, or moderate, when associated with symmetrical abdominal distention; and grade 3, or gross, when associated with marked abdominal distention. Encephalopathy, characterized by day-night reversal, asterixis, tremor, dysarthria, delirium, drowsiness, and, ultimately, coma also occurs late in the course except when precipitated by an acute hepatocellular insult or an episode of gastrointestinal bleeding or infection. Fever is present in up to 35% of patients and usually reflects associated alcohol-associated hepatitis, spontaneous bacterial peritonitis, or another intercurrent infection.

B. Laboratory Findings

Laboratory abnormalities are either absent or minimal in early or compensated cirrhosis. Anemia, a frequent

finding, is often macrocytic; causes include suppression of erythropoiesis by alcohol as well as folate deficiency, hemolysis, hypersplenism, and occult or overt blood loss from the gastrointestinal tract. The white blood cell count may be low, reflecting hypersplenism, or high, suggesting infection. Thrombocytopenia, the most common cytopenia in cirrhotic patients, is secondary to alcohol-induced marrow suppression, sepsis, folate deficiency, or splenic sequestration. Prolongation of the prothrombin time may result from reduced levels of clotting factors (except factor VIII). However, bleeding risk correlates poorly with the prothrombin time because of concomitant abnormalities of fibrinolysis, and among hospitalized patients under age 45, cirrhosis is associated with an increased risk of venous thromboembolism.

Blood chemistries reflect hepatocellular injury and dysfunction, manifested by modest elevations of AST and alkaline phosphatase and progressive elevation of the bilirubin. Serum albumin decreases as the disease progresses; gamma-globulin levels are increased and may be as high as in autoimmune hepatitis. The risk of diabetes mellitus is increased in patients with cirrhosis, particularly when associated with HCV infection, alcoholism, hemochromatosis, or NAFLD. Vitamin D deficiency has been reported in as many as 91% of patients with cirrhosis. In cirrhosis of all causes, the following are common: (1) blunted cardiac inotropic and chronotropic responses to exercise, stress, and drugs, (2) prolongation of the QT interval in the setting of a hyperkinetic circulation, and (3) systolic and diastolic ventricular dysfunction in the absence of other known causes of cardiac disease (“cirrhotic cardiomyopathy”). Relative adrenal insufficiency appears to be common in patients with advanced cirrhosis, even in the absence of sepsis, and in those with acute-on-chronic liver failure and may relate in part to reduced synthesis of cholesterol and increased levels of proinflammatory cytokines.

C. Imaging

Ultrasonography is helpful for assessing liver size and detecting ascites or hepatic nodules, including small hepatocellular carcinomas. Together with a Doppler study, it may establish patency of the splenic, portal, and hepatic veins. Hepatic nodules are characterized further by contrast-enhanced CT or MRI. Nodules indeterminant for malignancy may be biopsied under ultrasound or CT guidance.

D. Liver Biopsy

Liver biopsy may show inactive cirrhosis (fibrosis with regenerative nodules) with no specific features to suggest the underlying cause. Alternatively, there may be additional features of alcohol-associated liver disease, chronic hepatitis, NASH, or other specific causes of cirrhosis. Liver biopsy may be performed by laparoscopy or, in patients with coagulopathy and ascites, by a transjugular or endoscopic ultrasonographic approach. Combinations of routine blood tests (eg, AST, platelet count), including the FibroSure test, serum markers of hepatic fibrosis

(eg, hyaluronic acid, amino-terminal propeptide of type III collagen, tissue inhibitor of matrix metalloproteinase 1), and ultrasound or magnetic resonance elastography are potential alternatives to liver biopsy for the diagnosis or exclusion of cirrhosis. In persons with chronic hepatitis C, for example, a low FibroSure or elastography score reliably excludes advanced fibrosis, a high score reliably predicts advanced fibrosis, and intermediate scores are inconclusive. The combination of increased liver stiffness and a platelet count below 150,000/mcL ($150 \times 10^9/\text{L}$) is an indicator of clinically significant portal hypertension.

E. Other Tests

Esophagogastroduodenoscopy confirms the presence of varices and detects specific causes of bleeding in the esophagus, stomach, and proximal duodenum. In selected cases, wedged hepatic vein pressure measurement may establish the presence and cause of portal hypertension.

► Differential Diagnosis

The most common causes of cirrhosis are alcohol, chronic hepatitis C infection, NAFLD, and hepatitis B infection. Hemochromatosis is the most commonly identified genetic disorder that causes cirrhosis. Other diseases associated with cirrhosis include Wilson disease, alpha-1-antitrypsin (alpha-1-antiprotease) deficiency, and celiac disease. PBC occurs more frequently in women than men. Secondary biliary cirrhosis may result from chronic biliary obstruction due to a stone, stricture, or neoplasm. Heart failure and constrictive pericarditis may lead to hepatic fibrosis (“cardiac cirrhosis”) complicated by ascites. Hereditary hemorrhagic telangiectasia can lead to portal hypertension because of portosystemic shunting and nodular transformation of the liver as well as high-output heart failure. Many cases of cirrhosis are “cryptogenic,” in which unrecognized NAFLD may play a role.

► Complications

Upper gastrointestinal tract bleeding may occur from varices, portal hypertensive gastropathy, or gastroduodenal ulcer (see Chapter 15). Varices may also result from portal vein thrombosis, which may complicate cirrhosis. Liver failure may be precipitated by alcoholism, surgery, and infection. Hepatic Kupffer cell (reticuloendothelial) dysfunction and decreased opsonic activity lead to an increased risk of systemic infection (which may be increased further by the use of proton pump inhibitors, which increase mortality fourfold). These infections include nosocomial infections, which may be classified as spontaneous bloodstream infections, urinary tract infections, pulmonary infections, spontaneous bacterial peritonitis, *Clostridioides difficile* infection, and intervention-related infections. These nosocomial infections are increasingly caused by multidrug-resistant bacteria. Osteoporosis occurs in 12–55% of patients with cirrhosis. The risk of hepatocellular carcinoma is increased greatly in persons with cirrhosis (see Chapter 39). Varices, ascites, and encephalopathy may arise when there is clinically significant portal hypertension (hepatic venous pressure gradient greater than 10 mm Hg).

Treatment

A. General Measures

Most important is abstinence from alcohol. The diet should be palatable, with adequate calories (20–40 kcal/kg body weight per day depending on the patient's body mass index and the presence or absence of malnutrition) and protein (1.2–1.5 g/kg/day depending on the presence or absence of malnutrition) and, if there is fluid retention, sodium restriction. In the presence of hepatic encephalopathy, protein intake should be reduced to no less than 60–80 g/day. Vitamin supplementation is desirable. Muscle cramps may be helped by L-carnitine, 300 mg orally four times a day, calcium, quinidine, or muscle relaxants. Patients with cirrhosis should receive the HAV, HBV, and pneumococcal vaccines, a yearly influenza vaccine, and, when available, a COVID vaccine. Liver transplantation in appropriate candidates is curative. Care coordination and palliative care, when appropriate, have been shown to improve outcomes and reduce readmission rates.

B. Treatment of Complications

1. Ascites and edema—Diagnostic paracentesis is indicated for patients who have new ascites or who have been hospitalized for a complication of cirrhosis; it reduces mortality, especially if performed within 12 hours of admission. Serious complications of paracentesis, including bleeding, infection, or bowel perforation, occur in 1.6% of procedures and are associated with therapeutic (vs diagnostic) paracentesis and possibly with Child-Pugh class C, a platelet count less than 50,000/mcL ($50 \times 10^9/L$), and alcohol-associated cirrhosis. In patients with coagulopathy, however, pre-paracentesis prophylactic transfusions do not appear to be necessary. In addition to a cell count and culture, the ascitic albumin level should be determined: a serum-ascites albumin gradient (serum albumin minus ascitic fluid albumin) greater than or equal to 1.1 suggests portal hypertension. An elevated ascitic adenosine deaminase level is suggestive of tuberculous peritonitis, but the sensitivity of the test is reduced in patients with portal hypertension. Occasionally, cirrhotic ascites is chylous (rich in triglycerides); other causes of chylous ascites are malignancy, tuberculosis, and recent abdominal surgery or trauma.

In individuals with ascites, the urinary sodium concentration is often less than 10 mEq/L (10 mmol/L). Free water excretion is also impaired in cirrhosis, and hyponatremia may develop.

In all patients with cirrhotic ascites, dietary sodium intake may initially be restricted to 2000 mg/day; the intake of sodium may be liberalized slightly after diuresis ensues. NSAIDs are contraindicated, and aminoglycosides, angiotensin-converting enzyme inhibitors, and angiotensin II antagonists should be avoided. In some patients, ascites diminishes promptly with bed rest and dietary sodium restriction alone. Fluid intake is often restricted (to 800–1000 mL/day) in patients with hyponatremia. Treatment of severe hyponatremia (serum sodium less than 125 mEq/L [125 mmol/L]) with vasopressin receptor antagonists (eg, intravenous conivaptan, 20 mg daily) can

be considered, but such treatment is expensive, causes thirst, and does not improve survival; oral tolvaptan is contraindicated in patients with liver disease because of potential hepatotoxicity. Long-term intravenous administration of albumin has been reported to improve 18-month survival in patients with cirrhotic ascites.

A. DIURETICS—Spironolactone, generally in combination with furosemide, should be used in patients who do not respond to salt restriction alone. The dose of spironolactone is initially 100 mg orally daily and may be increased by 100 mg every 3–5 days (up to a maximal conventional daily dose of 400 mg/day, although higher doses have been used) until diuresis is achieved, typically preceded by a rise in the urinary sodium concentration. A “spot” urine sodium concentration that exceeds the potassium concentration correlates with a 24-hour sodium excretion greater than 78 mmol/day, which predicts diuresis in patients adherent to a salt-restricted diet. Monitoring for hyperkalemia is important. In patients who cannot tolerate spironolactone because of side effects, such as painful gynecomastia, amiloride (another potassium-sparing diuretic) may be used in a starting dose of 5–10 mg orally daily. Diuresis is augmented by the addition of a loop diuretic such as furosemide. This potent diuretic, however, will maintain its effect even with a falling glomerular filtration rate, with resulting prerenal azotemia. The dose of oral furosemide is increased in concert with spironolactone and ranges from 40 mg/day to 160 mg/day, and blood pressure, urinary output, mental status, and serum electrolytes (especially potassium) should be monitored in patients taking the drug. The goal of weight loss in the ascitic patient without associated peripheral edema should be no more than 1–1.5 lb/day (0.5–0.7 kg/day).

B. LARGE-VOLUME PARACENTESIS—In patients with massive ascites and respiratory compromise, ascites refractory to diuretics (“diuretic resistant”), or intolerable diuretic side effects (“diuretic intractable”), large-volume paracentesis (more than 5 L) is effective. Intravenous albumin concomitantly at a dosage of 6–8 g/L of ascites fluid removed protects the intravascular volume and may prevent post-paracentesis circulatory dysfunction, although the usefulness of this practice is debated and albumin is expensive. Large-volume paracentesis can be repeated daily until ascites is largely resolved and may decrease the need for hospitalization. If possible, diuretics should be continued in the hope of preventing recurrent ascites.

C. TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)—TIPS is an effective treatment of variceal bleeding refractory to standard therapy (eg, endoscopic band ligation) and has shown benefit in the treatment of severe refractory ascites. The technique involves insertion of an expandable metal stent between a branch of the hepatic vein and the portal vein over a catheter inserted via the internal jugular vein. Increased renal sodium excretion and control of ascites refractory to diuretics can be achieved in about 75% of selected cases. The success rate is lower in patients with underlying chronic kidney disease. TIPS appears to be the treatment of choice for refractory hepatic

hydrothorax (translocation of ascites across the diaphragm to the pleural space); video-assisted thoracoscopy with pleurodesis using talc may be effective when TIPS is contraindicated. Complications of TIPS include hepatic encephalopathy in 20–30% of cases, infection, shunt stenosis in up to 60% of cases, and shunt occlusion in up to 30% of cases when bare stents are used; polytetrafluoroethylene-covered stents are associated with long-term patency rates of 80–90%. Long-term patency often requires periodic shunt revisions. In most cases, patency can be maintained by balloon dilation, local thrombolysis, or placement of an additional stent. TIPS is particularly useful in patients who require short-term control of variceal bleeding or ascites until liver transplantation can be performed. In patients with refractory ascites, TIPS results in lower rates of ascites recurrence and hepatorenal syndrome but a higher rate of hepatic encephalopathy than occurs with repeated large-volume paracentesis; a benefit in survival has been demonstrated in one study and a meta-analysis. Chronic kidney disease, diastolic cardiac dysfunction, refractory encephalopathy, and hyperbilirubinemia (greater than 5 mg/dL [85.5 μmol/L]) are associated with mortality after TIPS, and patients with a serum bilirubin greater than 3 mg/dL (50 μmol/L), platelets less than 75,000/mcL ($75 \times 10^9/\text{L}$), preexisting encephalopathy, active infection, severe heart failure, or severe pulmonary hypertension may not benefit from TIPS.

2. Spontaneous bacterial peritonitis—Spontaneous bacterial peritonitis is heralded by abdominal pain, increasing ascites, fever, and progressive encephalopathy in a patient with cirrhotic ascites; symptoms are typically mild. (Analogously, spontaneous bacterial empyema may complicate hepatic hydrothorax and is managed similarly.) Risk factors in cirrhotic patients with ascites include gastroesophageal variceal bleeding and possibly use of a proton pump inhibitor. Paracentesis reveals an ascitic fluid with, most commonly, a total white cell count of up to 500 cells/mcL ($0.5 \times 10^9/\text{L}$) with a high polymorphonuclear (PMN) cell count (250/mcL [$0.25 \times 10^9/\text{L}$] or more) and a protein concentration of 1 g/dL (10 g/L) or less, corresponding to decreased ascitic opsonic activity. Cultures of ascites give the highest yield—80–90% positive—when specialized culture bottles are inoculated at the bedside. Common isolates are *Escherichia coli* and *Streptococcus* spp. Gram-positive cocci are the most common isolates in patients who have undergone an invasive procedure such as central venous line placement, and the frequency of enterococcal isolates is increasing. Anaerobes are uncommon. Pending culture results, if there are 250 or more PMNs/mcL or symptoms or signs of infection, intravenous antibiotic therapy should be initiated with cefotaxime, 2 g every 8–12 hours for at least 5 days. Alternative choices include ceftriaxone, amoxicillin-clavulanic acid, and levofloxacin (in patients not receiving fluoroquinolone prophylaxis). Oral ofloxacin, 400 mg twice daily for 7 days, or, in a patient not already taking a fluoroquinolone for prophylaxis against bacterial peritonitis, a 2-day course of intravenous ciprofloxacin, 200 mg twice daily, followed by oral ciprofloxacin, 500 mg twice daily for 5 days, may

be effective alternative regimens in selected patients. A carbapenem or piperacillin-tazobactam has been recommended for patients with hospital-acquired spontaneous bacterial peritonitis, which is increasingly caused by multi-drug-resistant organisms, and specific therapy should be guided by local resistance patterns. In patients with spontaneous bacterial peritonitis in the setting of acute-on-chronic liver failure, treatment with meropenem and daptomycin is recommended. Supplemental administration of intravenous albumin, 1.5 g/kg at diagnosis and 1 g/kg on day 3 (which may have anti-inflammatory effects in addition to expanding plasma volume), prevents further renal impairment and reduces mortality, particularly in patients with a serum creatinine greater than 1 mg/dL (83.3 μmol/L), blood urea nitrogen greater than 30 mg/dL (10.8 mmol/L), or total bilirubin greater than 4 mg/dL (68.4 μmol/L). Response to therapy can be documented, if necessary, by a decrease in the PMN count of at least 50% on repeat paracentesis 48 hours after initiation of therapy. The overall mortality rate is high—up to 30% during hospitalization and up to 70% by 1 year. Mortality may be predicted by the 22/11 model: MELD score greater than 22 and peripheral white blood cell count higher than 11,000/mcL ($11 \times 10^9/\text{L}$). Another model predictive of mortality includes the blood urea nitrogen, white blood cell count, Child-Pugh score, and mean arterial pressure. Patients with cirrhosis and septic shock have a high frequency of relative adrenal insufficiency, which if present requires administration of hydrocortisone.

In survivors of bacterial peritonitis, the risk of recurrent peritonitis may be decreased by long-term ciprofloxacin (eg, 500 mg orally once per day), norfloxacin (400 mg orally daily; no longer available in the United States), or trimethoprim-sulfamethoxazole (eg, one double-strength tablet once per day). In cases of recurrent peritonitis, the causative organism is often resistant to fluoroquinolones and may become multidrug resistant in some cases. In high-risk cirrhotic patients without prior peritonitis (eg, those with an ascitic protein less than 1.5 g/dL and serum bilirubin greater than 3 mg/dL (51.3 μmol/L), serum creatinine greater than 1.2 mg/dL (99.96 μmol/L), blood urea nitrogen 25 mg/dL (9 mmol/L) or more, sodium 130 mEq/L (130 mmol/L) or less, or Child-Pugh score of 9 or more, the risk of peritonitis, hepatorenal syndrome, and mortality for at least 1 year may be reduced by prophylactic trimethoprim-sulfamethoxazole, one double-strength tablet once per day, ciprofloxacin, 500 mg once per day, or norfloxacin, 400 mg orally once a day (though not in the United States). In patients hospitalized for acute variceal bleeding, intravenous ceftriaxone (1 g per day), followed by oral trimethoprim-sulfamethoxazole (one double-strength tablet once per day) or ciprofloxacin (500 mg every 12 hours), for a total of 7 days, reduces the risk of bacterial peritonitis. Nonantibiotic prophylactic strategies, including probiotics, bile acids, and statins, are under study.

3. Hepatorenal syndrome—Hepatorenal syndrome occurs in up to 10% of patients with advanced cirrhosis and ascites. It is characterized by azotemia (increase in serum creatinine level of greater than 0.3 mg/dL [26.5 μmol/L])

within 48 hours or increase by 50% or more from baseline within the previous 7 days or a urine volume less than 0.5 mL/kg/h for 6 hours or longer in the absence of (1) current or recent nephrotoxic drug use, (2) macroscopic signs of structural kidney injury, or (3) shock and failure of kidney function to improve following 2 days of diuretic withdrawal and volume expansion with albumin, 1 g/kg up to a maximum of 100 g/day. Oliguria, hyponatremia, and a low urinary sodium concentration are typical features. Hepatorenal syndrome is diagnosed only when other causes of acute kidney injury (including prerenal azotemia and acute tubular necrosis) have been excluded. Acute kidney injury-hepatorenal syndrome (formerly type 1 hepatorenal syndrome) is typically associated with at least doubling of the serum creatinine to a level greater than 2.5 mg/dL (208.25 mcmol/L) or by halving of the creatinine clearance to less than 20 mL/min (0.34 mL/s/1.73 m² BSA) in less than 2 weeks. Chronic kidney disease (or nonacute kidney injury)-hepatorenal syndrome (formerly type 2 hepatorenal syndrome) is more slowly progressive and chronic. An acute decrease in cardiac output is often the precipitant.

In addition to discontinuation of diuretics, clinical improvement and an increase in short-term survival may follow intravenous infusion of albumin in combination with one of the following vasoconstrictor regimens for 7–14 days: (1) intravenous terlipressin (not yet approved by the US FDA, which in 2020 requested more information regarding its risk-benefit profile; it remains the preferred agent where available); (2) intravenous norepinephrine; or (3) oral midodrine plus octreotide, subcutaneously or intravenously. Oral midodrine, 7.5 mg three times daily, added to diuretics, increases the blood pressure and has also been reported to convert refractory ascites to diuretic-sensitive ascites. Prolongation of survival has been associated with use of MARS, a modified dialysis method that selectively removes albumin-bound substances. Improvement and sometimes normalization of kidney function may also follow placement of a TIPS; survival after 1 year is reported to be predicted by the combination of a serum bilirubin level less than 3 mg/dL (50 mcmol/L) and a platelet count greater than 75,000/mcL ($75 \times 10^9/\text{L}$). Continuous venovenous hemofiltration and hemodialysis are of uncertain value in hepatorenal syndrome. Liver transplantation is the ultimate treatment of choice, but many patients die before a donor liver can be obtained. Mortality correlates with the MELD score and presence of a systemic inflammatory response. Acute kidney injury-hepatorenal syndrome is often irreversible in patients with a systemic infection. The 3-month probability of survival in cirrhotic patients with hepatorenal syndrome (15%) is lower than that for renal failure associated with infections (31%), hypovolemia (46%), and parenchymal kidney disease (73%).

4. Hepatic encephalopathy—Hepatic encephalopathy is a state of disordered central nervous system function resulting from failure of the liver to detoxify noxious agents of gut origin because of hepatocellular dysfunction and portosystemic shunting. The clinical spectrum ranges from day-night reversal and mild intellectual impairment to coma. Patients with covert (formerly minimal) hepatic

encephalopathy have no recognizable clinical symptoms but demonstrate mild cognitive, psychomotor, and attention deficits on standardized psychometric tests and an increased rate of traffic accidents. The stages of overt encephalopathy are (1) mild confusion, (2) drowsiness, (3) stupor, and (4) coma. A revised staging system known as SONIC (spectrum of neurocognitive impairment in cirrhosis) encompasses absent, covert, and stages 2 to 4 encephalopathy. Ammonia is the most readily identified and measurable toxin but is not solely responsible for the disturbed mental status. Bleeding into the intestinal tract may significantly increase the amount of protein in the bowel and precipitate encephalopathy. Other precipitants include constipation, alkalosis, and potassium deficiency induced by diuretics, opioids, hypnotics, and sedatives; medications containing ammonium or amino compounds; paracentesis with consequent hypovolemia; hepatic or systemic infection; and portosystemic shunts (including TIPS). In one study, risk factors for hepatic encephalopathy in patients with cirrhosis included a higher serum bilirubin level and use of a nonselective beta-blocker, whereas a higher serum albumin level and use of a statin were protective. The diagnosis is based primarily on detection of characteristic symptoms and signs, including asterixis. A smartphone app called EncephalApp using the “Stroop test” (asking the patient to name the color of a written word rather than the word itself, even when the word is the name of a different color) has proved useful for detecting covert hepatic encephalopathy. The role of neuroimaging studies (eg, cerebral PET, magnetic resonance spectroscopy) in the diagnosis of hepatic encephalopathy is evolving.

Oral protein intake is withheld during acute episodes if the patient cannot eat. When the patient resumes oral intake, protein intake should be 60–80 g/day as tolerated; vegetable protein is better tolerated than meat protein. Gastrointestinal bleeding should be controlled and blood purged from the gastrointestinal tract. This can be accomplished with 120 mL of magnesium citrate by mouth or nasogastric tube every 3–4 hours until the stool is free of gross blood or by administration of lactulose. The value of treating patients with covert hepatic encephalopathy is uncertain; probiotic agents may have some benefit.

Lactulose, a nonabsorbable synthetic disaccharide syrup, is digested by bacteria in the colon to short-chain fatty acids, resulting in acidification of colon contents. This acidification favors the formation of ammonium ion in the $\text{NH}_4^+ \leftrightarrow \text{NH}_3 + \text{H}^+$ equation; NH_4^+ is not absorbable, whereas NH_3 is absorbable and thought to be neurotoxic. Lactulose also leads to a change in bowel flora so that fewer ammonia-forming organisms are present. When given orally, the initial dose of lactulose for acute hepatic encephalopathy is 30 mL three or four times daily. The dose should then be titrated so that the patient produces 2–3 soft stools per day. When given rectally because the patient is unable to take medicines orally, the dose is 200 g/300 mL given as a solution of lactulose in saline or sorbitol in a retention enema for 30–60 minutes; it may be repeated every 4–6 hours. Bowel cleansing with a polyethylene glycol colonoscopy preparation is also effective in patients with acute overt hepatic encephalopathy and may be preferable. Continued use of

lactulose after an episode of acute encephalopathy reduces the frequency of recurrences.

The ammonia-producing intestinal flora may also be controlled with an oral antibiotic. The nonabsorbable agent rifaximin, 550 mg orally twice daily, is preferred and has been shown as well to maintain remission of and reduce the risk of rehospitalization for hepatic encephalopathy over a 24-month period, with or without the concomitant use of lactulose. Metronidazole, 250 mg orally three times daily, has also shown benefit. Patients who do not respond to lactulose alone may improve with a course of an antibiotic added to treatment with lactulose.

Opioids and sedatives metabolized or excreted by the liver should be avoided. If agitation is marked, oxazepam, 10–30 mg, which is not metabolized by the liver, may be given cautiously by mouth or by nasogastric tube. Zinc deficiency should be corrected, if present, with oral zinc sulfate, 600 mg/day in divided doses. Sodium benzoate, 5 g orally twice daily, ornithine aspartate, 9 g orally three times daily, and L-acyl-carnitine (an essential factor in the mitochondrial transport of long-chain fatty acids), 4 g orally daily, may lower blood ammonia levels, but there is less experience with these drugs than with lactulose. Flumazenil is effective in about 30% of patients with severe hepatic encephalopathy, but the drug is short-acting and intravenous administration is required. Use of special dietary supplements enriched with branched-chain amino acids is usually unnecessary except in occasional patients who are intolerant of standard protein supplements.

5. Coagulopathy—Hypoprothrombinemia caused by malnutrition and vitamin K deficiency may be treated with vitamin K (eg, phytonadione, 5 mg orally or intravenously daily); however, this treatment is ineffective when synthesis of coagulation factors is impaired because of hepatic disease. In such cases, correcting the prolonged prothrombin time would require large volumes of fresh frozen plasma (see Chapter 14). Because the effect is transient, plasma infusions are not indicated except for active bleeding or before an invasive procedure, and even then, their value has been questioned because of concomitant alterations in anti-hemostatic factors and because bleeding risk does not correlate with the INR. Recombinant activated factor VIIa may be an alternative but is expensive and poses a 1–2% risk of thrombotic complications. In fact, bleeding risk in critically ill patients with cirrhosis has been shown to correlate with bleeding on hospital admission, a platelet count less than 30,000/mcL ($30 \times 10^9/L$), a fibrinogen level less than 60 mg/dL (1.764 mcmol/L), and an activated partial thromboplastin time greater than 100 seconds. In patients with active bleeding or undergoing an invasive procedure, goals for management according to some guidelines include a hematocrit value greater than 25%, platelet count greater than 50,000/mcL ($50 \times 10^9/L$), and fibrinogen level greater than 120 mg/dL (3.528 mcmol/L). A thrombopoietin analog, eg, avatrombopag or lusutrombopag, reduces the need for platelet transfusions in patients with cirrhosis and a platelet count less than 50,000/mcL ($50 \times 10^9/L$) who undergo invasive procedures but must be administered for at least 3–5 days for the platelet count to start to rise.

Eltrombopag, the first-generation agent, was associated with an increased risk of portal vein thrombosis and arterial thromboembolism.

6. Hemorrhage from esophageal varices—See Chapter 15.

7. Hepatopulmonary syndrome and portopulmonary hypertension—Shortness of breath in patients with cirrhosis may result from pulmonary restriction and atelectasis caused by massive ascites or hepatic hydrothorax. The hepatopulmonary syndrome—the triad of chronic liver disease, an increased alveolar-arterial gradient while the patient is breathing room air, and intrapulmonary vascular dilatations or arteriovenous communications that result in a right-to-left intrapulmonary shunt—occurs in 5–32% of patients with cirrhosis. Patients often have greater dyspnea (platypnea) and arterial deoxygenation (orthodeoxia) in the upright than in the recumbent position. The diagnosis should be suspected in a cirrhotic patient with a pulse oximetry level of 94–96% or lower.

Contrast-enhanced echocardiography is a sensitive screening test for detecting pulmonary vascular dilatations, whereas macroaggregated albumin lung perfusion scanning is more specific and may be used to confirm the diagnosis. High-resolution CT may be useful for detecting dilated pulmonary vessels that may be amenable to embolization in patients with severe hypoxemia (PO_2 less than 60 mm Hg [7.8 kPa]) who respond poorly to supplemental oxygen.

Medical therapy has been disappointing. Long-term oxygen therapy is recommended for severely hypoxic patients. The syndrome may reverse with liver transplantation, although postoperative morbidity and mortality from severe hypoxic respiratory failure are increased in patients with a preoperative arterial PO_2 less than 44 mm Hg (5.9 kPa) or with substantial intrapulmonary shunting. TIPS may provide palliation in patients with hepatopulmonary syndrome awaiting transplantation.

Portopulmonary hypertension occurs in 0.7% of patients with cirrhosis. Female sex and autoimmune hepatitis have been reported to be risk factors, and large spontaneous portosystemic shunts are present in many affected patients and are associated with a lack of response to treatment. In cases confirmed by right-sided heart catheterization, treatment with the prostaglandins epoprostenol, iloprost, or treprostinal (the latter two are easier to administer); the endothelin-receptor antagonists bosentan (no longer used because of potential hepatotoxicity), ambrisentan, or macitentan; the phosphodiesterase-5 inhibitors sildenafil, tadalafil, or vardenafil; the oral prostacyclin receptor agonist selexipag; or the direct cyclic GMP analog riociguat may reduce pulmonary hypertension and thereby facilitate liver transplantation. Beta-blockers worsen exercise capacity and are contraindicated, and calcium channel blockers should be used with caution because they may worsen portal hypertension. Liver transplantation is contraindicated in patients with moderate to severe pulmonary hypertension (mean pulmonary pressure greater than 35 mm Hg).

C. Liver Transplantation

Liver transplantation is indicated in selected cases of irreversible, progressive chronic liver disease, acute-on-chronic

liver failure, acute liver failure, and certain metabolic diseases in which the metabolic defect is in the liver. Absolute contraindications include malignancy (except relatively small hepatocellular carcinomas in a cirrhotic liver—see Chapter 39), advanced cardiopulmonary disease (except hepatopulmonary syndrome), and sepsis. Relative contraindications include age over 70 years, morbid obesity, portal and mesenteric vein thrombosis, active alcohol or drug abuse, severe malnutrition, and lack of patient understanding. With the emergence of effective antiretroviral therapy for HIV disease, a major cause of mortality in these patients has shifted to liver disease caused by HCV and HBV infection; experience to date suggests that the outcome of liver transplantation is comparable to that for non-HIV-infected liver transplant recipients. Patients with alcoholism should generally be abstinent for 6 months. Liver transplantation should be considered in patients with worsening functional status, rising bilirubin, decreasing albumin, worsening coagulopathy, refractory ascites, recurrent variceal bleeding, or worsening encephalopathy; prioritization is based on the MELD (or MELD-Na) score. Treatment of HCV infection should be deferred until after transplantation in patients in whom the MELD score is 21 or higher. Combined liver-kidney transplantation is indicated in patients with associated kidney failure presumed to be irreversible. The major impediment to more widespread use of liver transplantation is a shortage of donor organs. Adult living donor liver transplantation is an option for some patients, and extended-criteria donors are used. Five-year survival rates over 80% are now reported. Hepatocellular carcinoma, hepatitis B and C, Budd-Chiari syndrome, and autoimmune liver disease may recur in the transplanted liver. The incidence of recurrence of hepatitis B can be reduced by preoperative and postoperative treatment with a nucleoside or nucleotide analog and perioperative administration of HBIG, and hepatitis C can be treated with direct-acting antiviral agents. Immunosuppression is achieved with combinations of cyclosporine, tacrolimus, sirolimus, corticosteroids, azathioprine, and mycophenolate mofetil and may be complicated by infections, advanced chronic kidney disease, neurologic disorders, and drug toxicity, as well as graft rejection, vascular occlusion, or bile leaks. Patients taking these drugs are at risk for obesity, diabetes mellitus, and hyperlipidemia and may develop recurrent or de novo NAFLD following transplantation.

► Prognosis

The risk of death from compensated cirrhosis is 4.7 times that of the risk in the general population, and the risk from decompensated cirrhosis is 9.7 times higher. Use of statins appears to decrease the risk of decompensation in patients with compensated cirrhosis, in whom the risk of decompensation can be predicted with a scoring system that includes serum albumin, serum bilirubin, age, serum AST and ALT, and platelet count. Prognostic scoring systems for cirrhosis include the Child-Pugh score and MELD score (Table 16-8). The MELD (or MELD-Na) score, which incorporates the serum bilirubin, creatinine, and sodium levels and the INR, is also a measure of mortality risk in patients with end-stage

Table 16-8. Child-Pugh and Model for End-Stage Liver Disease (MELD) scoring systems for staging cirrhosis.

Child-Pugh Scoring System			
Parameter	Numerical Score		
	1	2	3
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight to moderate	Moderate to severe
Bilirubin, mg/dL (μmol/L)	< 2.0 (34.2)	2–3 (34.2–51.3)	> 3.0 (51.3)
Albumin, g/dL (g/L)	> 3.5 (35)	2.8–3.5 (28–35)	< 2.8 (28)
Prothrombin time (seconds increased)	1–3	4–6	> 6.0
Total Numerical Score and Corresponding Child-Pugh Class			
Score	Class		
	5–6	A	
	7–9	B	
10–15	C		

MELD Scoring System	
Original MELD = $11.2 \log_e(\text{INR}) + 3.78 \log_e(\text{bilirubin [mg/dL]}) + 9.57 \log_e(\text{creatinine [mg/dL]}) + 6.43$.	(Range 6–40.)
The MELD-Na score was developed in 2016 by adding the serum sodium as a component: MELD-Na = MELD + $(140 - \text{Na}) \times (1 - 0.025 \times \text{MELD})$.	

INR, international normalized ratio.

liver disease and is particularly useful for predicting short- and intermediate-term survival and complications of cirrhosis (eg, bacterial peritonitis) as well as determining allocation priorities for donor livers. Additional (MELD-exception) points are given for patients with conditions such as hepatopulmonary syndrome and hepatocellular carcinoma that may benefit from liver transplantation. A MELD score of 17 or more is required for liver transplant listing. In patients with a relatively low MELD score (less than 21) and a low priority for liver transplantation, an elevated hepatic venous pressure gradient, persistent ascites, hepatic encephalopathy, and a low health-related quality of life are additional independent predictors of mortality, and further modifications of the MELD score are under consideration. Only 50% of patients with severe hepatic dysfunction (serum albumin less than 3 g/dL [30 g/L], bilirubin greater than 3 mg/dL [51.3 μmol/L], ascites, encephalopathy, cachexia, and upper gastrointestinal bleeding) survive 6 months without transplantation. The risk of death in this subgroup of patients with advanced cirrhosis is associated with muscle wasting, age 65 years or older, mean arterial pressure 82 mm Hg or less, severe kidney dysfunction, cognitive dysfunction, ventilatory insufficiency, prothrombin

time 16 seconds or longer, delayed and suboptimal treatment of sepsis, and second infections. For cirrhotic patients admitted to an intensive care unit, the Royal Free Hospital score, consisting of the serum bilirubin, INR, serum lactate, alveolar-arterial oxygen gradient, and blood urea nitrogen, has been reported to predict mortality. The combination of the MELD score and serum lactate at the time of hospitalization has been reported to predict inpatient mortality better than the MELD score alone. Severe kidney dysfunction increases mortality up to sevenfold in patients with cirrhosis, and at least 25% of patients who survive an episode of acute kidney injury develop chronic kidney disease. The ratio of neutrophils to lymphocytes in peripheral blood has been reported to correlate with mortality 1 year after a non-elective hospitalization in patients with cirrhosis. Obesity and diabetes mellitus appear to be risk factors for clinical deterioration and cirrhosis-related mortality, as is continued alcohol use in patients with alcohol-associated cirrhosis. The use of beta-blockers for portal hypertension is beneficial early in the course. However, beta-blockers become ineffective and may be associated with reduced survival in patients with refractory ascites, spontaneous bacterial peritonitis, sepsis, or severe alcohol-associated hepatitis because of their negative effect on cardiac compensatory reserve. In general, beta-blockers should be discontinued when the systolic blood pressure is less than 90 mm Hg, the serum sodium level is less than 130 mEq/L, or acute kidney injury has developed, although results of some studies have challenged these guidelines. Patients with cirrhosis are at risk for the development of hepatocellular carcinoma, with rates of 3–5% per year for alcohol-associated and viral hepatitis-related cirrhosis. Liver transplantation has markedly improved the outlook for patients with cirrhosis who are candidates and are referred for evaluation early in the course. Patients with compensated cirrhosis are given additional priority for liver transplantation if they are found to have a lesion larger than 2 cm in diameter consistent with hepatocellular carcinoma. In-hospital mortality from cirrhosis declined from 9.1% in 2002 to 5.4% in 2010 and that from variceal bleeding in patients with cirrhosis declined from over 40% in 1980 to 15% in 2000. Rates and costs of hospital admissions increased substantially between 2005 and 2015, primarily because of increases in the rates of cirrhosis caused by NAFLD. Patients hospitalized with cirrhosis and an infection are at high risk for subsequent infections, particularly if they are older, taking a proton pump inhibitor, or receiving antibiotic prophylaxis for spontaneous bacterial peritonitis.

► When to Refer

- For liver biopsy.
- When the MELD score is 14 or higher.
- For upper endoscopy to screen for gastroesophageal varices.

► When to Admit

- Gastrointestinal bleeding.
- Stage 3–4 hepatic encephalopathy.
- Worsening kidney function.

- Severe hyponatremia.
- Serious infection.
- Profound hypoxia.

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PRIMARY BILIARY CHOLANGITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Occurs in middle-aged women.
- ▶ Often asymptomatic.
- ▶ Elevation of alkaline phosphatase, positive antimitochondrial antibodies, elevated IgM, increased cholesterol.
- ▶ Characteristic liver biopsy.
- ▶ In later stages, can present with fatigue, jaundice, features of cirrhosis, xanthelasmata, xanthomas, steatorrhea.

► General Considerations

PBC is a chronic disease of the liver characterized by autoimmune destruction of small intrahepatic bile ducts and cholestasis. The designation “primary biliary cholangitis” has replaced “primary biliary cirrhosis” because many patients do not have cirrhosis. The disease is insidious in onset, occurs usually in women aged 40–60 years, and is often detected by the chance finding of elevated alkaline phosphatase levels. Estimated incidence and prevalence rates in the United States are 4.5 and 65.4 per 100,000, respectively, in women, and 0.7 and 12.1 per 100,000, respectively, in men. These rates may be increasing. The frequency of the disease among first-degree relatives of affected persons is 1.3–6%, the risk is increased in second- and third-degree relatives, and the concordance rate in identical twins is high. PBC is associated with HLA DRB1*08 and DQB1. The disease may be associated with Sjögren syndrome, autoimmune thyroid disease, Raynaud syndrome, systemic sclerosis (scleroderma), hypothyroidism, and celiac disease; all patients with PBC should be screened for these conditions. Infection with *Novosphingobium aromaticivorans* or *Chlamydophila pneumoniae* may trigger or cause PBC. A history of urinary tract infections (caused by *E. coli* or *Lactobacillus delbrueckii*) and smoking, and possibly use of hormone replacement therapy and hair dye, are risk

factors, and clustering of cases in time and space argues for a causative role of environmental agents.

► Clinical Findings

A. Symptoms and Signs

Many patients are asymptomatic for years. The onset of clinical illness is insidious and is heralded by fatigue (excessive daytime somnolence) and pruritus. With progression, physical examination reveals hepatosplenomegaly. Xanthomatous lesions may occur in the skin and tendons and around the eyelids. Jaundice, steatorrhea, and signs of portal hypertension are late findings, although occasional patients have esophageal varices despite an early histologic stage. Autonomic dysfunction, including orthostatic hypotension and associated fatigue and cognitive dysfunction, appear to be common. The risk of low bone density, osteoporosis, and fractures is increased in patients with PBC (who tend to be older women) possibly due in part to polymorphisms of the vitamin D receptor.

B. Laboratory Findings

Blood counts are normal early in the disease. Liver biochemical tests reflect cholestasis with elevation of alkaline phosphatase, cholesterol (especially high-density lipoproteins and lipoprotein X), and, in later stages, bilirubin. Antimitochondrial antibodies are present in 95% of patients, and serum IgM levels are elevated.

► Diagnosis

The diagnosis of PBC is based on the detection of cholestatic liver chemistries (often initially an isolated elevation of the alkaline phosphatase) and antimitochondrial antibodies in a titer greater than 1:40 in serum. Baseline ultrasonography should be obtained. Liver biopsy is not necessary for diagnosis unless antimitochondrial antibodies are absent but permits histologic staging: I, portal inflammation with granulomas; II, bile duct proliferation, periportal inflammation; III, interlobular fibrous septa; and IV, cirrhosis. Estimations of histologic stage by an “enhanced liver fibrosis (ELF) assay” which incorporates serum levels of hyaluronic acid, tissue inhibitor of metalloproteinase-1, and procollagen III amino peptide, and by elastography have shown promise.

► Differential Diagnosis

The disease must be differentiated from chronic biliary tract obstruction (stone or stricture), carcinoma of the bile ducts, primary sclerosing cholangitis, sarcoidosis, cholestatic drug toxicity (eg, chlorpromazine), and (in some cases) chronic hepatitis. Patients with a clinical and histologic picture of PBC but no antimitochondrial antibodies are said to have antimitochondrial antibody-negative PBC (previously termed “autoimmune cholangitis”), which has been associated with lower serum IgM levels and a greater frequency of smooth muscle antibodies and ANA. Many such patients are found to have antimitochondrial

antibodies by immunoblot against recombinant proteins (rather than standard immunofluorescence). Some patients have overlapping features of PBC and autoimmune hepatitis.

► Treatment

Cholestyramine (4 g) in water or juice three times daily may be beneficial for pruritus; colestipol and colesvelam may be better tolerated but have not been shown to reduce pruritus. Rifampin, 150–300 mg orally twice daily, is inconsistently beneficial. Opioid antagonists (eg, naloxone, 0.2 mcg/kg/min by intravenous infusion, or naltrexone, starting at 12.5 mg/day by mouth) show promise in the treatment of pruritus but may cause opioid withdrawal symptoms. The 5-hydroxytryptamine (5-HT₃) serotonin receptor antagonist ondansetron, 4 mg orally three times a day as needed, and the selective serotonin reuptake inhibitor sertraline, 75–100 mg/day orally, may also provide some benefit. For refractory pruritus, plasmapheresis or extracorporeal albumin dialysis may be needed. Modafinil, 100–200 mg/day orally, may improve daytime somnolence but is poorly tolerated. Deficiencies of vitamins A, D, and K may occur if steatorrhea is present and are aggravated when cholestyramine is administered.

Ursodeoxycholic acid (13–15 mg/kg/day in one or two doses) is the preferred medical treatment for PBC. It has been shown to slow the progression of disease (particularly in early-stage disease), stabilize histology, improve long-term survival, reduce the risk of developing esophageal varices, and delay (and possibly prevent) the need for liver transplantation, even in the absence of liver biochemical improvement. Complete normalization of liver biochemical tests occurs in 20% of treated patients within 2 years and 40% within 5 years, and survival is similar to that of healthy controls when the drug is given to patients with stage 1 or 2 PBC. The rate of improvement in the alkaline phosphatase to normal or near-normal levels has been reported to be lower in men than women (72% vs 80%) and higher in women diagnosed after age 70 than before age 30 (90% vs 50%). Ursodeoxycholic acid has also been reported to reduce the risk of recurrent colorectal adenomas in patients with PBC. Side effects include weight gain and rarely loose stools. The drug can be continued during pregnancy.

Obeticholic acid, a farnesoid-X receptor agonist, was approved by the FDA in 2016 for the treatment of PBC in patients with an incomplete response or intolerance to ursodeoxycholic acid. Obeticholic acid is begun in a dose of 5 mg orally daily and increased to 10 mg daily at 6 months if tolerated, based on the decline in serum alkaline phosphatase and bilirubin levels. In patients with Child-Pugh class B or C cirrhosis, the initial dose is 5 mg weekly. Treatment with obeticholic acid has been shown to stabilize or reverse hepatic fibrosis. The principal side effect is pruritus. Given the expense of the drug, the cost-effectiveness of obeticholic acid has been questioned.

Bezafibrate (not available in the United States) and fenofibrate, which activate peroxisome proliferator-

activated receptors (PPARs) and inhibit bile acid synthesis, have shown promise as second-line agents and improve symptoms, liver biochemical test levels, and fibrosis. Colchicine (0.6 mg orally twice daily) and methotrexate (15 mg/wk orally) have had some reported benefit in improving symptoms and serum levels of alkaline phosphatase and bilirubin. Methotrexate may also improve liver histology in some patients, but overall response rates have been disappointing. For patients with advanced disease, liver transplantation is the treatment of choice.

► Prognosis

Without liver transplantation, survival averages 7–10 years once symptoms develop but has improved for younger women since the introduction of ursodeoxycholic acid. Progression to liver failure and portal hypertension may be accelerated by smoking. Patients with early-stage disease in whom the alkaline phosphatase and AST are less than 1.5 times normal and bilirubin is 1 mg/dL (17.1 μmol/L) or less after 1 year of therapy with ursodeoxycholic acid (Paris II criteria) are at low long-term risk for cirrhosis and have a life expectancy similar to that of the healthy population. Attainment of a serum bilirubin level less than 0.6 times the upper limit of normal or a normal alkaline phosphatase level is associated with the lowest risk for liver transplantation or death. Pregnancy is well tolerated in younger patients. In advanced disease, an adverse prognosis is indicated by a high Mayo risk score that includes older age, high serum bilirubin, edema, low serum albumin, and prolonged prothrombin time as well as by variceal hemorrhage. Other prognostic models include the Globe index, which is based on age, serum bilirubin, serum albumin, serum alkaline phosphatase, and platelet count and, in treated patients, the UK-PBC score, which is based on the baseline serum albumin and platelet count and the serum bilirubin, aminotransferases, and alkaline phosphatase after 12 months of ursodeoxycholic acid. An increase in liver stiffness of more than 2.1 kilopascals per year indicates an adverse prognosis. A prediction tool for varices has been proposed based on the serum albumin, serum alkaline phosphatase, platelet count, and splenomegaly. Fatigue is associated with an increased risk of cardiac mortality and may not be reversed by liver transplantation. Among asymptomatic patients, a decline in liver function is observed in up to 50% by 5 years, and at least one-third will become symptomatic within 15 years. The risk of hepatocellular carcinoma appears to be increased in patients with PBC; risk factors include older age, male sex, prior blood transfusions, advanced histologic stage, signs of cirrhosis or portal hypertension, and a biochemical nonresponse to ursodeoxycholic acid. Liver transplantation should be considered when the MELD-Na score is at least 15, total serum bilirubin at least 6, or Mayo risk score at least 7.8. Liver transplantation for advanced PBC is associated with a 1-year survival rate of 85–90%. The disease recurs in the graft in 20% of patients by 3 years and 37% by 10 years. A reduced risk of recurrence, graft loss, and death is associated with preventive treatment with ursodeoxycholic acid in combination with cyclosporine (rather than tacrolimus).

► When to Refer

- For liver biopsy.
- For liver transplant evaluation.

► When to Admit

- Gastrointestinal bleeding.
- Stage 3–4 hepatic encephalopathy.
- Worsening kidney function.
- Severe hyponatremia.
- Profound hypoxia.

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HEMOCHROMATOSIS



ESSENTIALS OF DIAGNOSIS

- Usually suspected because of a family history or an elevated iron saturation or serum ferritin.
- Most patients are asymptomatic; the disease is rarely recognized clinically before the fifth decade.
- Hepatic abnormalities and cirrhosis, heart failure, hypogonadism, and arthritis.
- *HFE* gene mutation (usually C282Y/C282Y) is found in most cases.

► General Considerations

Hemochromatosis is an autosomal recessive disease caused in most cases by a mutation in the *HFE* gene on chromosome 6. The *HFE* protein is thought to play an important role in the process by which duodenal crypt cells sense body iron stores, and a mutation of the gene leads to increased iron absorption from the duodenum. A decrease in the synthesis or expression of hepcidin, the principal iron regulatory hormone, is thought to be a key pathogenic factor in all forms of hemochromatosis. About 85% of persons with well-established hemochromatosis are homozygous for the C282Y mutation (type 1a hemochromatosis). The frequency of the C282Y mutation averages 7% in Northern European and North American White populations, resulting in a 0.5% frequency of homozygotes (of whom 38–50% will develop biochemical evidence of iron

overload but only 28% of men and 1% of women will develop clinical symptoms). The C282Y mutation and hemochromatosis are uncommon in Blacks and Asian American populations. A second genetic mutation (H63D) may contribute to the development of iron overload in a small percentage (1.5%) of persons who are compound heterozygotes for C282Y and H63D (type 1b); iron overload-related disease develops in only a few patients (particularly those who have a comorbidity such as diabetes mellitus and fatty liver). A third mutation (S65C) may lead to increased serum iron and ferritin levels without clinical significance (type 1c). High serum ferritin levels are seen in hyperferritinemia cataract syndrome associated with mutations in the *FTL* (ferritin L-chain) gene. An uncommon juvenile-onset variant that is characterized by severe iron overload, cardiac dysfunction, hypogonadotropic hypogonadism, and a high mortality rate is usually linked to a mutation of a gene on chromosome 1q designated *HJV* that produces a protein called hemojuvelin (type 2a) or, rarely, to a mutation in the *HAMP* gene on chromosome 19 that encodes hepcidin (type 2b). Rare instances of hemochromatosis result from mutations in the genes that encode transferrin receptor 2 (*TFR2*) (type 3) and ferroportin (*SLC40A1*) (type 4a). Type 4b hemochromatosis is characterized by resistance of ferroportin to hepcidin.

Hemochromatosis is characterized by increased accumulation of iron as hemosiderin in the liver, pancreas, heart, adrenals, testes, pituitary, and kidneys. Cirrhosis is more likely to develop in affected persons who drink alcohol excessively or have obesity-related hepatic steatosis than in those who do not; other risk factors include age and diabetes mellitus. Eventually, hepatic and pancreatic insufficiency, heart failure, and hypogonadism may develop; overall mortality is increased slightly. Heterozygotes do not develop cirrhosis in the absence of associated disorders such as viral hepatitis or NAFLD.

Clinical Findings

A. Symptoms and Signs

The onset of clinical disease is usually after age 50 years—earlier in men than in women; however, because of widespread liver biochemical testing and iron screening, the diagnosis is usually made long before symptoms develop. Early symptoms are nonspecific (eg, fatigue, arthralgia). Later clinical manifestations include a symmetric arthropathy that is similar to osteoarthritis and calcium pyrophosphate deposition disease (and ultimately the need for joint replacement surgery in some cases), hepatomegaly and evidence of hepatic dysfunction, skin pigmentation (combination of slate-gray due to iron and brown due to melanin, sometimes resulting in a bronze color), cardiac enlargement with or without heart failure or conduction defects, diabetes mellitus with its complications, and erectile dysfunction in men. Interestingly, population studies have shown an increased prevalence of liver disease but not of diabetes mellitus, arthritis, or heart disease in C282Y homozygotes. In patients in whom cirrhosis develops, bleeding from esophageal varices may occur, and there is a 15–20% frequency of hepatocellular carcinoma. Affected

patients are at increased risk of infection with *Vibrio vulnificus*, *Listeria monocytogenes*, *Yersinia enterocolitica*, and other siderophilic organisms. The risk of porphyria cutanea tarda is increased in persons with the C282Y or H63D mutation, and C282Y homozygotes have twice the risk of colorectal and breast cancer than persons without the C282Y variant.

B. Laboratory Findings

Laboratory findings include mildly abnormal liver tests (AST, alkaline phosphatase), an elevated plasma iron with greater than 45% transferrin saturation, a low unsaturated iron-binding capacity, and an elevated serum ferritin (although a normal iron saturation or a normal ferritin does not exclude the diagnosis). Affected men are more likely than affected women to have an elevated ferritin level. Testing for *HFE* mutations is indicated in any patient with evidence of iron overload. Interestingly, in persons with an elevated serum ferritin, the likelihood of detecting C282Y homozygosity decreases with increasing ALT and AST levels, which likely reflect hepatic inflammation and secondary iron overload. In contrast to secondary iron overload, the serum ALT level is often normal.

C. Imaging

MRI and CT may show changes consistent with iron overload of the liver, and MRI-based techniques (eg, T2 spin echo and T2^{*} gradient-recalled echo MRI) can quantitate hepatic iron stores and help assess the degree of hepatic fibrosis.

D. Liver Biopsy

In patients who are homozygous for C282Y, liver biopsy is often indicated to determine whether cirrhosis is present. Biopsy can be deferred, however, in patients in whom the serum ferritin level is less than 1000 mcg/L, serum AST level is normal, and hepatomegaly is absent; the likelihood of cirrhosis is low in these persons. Risk factors for advanced fibrosis include male sex, excess alcohol consumption, and diabetes mellitus. Liver biopsy also may be indicated when iron overload is suspected even though the patient is neither homozygous for C282Y nor a C282Y/H63D compound heterozygote. In patients with hemochromatosis, the liver biopsy characteristically shows extensive iron deposition in hepatocytes and in bile ducts, and the hepatic iron index—hepatic iron content per gram of liver converted to micromoles and divided by the patient's age—is generally higher than 1.9 (though no longer used for diagnosis). Only 5% of patients with hereditary hemochromatosis identified by screening in a primary care setting have cirrhosis.

Screening

Iron studies and *HFE* testing are recommended for all first-degree family members of a proband; children of an affected person (C282Y homozygote) need to be screened only if the patient's spouse carries the C282Y or H63D mutation. General population screening for

hemochromatosis is not recommended because the clinical penetrance of C282Y homozygosity and morbidity and mortality from hemochromatosis are low. Patients with otherwise unexplained chronic liver disease, chondrocalcinosis, erectile dysfunction, and type 1 diabetes mellitus (especially late-onset) should be screened for iron overload.

► Treatment

Affected persons are advised to avoid foods rich in iron (such as red meat), alcohol, vitamin C, raw shellfish, and supplemental iron, although dietary restrictions may not be necessary in those undergoing phlebotomy. Weekly phlebotomies of 1 or 2 units (250–500 mL) of blood (each containing about 250 mg of iron) are indicated in all symptomatic patients, and those with a serum ferritin level of at least 300 mcg/L (men) or 200 mcg/L (women) with an increased fasting iron saturation (greater than or equal to 45%); these phlebotomies should be continued for up to 2–3 years to achieve depletion of iron stores. The hematocrit and serum iron values should be monitored. When iron store depletion is achieved (iron saturation less than 50% and serum ferritin level 50–100 mcg/L), phlebotomies (every 2–4 months) to maintain serum ferritin levels between 50 mcg/L and 100 mcg/L are continued, although compliance has been reported to decrease with time. Administration of a proton pump inhibitor, which reduces intestinal iron absorption, decreases the maintenance phlebotomy volume requirement. In C282Y homozygous women, a body mass index greater than 28 is associated with a lower phlebotomy requirement, possibly because hepcidin levels are increased by overweight. Complications of hemochromatosis—arthropathy, diabetes mellitus, heart disease, portal hypertension, and hypopituitarism—also require treatment.

The chelating agent deferoxamine is indicated for patients with hemochromatosis and anemia or in those with secondary iron overload due to thalassemia who cannot tolerate phlebotomies. The drug is administered intravenously or subcutaneously in a dose of 20–40 mg/kg/day infused over 24 hours and can mobilize 30 mg of iron per day; however, treatment is painful and time-consuming. Two oral chelators, deferasirox, 20 mg/kg once daily, and deferiprone, 25 mg/kg three times daily, have been approved for treatment of iron overload due to blood transfusions and may be appropriate in persons with hemochromatosis who cannot tolerate phlebotomy; however, these agents have a number of side effects and drug-drug interactions.

The course of hemochromatosis appears to be favorably altered by phlebotomy therapy, although the evidence for a benefit is surprisingly sparse. There is some evidence that persons with hemochromatosis have better survival than that of the general population. With phlebotomy therapy, hepatic fibrosis may regress, and in precirrhotic patients, cirrhosis may be prevented. Cardiac conduction defects may improve with treatment. Joint disease, diabetes mellitus, and hypogonadism may not reverse with treatment of hemochromatosis. More severe joint symptoms are associated with persistent increases in the transferrin saturation, even if the serum ferritin level is maintained below

50 mcg/L. In patients with cirrhosis, varices may reverse, the risk of variceal bleeding declines, and the risk of hepatocellular carcinoma may be reduced. In those with an initial serum ferritin level greater than 1000 mcg/L (2247 pmol/L), the risk of death is fivefold greater than in those with a serum ferritin of 1000 mcg/L (2247 pmol/L) or less. In treated patients, only those with a serum ferritin greater than 2000 mcg/L (4494 pmol/L) are reported to have increased mortality, mainly related to liver disease. Since 1997, posttransplant survival rates have been excellent. Following liver transplantation, serum iron studies and hepcidin levels are normal, and phlebotomy is not required.

► When to Refer

- For liver biopsy.
- For initiation of therapy.

Bardou-Jacquet E et al. Regression of fibrosis stage with treatment reduces long-term risk of liver cancer in patients with hemochromatosis caused by mutation in *HFE*. *Clin Gastroenterol Hepatol*. 2020;18:1851. [PMID: 31622736]

Kowdley KV et al. ACG Clinical Guideline: hereditary hemochromatosis. *Am J Gastroenterol*. 2019;114:1202. [PMID: 31335359]

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WILSON DISEASE



ESSENTIALS OF DIAGNOSIS

- Rare autosomal recessive disorder that usually occurs in persons under age 40.
- Excessive deposition of copper in the liver and brain.
- Serum ceruloplasmin, the plasma copper-carrying protein, is low.
- Urinary excretion of copper and hepatic copper concentration are high.

► General Considerations

Wilson disease (hepatolenticular degeneration) is a rare autosomal recessive disorder that usually occurs in persons between 3 and 55 years of age. The worldwide prevalence is generally stated to be about 30 per million population, but the frequency of the allele appears to be greater than implied by this estimate. The condition is characterized by excessive deposition of copper in the liver and brain. The genetic defect, localized to chromosome 13 (*ATP7B*), has been shown to affect a copper-transporting adenosine triphosphatase in the liver and leads to copper accumulation in the liver and oxidative damage of hepatic mitochondria. Most patients are compound heterozygotes (ie, carry two different mutations). Over 600 mutations in the Wilson disease gene have been identified. The H1069Q mutation

accounts for 37–63% of disease alleles in populations of Northern European descent. The major physiologic aberration in Wilson disease is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver, resulting in increased tissue deposition, especially in the liver, brain, cornea, and kidney.

► Clinical Findings

Wilson disease tends to present as liver disease in adolescents (more common in females) and neuropsychiatric disease in young adults (more common in males), but there is great variability, and onset of symptoms after age 40 is more common than previously thought. The diagnosis should always be considered in any child or young adult with hepatitis, splenomegaly with hypersplenism, Coombs-negative hemolytic anemia, portal hypertension, and neurologic or psychiatric abnormalities. Wilson disease should also be considered in persons under 40 years of age with chronic hepatitis or acute liver failure.

Hepatic involvement may range from elevated liver biochemical tests (although the alkaline phosphatase may be low, particularly in patients with acute severe liver disease) to cirrhosis and portal hypertension. In patients with acute liver failure (seen much more often in females than males), the diagnosis of Wilson disease is suggested by an alkaline phosphatase (in units/L)-to-total bilirubin (in mg/dL) ratio less than 4 and an AST-to-ALT ratio greater than 2.2. The neurologic manifestations of Wilson disease are related to basal ganglia dysfunction and include an akinetic-rigid syndrome similar to parkinsonism, pseudosclerosis with tremor, ataxia, and a dystonic syndrome. Dysarthria, dysphagia, incoordination, and spasticity are common. Migraines, insomnia, and seizures have been reported. Psychiatric features include behavioral and personality changes and emotional lability and may precede characteristic neurologic features. The risk of depression is increased. The pathognomonic sign of the condition is the brownish or gray-green Kayser-Fleischer ring, which represents fine pigmented granular deposits in Descemet membrane in the cornea (Figure 16–4). The ring is usually most marked at the superior and inferior poles of the cornea. It is sometimes seen with the naked eye and is readily detected by slit-lamp examination. It may be absent in patients with hepatic manifestations only but is usually present in those with neuropsychiatric disease. Renal calculi, aminoaciduria, renal tubular acidosis, hypoparathyroidism, infertility, hemolytic anemia, and subcutaneous lipomas may occur.

► Diagnosis

The diagnosis can be challenging, even with the use of scoring systems (eg, the Leipzig criteria), and is generally based on demonstration of increased urinary copper excretion (greater than 40 mcg/24 h and usually greater than 100 mcg/24 h) or low serum ceruloplasmin levels (less than 14 mg/dL [140 mg/L]; less than 10 mg/dL [100 mg/L] strongly suggests the diagnosis), and elevated hepatic copper concentration (greater than 250 mcg/g of



▲ **Figure 16–4.** Brownish Kayser-Fleischer ring at the rim of the cornea in a patient with Wilson disease. (Used, with permission, from Marc Solioz, University of Berne in Usatine RP, Smith MA, Chumley H, Mayeaux EJ Jr. *The Color Atlas of Family Medicine*, 2nd ed. New York, NY: McGraw-Hill, 2013.)

dry liver) as well as Kayser-Fleischer rings, neurologic symptoms, and Coombs-negative hemolytic anemia. However, increased urinary copper (on three separate 24-hour collections) and a low serum ceruloplasmin level (by a standard immunologic assay), while useful, are neither completely sensitive nor specific for Wilson disease, although an enzymatic assay for ceruloplasmin appears to be more accurate; lipemia can interfere with the measurement of ceruloplasmin by the standard assay. The ratio of exchangeable copper to total copper in serum has been reported to be a reliable test for the diagnosis of Wilson disease. In the past, demonstration of a rise in urinary copper after a penicillamine challenge was used in equivocal cases (when the serum ceruloplasmin level was normal), but the test has been validated only in children, lacks sensitivity, and is rarely used now. Liver biopsy may show acute or chronic hepatitis or cirrhosis. MRI of the brain may show evidence of increased basal ganglia, brainstem, and cerebellar copper even early in the course of the disease. If available, molecular analysis of *ATP7B* mutations can be diagnostic.

► Treatment

Early treatment to remove excess copper before it can produce hepatic or neurologic damage is essential. Initially, restriction of dietary copper (shellfish, organ foods, nuts, mushrooms, and chocolate) may be of value. Oral D-penicillamine (0.75–2 g/day in divided doses taken 1 hour before or 2 hours after food) has traditionally been the drug of choice and enhances urinary excretion of chelated copper. Oral pyridoxine, 50 mg per week, is added because D-penicillamine is an antimetabolite of this vitamin. If D-penicillamine treatment cannot be tolerated because of gastrointestinal intolerance, hypersensitivity, autoimmune reactions, nephrotoxicity, or bone marrow toxicity, trientine, 250–500 mg three times a day, a chelating agent as effective as D-penicillamine but with a lower

rate of adverse effects, is used. Trientine is increasingly used as a first-line agent, although its cost has become exorbitant. Oral zinc acetate or zinc gluconate, 50 mg of elemental zinc three times a day taken 30 minutes before or 2 hours after a meal, interferes with intestinal absorption of copper, promotes fecal copper excretion, and has been used as first-line therapy in asymptomatic or pregnant patients and those with neurologic disease, in combination with a chelating agent, or as maintenance therapy after decoppering with a chelating agent, but adverse gastrointestinal effects often lead to discontinuation and its long-term efficacy and safety (including a risk of hepatotoxicity) have been questioned; it can lead to copper deficiency in normal persons. Ammonium tetrathiomolybdate, which complexes copper in the intestinal tract, showed promise as initial therapy for neurologic Wilson disease, and a newer formulation, bis-choline tetrathiomolybdate, is more chemically stable and appears to be effective.

Treatment should continue indefinitely. The doses of penicillamine and trientine should be reduced during pregnancy. Supplemental vitamin E, an antioxidant, has been recommended but not rigorously studied. Once the serum nonceruloplasmin copper level is within the normal range (50–150 mcg/L), the dose of chelating agent can be reduced to the minimum necessary for maintaining that level. The prognosis is good in patients who are effectively treated before liver or brain damage has occurred, but long-term survival is reduced in patients with cirrhosis at diagnosis (84% after 20 years). Liver transplantation is indicated for acute liver failure (often after plasma exchange or dialysis with MARS as a stabilizing measure) and decompensated cirrhosis (with excellent outcomes). Liver transplantation is generally not recommended for intractable isolated neuropsychiatric disease. All first-degree relatives, especially siblings, require screening with serum ceruloplasmin, liver biochemical tests, and slit-lamp examination or, if the causative mutation is known, with mutation analysis.

► When to Refer

All patients with Wilson disease should be referred for diagnosis and treatment.

► When to Admit

- Acute liver failure.
- Gastrointestinal bleeding.
- Stage 3–4 hepatic encephalopathy.
- Worsening kidney function.
- Severe hyponatremia.
- Profound hypoxia.

Ferrarese A et al. Outcomes of liver transplant for adults with Wilson's disease. *Liver Transpl*. 2020;26:507. [PMID: 31901209]

Shribman S et al. Clinical presentations of Wilson disease. *Ann Transl Med*. 2019;7:S60. [PMID: 31179297]

HEPATIC VENOUS OUTFLOW OBSTRUCTION (Budd-Chiari Syndrome)

ESSENTIALS OF DIAGNOSIS

- ▶ Right upper quadrant pain and tenderness.
- ▶ Ascites.
- ▶ Imaging studies show occlusion/absence of flow in the hepatic vein(s) or inferior vena cava.
- ▶ Clinical picture is similar in sinusoidal obstruction syndrome but major hepatic veins are patent.

► General Considerations

Factors that predispose patients to hepatic venous outflow obstruction, or Budd-Chiari syndrome, including hereditary and acquired hypercoagulable states, can be identified in 75% of affected patients; multiple disorders are found in up to 45%. Up to 50% of cases are associated with polycythemia vera or other myeloproliferative neoplasms (which entail a 1% risk of Budd-Chiari syndrome). These cases are often associated with a specific mutation (*V617F*) in the gene that codes for JAK2 tyrosine kinase and may otherwise be subclinical. Other predispositions to thrombosis (eg, activated protein C resistance [factor V Leiden mutation] [25% of cases], protein C or S or antithrombin deficiency, hyperprothrombinemia [factor II *G20210A* mutation] [rarely], the methylenetetrahydrofolate reductase *TT677* mutation, antiphospholipid antibodies) may be identified in other cases. Hepatic vein obstruction may be associated with caval webs, right-sided heart failure or constrictive pericarditis, neoplasms that cause hepatic vein occlusion, paroxysmal nocturnal hemoglobinuria, Behcet syndrome, vasculitis, sarcoidosis, inflammatory bowel disease, blunt abdominal trauma, use of oral contraceptives, and pregnancy. In India, China, and South Africa, Budd-Chiari syndrome is associated with a poor standard of living and often the result of occlusion of the hepatic portion of the inferior vena cava, presumably due to prior thrombosis. The clinical presentation is mild but the course is frequently complicated by hepatocellular carcinoma.

Some cytotoxic agents and pyrrolizidine alkaloids (comfrey or "bush teas") may cause *sinusoidal obstruction syndrome* (previously known as veno-occlusive disease because the terminal venules are often occluded), which mimics Budd-Chiari syndrome clinically. Sinusoidal obstruction syndrome may occur in patients who have undergone hematopoietic stem cell transplantation, particularly those with pretransplant serum aminotransferase elevations or fever during cytoreductive therapy with cyclophosphamide, azathioprine, carmustine, busulfan, etoposide, or gemtuzumab ozogamicin or those receiving high-dose cytoreductive therapy or high-dose total body irradiation.

► Clinical Findings

A. Symptoms and Signs

The presentation is most commonly subacute but may be fulminant, acute, or chronic; it may present as acute-on-chronic liver failure (see Cirrhosis). Clinical manifestations generally include tender, painful hepatic enlargement, jaundice, splenomegaly, and ascites. With chronic disease, bleeding varices and hepatic encephalopathy may be evident; hepatopulmonary syndrome may occur.

B. Imaging

Hepatic imaging studies may show a prominent caudate lobe, since its venous drainage may be occluded. The screening test of choice is contrast-enhanced, color, or pulsed-Doppler ultrasonography, which has a sensitivity of 85% for detecting evidence of hepatic venous or inferior vena caval thrombosis. MRI with spin-echo and gradient-echo sequences and intravenous gadolinium injection allows visualization of the obstructed veins and collateral vessels. Direct venography can delineate caval webs and occluded hepatic veins (“spider-web” pattern) most precisely but is rarely required. Concomitant splanchnic vein thrombosis may be found in 4–21% of cases.

C. Liver Biopsy

Percutaneous or transjugular liver biopsy in Budd-Chiari syndrome may be considered when the results of noninvasive imaging are inconclusive and frequently shows characteristic centrilobular congestion and fibrosis and often multiple large regenerative nodules. Liver biopsy is rarely required, however, and is often contraindicated in sinusoidal obstruction syndrome because of thrombocytopenia, and the diagnosis is based on clinical findings.

► Treatment

Ascites should be treated with salt restriction and diuretics. Treatable causes of Budd-Chiari syndrome should be sought. Prompt recognition and treatment of an underlying hematologic disorder may avoid the need for surgery; however, the optimal anticoagulation regimen is uncertain, and anticoagulation is associated with a high risk of bleeding, particularly in patients with portal hypertension and those undergoing invasive procedures. Low-molecular-weight heparins are preferred over unfractionated heparin because of a high rate of heparin-induced thrombocytopenia with the latter. Warfarin is also an acceptable treatment, but direct-acting oral anticoagulants have not been well studied for this indication. Infusion of a thrombolytic agent into recently occluded veins has been attempted with success. Defibrotide, an adenosine receptor agonist that increases endogenous tissue plasminogen activator levels, has been approved by the FDA for the prevention and treatment of the sinusoidal obstruction

syndrome. The drug is given as an intravenous infusion every 6 hours for a minimum of 21 days. Serious adverse effects include hypotension and hemorrhage; the drug is expensive and has no benefit in severe sinusoidal obstruction syndrome.

TIPS placement may be attempted in patients with Budd-Chiari syndrome and persistent hepatic congestion or failed thrombolytic therapy and possibly in those with sinusoidal obstruction syndrome. Late TIPS dysfunction is less frequent with the use of polytetrafluoroethylene-covered stents than uncovered stents. TIPS is now preferred over surgical decompression (side-to-side portacaval, mesocaval, or mesoatrial shunt), which, in contrast to TIPS, has generally not been proven to improve long-term survival. Older age, a higher serum bilirubin level, and a greater INR predict a poor outcome with TIPS. When TIPS is technically not feasible because of complete hepatic vein obstruction, ultrasound-guided direct intrahepatic portosystemic shunt is an alternative approach. Balloon angioplasty, in some cases with placement of an intravascular metallic stent, is preferred in patients with an inferior vena caval web and is being performed increasingly in patients with a short segment of thrombosis in the hepatic vein. Liver transplantation can be considered in patients with acute liver failure, cirrhosis with hepatocellular dysfunction, and failure of a portosystemic shunt, and outcomes have improved with the advent of patient selection based on the MELD score. Patients with Budd-Chiari syndrome often require lifelong anticoagulation and treatment of the underlying myeloproliferative disease; antiplatelet therapy with aspirin and hydroxyurea has been suggested as an alternative to warfarin in patients with a myeloproliferative disorder. For all patients with Budd-Chiari syndrome, a poor outcome has been reported to correlate with Child-Pugh class C and a lack of response to interventional therapy of any kind.

► Prognosis

The overall 5-year survival rate is 50–90% with treatment (but less than 10% without intervention). Adverse prognostic factors in patients with Budd-Chiari syndrome are older age, high Child-Pugh score, ascites, encephalopathy, elevated total bilirubin, prolonged prothrombin time, elevated serum creatinine, concomitant portal vein thrombosis, and histologic features of acute liver disease superimposed on chronic liver injury. The 3-month mortality may be predicted by the Rotterdam score, which is based on encephalopathy, ascites, prothrombin time, and bilirubin. A serum ALT level at least fivefold above the upper limit of normal on presentation indicates hepatic ischemia and also predicts a poor outcome, particularly when the ALT level decreases slowly. The risk of hepatocellular carcinoma is increased, and patients with chronic Budd-Chiari syndrome should undergo surveillance with abdominal ultrasonography and serum alpha-fetoprotein levels every 6 months; risk factors include cirrhosis, combined hepatic vein and inferior vena cava obstruction, and a long-segment inferior vena cava block.

► When to Admit

All patients with hepatic vein obstruction should be hospitalized.

Haque LYK et al. Budd-Chiari syndrome: an uncommon cause of chronic liver disease that cannot be missed. *Clin Liver Dis.* 2020;24:453. [PMID: 32620283]

Simonetto DA et al. ACG Clinical Guideline: disorders of the hepatic and mesenteric circulation. *Am J Gastroenterol.* 2020;115:18. [PMID: 31895720]

THE LIVER IN HEART FAILURE

Ischemic hepatitis, also called **ischemic hepatopathy, hypoxic hepatitis, shock liver, or acute cardiogenic liver injury**, may affect 2.5 of every 100 patients admitted to an intensive care unit and results from an acute fall in cardiac output due to acute myocardial infarction, arrhythmia, or septic or hemorrhagic shock, usually in a patient with passive congestion of the liver. Rare cases have occurred in patients with COVID-19. Clinical hypotension may be absent (or unwitnessed). In some cases, the precipitating event is arterial hypoxemia due to respiratory failure, sleep apnea, severe anemia, heat stroke, carbon monoxide poisoning, cocaine use, or bacterial endocarditis. More than one precipitant is common. Statin therapy prior to admission may protect against ischemic hepatitis.

The hallmark of ischemic hepatitis is a rapid and striking elevation of serum aminotransferase levels (often greater than 5000 units/L); an early rapid rise in the serum lactate dehydrogenase (LD) level (with an ALT-to-LD ratio less than 1.5) is also typical. Elevations of serum alkaline phosphatase and bilirubin are usually mild, but jaundice is associated with worse outcomes. The prothrombin time may be prolonged, and encephalopathy or hepatopulmonary syndrome may develop. The mortality rate due to the underlying disease is high (particularly in patients receiving vasopressor therapy or with septic shock, acute kidney disease, or coagulopathy), but in patients who recover, the aminotransferase levels return to normal quickly, usually within 1 week—in contrast to viral hepatitis.

In patients with **passive congestion of the liver** (“nutmeg liver”) due to right-sided heart failure, the serum bilirubin level may be elevated, occasionally as high as 40 mg/dL (684 mcmol/L), due in part to hypoxia of periportal hepatocytes, and its level is a predictor of mortality and morbidity. Serum alkaline phosphatase levels are normal or slightly elevated, and, in the absence of superimposed ischemia, aminotransferase levels are only mildly elevated. Hepatojugular reflux is present, and with tricuspid regurgitation the liver may be pulsatile. Ascites may be out of proportion to peripheral edema, with a high serum ascites-albumin gradient (greater than or equal to 1.1) and an ascitic fluid protein level of more than 2.5 g/dL (25 g/L). A markedly elevated serum N-terminal-proBNP or BNP level (greater than 364 pg/mL [364 ng/L]) has been reported to distinguish ascites due to heart failure from ascites due to cirrhosis in the absence of renal insufficiency.

In severe cases, signs of encephalopathy may develop. Liver stiffness measurement by elastography is increased even in the absence of fibrosis. Mortality is generally attributable to the underlying heart disease but has also been reported to correlate with a noninvasive measure of liver stiffness. The MELD score excluding the INR (MELD-XI) predicts the clinical outcome.

Breu AC et al. A multicenter study into causes of severe acute liver injury. *Clin Gastroenterol Hepatol.* 2019;17:1201. [PMID: 30103039]

Horvatits T et al. Liver injury and failure in critical illness. *Hepatology.* 2019;70:2204. [PMID: 31215660]

Kudaravalli P et al. Case series and review of liver dysfunction in COVID-19 patients. *Eur J Gastroenterol Hepatol.* 2020; 32:1244. [PMID: 32568805]

NONCIRRHOTIC PORTAL HYPERTENSION



ESSENTIALS OF DIAGNOSIS

- ▶ Splenomegaly or upper gastrointestinal bleeding from esophageal or gastric varices in patients without liver disease.
- ▶ Portal vein thrombosis complicating cirrhosis.

► General Considerations

Causes of noncirrhotic portal hypertension include extrahepatic portal vein obstruction (portal vein thrombosis often with cavernous transformation [portal cavernoma]), splenic vein obstruction (presenting as gastric varices without esophageal varices), schistosomiasis, nodular regenerative hyperplasia, and arterial-portal vein fistula. Idiopathic noncirrhotic portal hypertension is common in India and has been attributed to chronic infections, exposure to medications or toxins, prothrombotic disorders, immunologic disorders, and genetic disorders that result in obliterative vascular lesions in the liver. It is rare in Western countries, where increased mortality is attributable to associated disorders and older age; the term portosinusoidal vascular disease has been proposed.

Portal vein thrombosis may occur in 10–25% of patients with cirrhosis, is associated with the severity of the liver disease and related in part to acquired protein C deficiency and splenorenal shunts (resulting in stagnant portal venous blood flow), and may be associated with hepatocellular carcinoma but not with increased mortality. Other risk factors are oral contraceptive use, pregnancy, chronic inflammatory diseases (including pancreatitis), injury to the portal venous system (including surgery), other malignancies, and treatment of thrombocytopenia with eltrombopag. Portal vein thrombosis may be classified as type 1, involving the main portal vein; type 2, involving one (2a) or both (2b) branches of the portal vein; or type 3, involving the trunk and branches of the portal vein. Additional descriptors are occlusive or nonocclusive, recent or chronic,

and extension (into the mesenteric vein) as well as the nature of any underlying liver disease. Splenic vein thrombosis may complicate pancreatitis or pancreatic cancer. Pylephlebitis (septic thrombophlebitis of the portal vein) may complicate intra-abdominal inflammatory disorders such as appendicitis or diverticulitis, particularly when anaerobic organisms (especially *Bacteroides* species) are involved. Nodular regenerative hyperplasia results from altered hepatic perfusion and can be associated with collagen vascular diseases; myeloproliferative disorders; and drugs, including azathioprine, 5-fluorouracil, oxaliplatin, and thioguanine. In patients infected with HIV, long-term use of didanosine and use of a combination of didanosine and stavudine have been reported to account for some cases of noncirrhotic portal hypertension often due to nodular regenerative hyperplasia; genetic factors may play a role. The term “obliterative portal venopathy” is used to describe primary occlusion of intrahepatic portal veins in the absence of cirrhosis, inflammation, or hepatic neoplasia.

► Clinical Findings

A. Symptoms and Signs

Acute portal vein thrombosis usually causes abdominal pain. Aside from splenomegaly, the physical findings are not remarkable, although hepatic decompensation can follow severe gastrointestinal bleeding, and a concurrent hepatic disorder or intestinal infarction may occur when portal vein thrombosis is associated with mesenteric venous thrombosis. Ascites may occur in 25% of persons with noncirrhotic portal hypertension. Covert hepatic encephalopathy is reported to be common in patients with noncirrhotic portal vein thrombosis.

B. Laboratory Findings

Liver biochemical test levels are usually normal, but there may be findings of hypersplenism. An underlying hypercoagulable state is found in many patients with portal vein thrombosis; this includes myeloproliferative neoplasms (often associated with a specific mutation [V617F] in the gene coding for JAK2 tyrosine kinase, which is found in 24% of cases of portal vein thrombosis), mutation G20210A of prothrombin, factor V Leiden mutation, protein C and S deficiency, antiphospholipid syndrome, mutation TT677 of methylenetetrahydrofolate reductase, elevated factor VIII levels, hyperhomocysteinemia, and a mutation in the gene that codes for thrombin-activatable fibrinolysis inhibitor. It is possible, however, that in many cases evidence of hypercoagulability is a secondary phenomenon due to portosystemic shunting and reduced hepatic blood flow.

C. Imaging

Color Doppler ultrasonography is usually the initial diagnostic test for portal vein thrombosis. Contrast-enhanced CT or magnetic resonance angiography (MRA) of the portal system is generally confirmatory and can assess extension of thrombus into the mesenteric veins and

exclude tumor thrombus in patients with cirrhosis. EUS may be helpful in some cases. In patients with jaundice, magnetic resonance cholangiography may demonstrate compression of the bile duct by a large portal cavernoma (portal biliopathy), a finding that may be more common in patients with an underlying hypercoagulable state than in those without one. In patients with pylephlebitis, CT may demonstrate an intra-abdominal source of infection, thrombosis or gas in the portal venous system, or a hepatic abscess.

D. Other Studies

Endoscopy shows esophageal or gastric varices. Needle biopsy of the liver may be indicated to diagnose schistosomiasis, nodular regenerative hyperplasia, and noncirrhotic portal fibrosis and may demonstrate sinusoidal dilatation. A low liver stiffness measurement by elastography may help distinguish noncirrhotic portal hypertension from cirrhosis.

► Treatment

If splenic vein thrombosis is the cause of variceal bleeding, splenectomy is curative. For other causes of noncirrhotic portal hypertension, band ligation followed by beta-blockers to reduce portal pressure is initiated for variceal bleeding, with portosystemic shunting (including TIPS) reserved for failures of endoscopic therapy; rarely, progressive liver dysfunction requires liver transplantation. Anticoagulation, particularly with low-molecular-weight or unfractionated heparin or thrombolytic therapy, may be indicated for isolated acute portal vein thrombosis (and leads to at least partial recanalization in up to 75% of cases when started within 6 months of thrombosis) and possibly for acute splenic vein thrombosis; an oral anticoagulant is continued long-term if a hypercoagulable disorder is identified or if an acute portal vein thrombosis extends into the mesenteric veins. The decision to prescribe an anticoagulant for a patient with cirrhosis and portal vein thrombosis depends on the presence of ascites, the patient's fall risk, and the patient's candidacy for liver transplantation. Moreover, partial portal vein thrombosis may resolve in 30–50% of cases. There is a paucity of data on the use of direct-acting oral anticoagulants in patients with cirrhosis and portal vein thrombosis. The use of enoxaparin to prevent portal vein thrombosis and hepatic decompensation in patients with cirrhosis has shown promise.

► When to Refer

All patients with noncirrhotic portal hypertension should be referred.

Khanna R et al. Noncirrhotic portal hypertension: current and emerging perspectives. Clin Liver Dis. 2019;23:781. [PMID: 31563222]

Simonetto DA et al. ACG Clinical Guideline: disorders of the hepatic and mesenteric circulation. Am J Gastroenterol. 2020;115:18. [PMID: 31895720]

Valla DC. Recent developments in the field of vascular liver diseases. Liver Int. 2020;40:142. [PMID: 32077611]

PYOGENIC HEPATIC ABSCESS



ESSENTIALS OF DIAGNOSIS

- ▶ Fever, right upper quadrant pain, jaundice.
- ▶ Often occur in setting of biliary disease, but up to 40% are “cryptogenic” in origin.
- ▶ Detected by imaging studies.

General Considerations

The incidence of liver abscess is 3.6 per 100,000 population in the United States and has increased since the 1990s. The liver can be invaded by bacteria via (1) the bile duct (acute “suppurative” [formerly ascending] cholangitis); (2) the portal vein (pylephlebitis); (3) the hepatic artery, secondary to bacteremia; (4) direct extension from an infectious process; and (5) traumatic implantation of bacteria through the abdominal wall or gastrointestinal tract (eg, a fish or chicken bone). Risk factors for liver abscess include older age and male sex. Predisposing conditions and factors include presence of malignancy, diabetes mellitus, inflammatory bowel disease, and cirrhosis; necessity for liver transplantation; endoscopic sphincterotomy; and use of a proton pump inhibitor. Statin use may reduce the risk of pyogenic liver abscess. Pyogenic liver abscess has been observed to be associated with a subsequent increased risk of gastrointestinal malignancy and hepatocellular carcinoma.

Acute cholangitis resulting from biliary obstruction due to a stone, stricture, or neoplasm is the most common identifiable cause of hepatic abscess in the United States. In 10% of cases, liver abscess is secondary to appendicitis or diverticulitis. At least 40% of abscesses have no demonstrable cause and are classified as cryptogenic; a dental source is identified in some cases. The most frequently encountered organisms are *E coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Enterobacter aerogenes*, and multiple microaerophilic and anaerobic species (eg, *Streptococcus anginosus* [also known as *S milleri*]). Liver abscess caused by virulent strains of *K pneumoniae* may be associated with thrombophlebitis of the portal or hepatic veins and hematogenously spread septic ocular or central nervous system complications; the abscess may be gas-forming, associated with diabetes mellitus, and result in a high mortality rate. *Staphylococcus aureus* is usually the causative organism in patients with chronic granulomatous disease. Uncommon causative organisms include *Salmonella*, *Haemophilus*, *Yersinia*, and *Listeria*. Hepatic candidiasis, tuberculosis, and actinomycosis are seen in immunocompromised patients and those with hematologic malignancies. Rarely, hepatocellular carcinoma can present as a pyogenic abscess because of tumor necrosis, biliary obstruction, and superimposed bacterial infection (see Chapter 39); even more rarely, liver abscess may be the result of a necrotic liver metastasis. The possibility of an amoebic liver abscess must always be considered (see Chapter 35).

Clinical Findings

A. Symptoms and Signs

The presentation is often insidious. Fever (either steady or spiking fever) is almost always present and may antedate other symptoms or signs. Pain may be a prominent complaint and is localized to the right upper quadrant or epigastric area. Jaundice and tenderness in the right upper abdomen are the chief physical findings. The risk of acute kidney injury is increased.

B. Laboratory Findings

Laboratory examination reveals leukocytosis with a shift to the left. Liver biochemical tests are nonspecifically abnormal. Blood cultures are positive in 50–100% of cases.

C. Imaging

Chest films usually reveal elevation of the diaphragm if the abscess is in the right lobe of the liver. Ultrasonography, CT, or MRI may reveal the presence of intrahepatic lesions. On MRI, characteristic findings include high signal intensity on T2-weighted images and rim enhancement. The characteristic CT appearance of hepatic candidiasis, usually seen in the setting of systemic candidiasis, is that of multiple “bull’s-eyes,” but imaging studies may be negative in neutropenic patients.

Treatment

Treatment should consist of antimicrobial agents (generally a third-generation cephalosporin such as ceftriaxone 2 g intravenously every 24 hours and metronidazole 500 mg intravenously every 6 hours) that are effective against coliform organisms and anaerobes. Antibiotics are administered for 2–3 weeks, and sometimes up to 6 weeks. If the abscess is at least 5 cm in diameter or the response to antibiotic therapy is not rapid, intermittent needle aspiration, percutaneous or EUS-guided catheter drainage or stent placement or, if necessary, surgical (eg, laparoscopic) drainage should be done. Other suggested indications for abscess drainage are patient age of at least 55 years, symptom duration of at least 7 days, and involvement of two lobes of the liver. The underlying source (eg, biliary disease, dental infection) should be identified and treated. The mortality rate is still substantial (at least 5% in most studies) and is highest in patients with underlying biliary malignancy or severe multiorgan dysfunction. Other risk factors for mortality include older age, cirrhosis, chronic kidney disease, and other cancers. Hepatic candidiasis often responds to intravenous amphotericin B (total dose of 2–9 g). Fungal abscesses are associated with mortality rates of up to 50% and are treated with intravenous amphotericin B and drainage.

When to Admit

Nearly all patients with pyogenic hepatic abscess should be hospitalized.

Kubovy J et al. Pyogenic liver abscess: incidence, causality, management and clinical outcomes in a New Zealand cohort. *N Z Med J*. 2019;132:30. [PMID: 30921309]

Mukthinuthalapati VVPK et al. Risk factors, management, and outcomes of pyogenic liver abscess in a US safety net hospital. *Dig Dis Sci*. 2020;65:1529. [PMID: 31559551]

BENIGN LIVER NEOPLASMS

Benign neoplasms of the liver must be distinguished from hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and metastases (see Chapter 39). The most common benign neoplasm of the liver is the **cavernous hemangioma**, often an incidental finding on ultrasonography or CT. This lesion may enlarge in women who take hormonal therapy and must be differentiated from other space-occupying intrahepatic lesions, usually by contrast-enhanced MRI, CT, or ultrasonography. Rarely, fine-needle biopsy is necessary to differentiate these lesions and does not appear to carry an increased risk of bleeding. Surgical resection of cavernous hemangiomas is infrequently necessary but may be required for abdominal pain or rapid enlargement, to exclude malignancy, or to treat Kasabach-Merritt syndrome (consumptive coagulopathy complicating a hemangioendothelioma or rapidly growing hemangioma, usually in infants).

In addition to rare instances of sinusoidal dilatation and peliosis hepatitis, two distinct benign lesions with characteristic clinical, radiologic, and histopathologic features are focal nodular hyperplasia and hepatocellular adenoma. **Focal nodular hyperplasia** occurs at all ages and in both sexes and is probably not caused by oral contraceptives. It is often asymptomatic and appears as a hypervascular mass, often with a central hypodense "stellate" scar on contrast-enhanced ultrasonography, CT, or MRI. Microscopically, focal nodular hyperplasia consists of hyperplastic units of hepatocytes that stain positively for glutamine synthetase with a central stellate scar containing proliferating bile ducts. It is not a true neoplasm but a proliferation of hepatocytes in response to altered blood flow. Focal nodular hyperplasia may also occur in patients with cirrhosis, with exposure to certain drugs such as azathioprine, and with antiphospholipid syndrome. The prevalence of hepatic hemangiomas is increased in patients with focal nodular hyperplasia.

Hepatocellular adenoma occurs most commonly in women in the third and fourth decades of life and is usually caused by oral contraceptives; acute abdominal pain may occur if the tumor undergoes necrosis or hemorrhage. The tumor may be associated with mutations in a variety of genes, some of which are associated with an increased risk of malignant transformation. Unclassified adenomas account for up to 7% of tumors. Rare instances of multiple hepatocellular adenomas in association with maturity-onset diabetes of the young occur in families with a germline mutation in *HNF1alpha*. Hepatocellular adenomas (inflammatory or unclassified adenomas) also occur in patients with glycogen storage disease and familial adenomatous polyposis. The tumor is hypovascular. Grossly, the cut surface appears structureless. As seen microscopically, the hepatocellular adenoma consists of sheets of hepatocytes without portal tracts or central veins.

Cystic neoplasms of the liver, such as cystadenoma and cystadenocarcinoma, must be distinguished from simple and echinococcal cysts, von Meyenburg complexes (hamartomas), and polycystic liver disease.

Clinical Findings

The only physical finding in focal nodular hyperplasia or hepatocellular adenoma is a palpable abdominal mass in a minority of cases. Liver function is usually normal. Contrast-enhanced ultrasonography, arterial phase helical CT, and especially multiphase dynamic MRI with contrast can distinguish an adenoma from focal nodular hyperplasia without the need for biopsy in 80–90% of cases and may suggest a specific subtype of adenoma (eg, homogeneous fat pattern in *HNF1alpha*-mutated adenomas and marked and persistent arterial enhancement in inflammatory adenomas).

Treatment

Oral contraceptives should not necessarily be discontinued in women who have focal nodular hyperplasia, and affected women who continue taking oral contraceptives should have annual ultrasonography for 2–3 years to ensure that the lesion is not enlarging. The prognosis is excellent.

Hepatocellular adenoma may undergo bleeding, necrosis, and rupture, often after hormone therapy; in the third trimester of pregnancy; or in men, in whom the rate of malignant transformation is high. A lesion less than 5 cm in diameter, however, poses little risk of complications to a pregnant woman, who should undergo ultrasonography during each trimester and 12 weeks postpartum. Resection is advised in all affected men and in women in whom the tumor causes symptoms or is 5 cm or greater in diameter, even in the absence of symptoms. If an adenoma is less than 5 cm in size, resection is also recommended if a beta-catenin gene mutation is present in a biopsy sample. In selected cases, laparoscopic resection or percutaneous radiofrequency ablation may be feasible. Rarely, liver transplantation is required. Regression of benign hepatic tumors may follow cessation of oral contraceptives. Transarterial embolization is the initial treatment for adenomas complicated by hemorrhage.

When to Refer

- Diagnostic uncertainty.
- For surgery.

When to Admit

- Severe pain.
- Rupture.

Gaspersz MP et al. Growth of hepatocellular adenoma during pregnancy: a prospective study. *J Hepatol.* 2020;72:119. [PMID: 31550458]

Myers L et al. Focal nodular hyperplasia and hepatic adenoma: evaluation and management. *Clin Liver Dis.* 2020;24:389. [PMID: 32620279]

DISEASES OF THE BILIARY TRACT

See Chapter 39 for Carcinoma of the Biliary Tract.

CHOLELI THIASIS (Gallstones)



ESSENTIALS OF DIAGNOSIS

- ▶ Often asymptomatic.
- ▶ Classic biliary pain ("episodic gallbladder pain") characterized by infrequent episodes of steady severe pain in epigastrium or right upper quadrant with radiation to right scapula.
- ▶ Gallstones detected on ultrasonography.

► General Considerations

Gallstones are more common in women than in men and increase in incidence in both sexes and all races with age. In the United States, the prevalence of gallstones is 8.6% in women and 5.5% in men. The highest rates are in persons over age 60, and rates are higher in Mexican Americans than in non-Hispanic Whites and Blacks. Although cholesterol gallstones are less common in Black people, cholelithiasis attributable to hemolysis occurs in over a third of individuals with sickle cell disease. Native Americans of both the Northern and Southern Hemispheres have a high rate of cholesterol cholelithiasis, probably because of a predisposition resulting from "thrifty" (LITH) genes that promote efficient calorie utilization and fat storage. As many as 75% of Pima and other American Indian women over 25 years of age have cholelithiasis. Other genetic mutations that predispose persons to gallstones have been identified. Obesity is a risk factor for gallstones, especially in women. Rapid weight loss, as occurs after bariatric surgery, also increases the risk of symptomatic gallstone formation. Diabetes mellitus, glucose intolerance, and insulin resistance are risk factors for gallstones, and a high intake of carbohydrate and high dietary glycemic load increase the risk of cholecystectomy in women. Hypertriglyceridemia may promote gallstone formation by impairing gallbladder motility. The prevalence of gallbladder disease is increased in men (but not women) with cirrhosis and hepatitis C virus infection. Moreover, cholecystectomy has been reported to be associated with an increased risk of NAFLD and cirrhosis, possibly because gallstones and liver disease share risk factors. Gallstone disease is associated with increased overall, cardiovascular, and cancer mortality.

The incidence of gallstones is high in individuals with Crohn disease; approximately one-third of those with inflammatory involvement of the terminal ileum have gallstones due to disruption of bile salt resorption that results in decreased solubility of the bile. Drugs such as clofibrate, octreotide, and ceftriaxone can cause gallstones. Prolonged fasting (over 5–10 days) can lead to formation of biliary "sludge" (microlithiasis), which usually resolves with refeeding but can lead to gallstones or biliary symptoms. Pregnancy, particularly in obese women and those with insulin resistance, is associated with an increased risk of gallstones and of symptomatic gallbladder disease. Hormone replacement therapy appears to increase the risk of

gallbladder disease and need for cholecystectomy; the risk is lower with transdermal than oral therapy. Gallstones detected by population screening have been reported to be associated with an increased risk of right-sided colon cancers. A low-carbohydrate diet and a Mediterranean diet as well as physical activity and cardiorespiratory fitness may help prevent gallstones. Consumption of caffeinated coffee appears to protect against gallstones in women, and a high intake of magnesium and of polyunsaturated and monounsaturated fats reduces the risk of gallstones in men. A diet high in fiber and rich in fruits and vegetables and statin use reduce the risk of cholecystectomy, particularly in women. Aspirin and other NSAIDs may protect against gallstones.

Gallstones are classified according to their predominant chemical composition as cholesterol or calcium bilirubinate stones. The latter comprise less than 20% of the gallstones found in patients in the United States or Europe but 30–40% of gallstones found in patients in Japan.

► Clinical Findings

Table 16–9 lists the clinical and laboratory features of several diseases of the biliary tract as well as their treatment. Cholelithiasis is frequently asymptomatic and is discovered during a routine imaging study, surgery, or autopsy. Symptoms (biliary [or "episodic gallbladder"] pain) develop in 10–25% of patients (1–4% annually), and acute cholecystitis develops in 20% of these symptomatic persons over time. Risk factors for the development of symptoms or complications include female sex; young age; awareness of having gallstones; and large, multiple, and older stones. Occasionally, small intestinal obstruction due to "gallstone ileus" (or Bouveret syndrome when the obstructing stone is in the pylorus or duodenum) presents as the initial manifestation of cholelithiasis.

► Treatment

NSAIDs (eg, diclofenac 50–75 mg intramuscularly) can be used to relieve biliary pain. Laparoscopic cholecystectomy is the treatment of choice for symptomatic gallbladder disease. Pain relief after cholecystectomy is most likely in patients with episodic pain (generally once a month or less), pain lasting 30 minutes to 24 hours, pain in the evening or at night, and the onset of symptoms 1 year or less before presentation. Patients may go home within 1 day of the procedure and return to work within days (instead of weeks for those undergoing open cholecystectomy). The procedure is often performed on an outpatient basis and is suitable for most patients, including those with acute cholecystitis. Conversion to a conventional open cholecystectomy may be necessary in 2–8% of cases (higher for acute cholecystitis than for uncomplicated cholelithiasis). Bile duct injuries occur in 0.1% of cases done by experienced surgeons, and the overall complication rate is 11% and correlates with the patient's comorbidities, duration of surgery, and emergency admissions for gallbladder disease prior to cholecystectomy. There is generally no need for prophylactic cholecystectomy in an asymptomatic person unless the gallbladder is calcified, gallstones are 3 cm or greater in diameter, or the patient is a Native American or a candidate for bariatric surgery or cardiac transplantation.

Table 16–9. Diseases of the biliary tract.

	Clinical Features	Laboratory Features	Diagnosis	Treatment
Asymptomatic gallstones	Asymptomatic	Normal	Ultrasonography	None
Symptomatic gallstones	Biliary pain	Normal	Ultrasonography	Laparoscopic cholecystectomy
Cholesterolosis of gallbladder	Usually asymptomatic	Normal	Oral cholecystography	None
Adenomyomatosis	May cause biliary pain	Normal	Oral cholecystography	Laparoscopic cholecystectomy if symptomatic
Porcelain gallbladder	Usually asymptomatic, high risk of gallbladder cancer	Normal	Radiograph or CT	Laparoscopic cholecystectomy
Acute cholecystitis	Epigastric or right upper quadrant pain, nausea, vomiting, fever, Murphy sign	Leukocytosis	Ultrasonography, HIDA scan	Antibiotics, laparoscopic cholecystectomy
Chronic cholecystitis	Biliary pain, constant epigastric or right upper quadrant pain, nausea	Normal	Ultrasonography (stones), oral cholecystography (nonfunctioning gallbladder)	Laparoscopic cholecystectomy
Choledocholithiasis	Asymptomatic or biliary pain, jaundice, fever; gallstone pancreatitis	Cholestatic liver biochemical tests; leukocytosis and positive blood cultures in cholangitis; elevated amylase and lipase in pancreatitis	Ultrasonography (dilated ducts), EUS, MRCP, ERCP	Endoscopic sphincterotomy and stone extraction; antibiotics for cholangitis

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HIDA, hepatic iminodiacetic acid; MRCP, magnetic resonance cholangiopancreatography.

Cholecystectomy may increase the risk of esophageal, proximal small intestinal, and colonic adenocarcinomas as well as hepatocellular carcinoma because of increased duodenogastric reflux and changes in intestinal exposure to bile. In pregnant patients, a conservative approach to biliary pain is advised, but for patients with repeated attacks of biliary pain or acute cholecystitis, cholecystectomy can be performed—even by the laparoscopic route—preferably in the second trimester. Enterolithotomy alone is considered adequate treatment in most patients with gallstone ileus.

Ursodeoxycholic acid is a bile salt that when given orally for up to 2 years dissolves some cholesterol stones and may be considered in occasional, selected patients who refuse cholecystectomy. The dose is 8–10 mg/kg in two or three divided doses daily. It is most effective in patients with a functioning gallbladder, as determined by gallbladder visualization on oral cholecystography, and multiple small “floating” gallstones (representing not more than 15% of patients with gallstones). In half of patients, gallstones recur within 5 years after treatment is stopped. Ursodeoxycholic acid, 500–600 mg daily, and diets higher in fat reduce the risk of gallstone formation with rapid weight loss. Lithotripsy in combination with bile salt therapy for single radiolucent stones smaller than 20 mm in diameter was an option in the past but is no longer generally used in the United States.

► When to Refer

Patients should be referred when they require surgery.

Gutt C et al. The treatment of gallstone disease. *Dtsch Arztebl Int.* 2020;117:148. [PMID: 32234195]

Sutherland JM et al. A cost-utility study of laparoscopic cholecystectomy for the treatment of symptomatic gallstones. *J Gastrointest Surg.* 2020;24:1314. [PMID: 31144191]

ACUTE CHOLECYSTITIS



ESSENTIALS OF DIAGNOSIS

- Steady, severe pain and tenderness in the right hypochondrium or epigastrium.
- Nausea and vomiting.
- Fever and leukocytosis.

► General Considerations

Cholecystitis is associated with gallstones in over 90% of cases. It occurs when a stone becomes impacted in the

cystic duct and inflammation develops behind the obstruction. Acalculous cholecystitis should be considered when unexplained fever or right upper quadrant pain occurs within 2–4 weeks of major surgery or in a critically ill patient who has had no oral intake for a prolonged period; multiorgan failure is often present. Acute cholecystitis may be caused by infectious agents (eg, cytomegalovirus, cryptosporidiosis, microsporidiosis) in patients with AIDS or by vasculitis (eg, polyarteritis nodosa, Henoch-Schönlein purpura).

► Clinical Findings

A. Symptoms and Signs

The acute attack is often precipitated by a large or fatty meal and is characterized by the sudden appearance of steady pain localized to the epigastrium or right hypochondrium, which may gradually subside over a period of 12–18 hours. Vomiting occurs in about 75% of patients and in half of instances affords variable relief. Fever is typical. Right upper quadrant abdominal tenderness (often with a Murphy sign, or inhibition of inspiration by pain on palpation of the right upper quadrant) is almost always present and is usually associated with muscle guarding and rebound tenderness (Table 16–9). A palpable gallbladder is present in about 15% of cases. Jaundice is present in about 25% of cases and, when persistent or severe, suggests the possibility of choledocholithiasis.

B. Laboratory Findings

The white blood cell count is usually high (12,000–15,000/mcL [$12\text{--}15 \times 10^9/\text{L}$]). Total serum bilirubin values of 1–4 mg/dL (17.1–68.4 mcmol/L) may be seen even in the absence of bile duct obstruction. Serum aminotransferase and alkaline phosphatase levels are often elevated—the former as high as 300 units/mL, and even higher when associated with acute cholangitis. Serum amylase may also be moderately elevated.

C. Imaging

Plain films of the abdomen may show radiopaque gallstones in 15% of cases. ^{99m}Tc hepatobiliary imaging (using iminodiacetic acid compounds), also known as the hepatic iminodiacetic acid (HIDA) scan, is useful in demonstrating an obstructed cystic duct, which is the cause of acute cholecystitis in most patients. This test is reliable if the bilirubin is under 5 mg/dL (85.5 mcmol/L) (98% sensitivity and 81% specificity for acute cholecystitis). False-positive results can occur with prolonged fasting, liver disease, and chronic cholecystitis, and the specificity can be improved by intravenous administration of morphine, which induces spasm of the sphincter of Oddi. Right upper quadrant abdominal ultrasonography, which is often performed first, may show gallstones but is not as sensitive for acute cholecystitis (67% sensitivity, 82% specificity); findings suggestive of acute cholecystitis are gallbladder wall thickening, pericholecystic fluid, and a sonographic Murphy sign. CT may show complications of acute cholecystitis, such as perforation or gangrene.

► Differential Diagnosis

The disorders most likely to be confused with acute cholecystitis are perforated peptic ulcer, acute pancreatitis, appendicitis in a high-lying appendix, perforated colonic carcinoma or diverticulum of the hepatic flexure, liver abscess, hepatitis, pneumonia with pleurisy on the right side, and myocardial ischemia. Definite localization of pain and tenderness in the right upper quadrant, with radiation of pain around to the infrascapular area, strongly favors the diagnosis of acute cholecystitis. True cholecystitis without stones suggests acalculous cholecystitis.

► Complications

A. Gangrene of the Gallbladder

Continuation or progression of right upper quadrant abdominal pain, tenderness, muscle guarding, fever, and leukocytosis after 24–48 hours suggests severe inflammation and possible gangrene of the gallbladder, resulting from ischemia due to splanchnic vasoconstriction and intravascular coagulation. Necrosis may occasionally develop without specific signs in the obese, diabetic, elderly, or immunosuppressed patient. Gangrene may lead to gallbladder perforation, usually with formation of a pericholecystic abscess, and rarely to generalized peritonitis. Other serious acute complications include emphysematous cholecystitis (secondary infection with a gas-forming organism) and empyema.

B. Chronic Cholecystitis and Other Complications

Chronic cholecystitis results from repeated episodes of acute cholecystitis or chronic irritation of the gallbladder wall by stones and is characterized pathologically by varying degrees of chronic inflammation of the gallbladder. Calculi are usually present. In about 4–5% of cases, the villi of the gallbladder undergo polypoid enlargement due to deposition of cholesterol that may be visible to the naked eye ("strawberry gallbladder," cholesterolosis). In other instances, hyperplasia of all or part of the gallbladder wall may be so marked as to give the appearance of a myoma (adenomyomatosis). Hydrops of the gallbladder results when acute cholecystitis subsides but cystic duct obstruction persists, producing distention of the gallbladder with a clear mucoid fluid. Occasionally, a stone in the neck of the gallbladder may compress the common hepatic duct and cause jaundice (Mirizzi syndrome). Xanthogranulomatous cholecystitis is a rare, aggressive variant of chronic cholecystitis characterized by grayish-yellow nodules or streaks, representing lipid-laden macrophages, in the wall of the gallbladder and often presents with acute jaundice.

Cholelithiasis with chronic cholecystitis may be associated with acute exacerbations of gallbladder inflammation, bile duct stone, fistulization to the bowel, pancreatitis and, rarely, carcinoma of the gallbladder. Calcified (porcelain) gallbladder is associated with gallbladder carcinoma and is generally an indication for cholecystectomy; the risk of gallbladder cancer may be higher when calcification is mucosal rather than intramural.

► Treatment

Acute cholecystitis usually subsides on a conservative regimen, including withholding oral feedings, intravenous alimentation, analgesics, and intravenous antibiotics (generally a second- or third-generation cephalosporin such as ceftriaxone 1 g intravenously every 24 hours, with the addition of metronidazole, 500 mg intravenously every 6 hours), although the need for antibiotics has been questioned in patients undergoing immediate cholecystectomy. In severe cases, a fluoroquinolone such as ciprofloxacin, 400 mg intravenously every 12 hours, plus metronidazole may be given. Morphine or meperidine may be administered for pain. Because of the high risk of recurrent attacks (up to 10% by 1 month and over 20% by 1 year), cholecystectomy—generally laparoscopically—should be performed within 24 hours of admission to the hospital for acute cholecystitis. Compared with delayed surgery, surgery within 24 hours is associated with a shorter length of stay, lower costs, and greater patient satisfaction. If nonsurgical treatment has been elected, the patient (especially if diabetic or elderly) must be watched carefully for recurrent symptoms, evidence of gangrene of the gallbladder, or cholangitis. In high-risk patients, ultrasound-guided aspiration of the gallbladder, if feasible, percutaneous or EUS-guided cholecystostomy, or endoscopic insertion of a stent or nasobiliary drain into the gallbladder may postpone or even avoid the need for surgery. Immediate cholecystectomy is mandatory when there is evidence of gangrene or perforation. Surgical treatment of chronic cholecystitis is the same as for acute cholecystitis. If indicated, cholangiography can be performed during laparoscopic cholecystectomy. Choledocholithiasis can also be excluded by either preoperative or postoperative MRCP or ERCP.

► Prognosis

The overall mortality rate of cholecystectomy is less than 0.2%, but hepatobiliary tract surgery is a more formidable procedure in older patients, in whom mortality rates are higher; mortality rates are also higher in persons with diabetes mellitus and cirrhosis. A technically successful surgical procedure in an appropriately selected patient is generally followed by complete resolution of symptoms.

► When to Admit

All patients with acute cholecystitis should be hospitalized.

Fleming CA et al. Clinical and survival outcomes using percutaneous cholecystostomy tube alone or subsequent interval cholecystectomy to treat acute cholecystitis. *J Gastrointest Surg*. 2020;24:627. [PMID: 30887298]

Teoh AYB et al. Endosonography-guided gallbladder drainage versus percutaneous cholecystostomy in very high-risk surgical patients with acute cholecystitis: an international randomised multicentre controlled superiority trial (DRAC 1). *Gut*. 2020;69:1085. [PMID: 32165407]

van Heeswijk AE et al. Outcome after cholecystectomy in the elderly. *Am J Surg*. 2019;218:368. [PMID: 30587332]

PRE- & POSTCHOLECYSTECTOMY SYNDROMES

1. Precholecystectomy

In a small group of patients (mostly women) with biliary pain, conventional radiographic studies of the upper gastrointestinal tract and gallbladder—including cholangiography—are unremarkable. Emptying of the gallbladder may be markedly reduced on gallbladder scintigraphy following injection of cholecystokinin; cholecystectomy may be curative in such cases. Histologic examination of the resected gallbladder may show chronic cholecystitis or microlithiasis. An additional diagnostic consideration is sphincter of Oddi dysfunction.

2. Postcholecystectomy

Following cholecystectomy, some patients complain of continuing symptoms, ie, right upper quadrant pain, flatulence, and fatty food intolerance. The persistence of symptoms in this group of patients suggests the possibility of an incorrect diagnosis prior to cholecystectomy, eg, esophagitis, pancreatitis, radiculopathy, or functional bowel disease. Choledocholithiasis or bile duct stricture should be ruled out. Pain may also be associated with dilatation of the cystic duct remnant, neuroma formation in the ductal wall, foreign body granuloma, anterior cutaneous nerve entrapment syndrome, or traction on the bile duct by a long cystic duct.

The clinical presentation of right upper quadrant pain, chills, fever, or jaundice suggests biliary tract disease. EUS is recommended to demonstrate or exclude a stone or stricture. Biliary pain associated with elevated liver biochemical tests or a dilated bile duct in the absence of an obstructing lesion suggests sphincter of Oddi dysfunction. Biliary manometry may be useful for documenting elevated baseline sphincter of Oddi pressures typical of sphincter dysfunction when biliary pain is associated with elevated liver biochemical tests (twofold) or a dilated bile duct (greater than 10 mm) ("sphincter disorder," formerly type II sphincter of Oddi dysfunction), but is not necessary when both are present ("sphincter stenosis," formerly type I sphincter of Oddi dysfunction) and is associated with a high risk of pancreatitis. In the absence of either elevated liver biochemical tests or a dilated bile duct ("functional pain," formerly type III sphincter of Oddi dysfunction), a nonbiliary source of symptoms should be suspected, and biliary sphincterotomy does not benefit this group. (Analogous criteria have been developed for pancreatic sphincter dysfunction.) Biliary scintigraphy after intravenous administration of morphine and MRCP following intravenous administration of secretin have been studied as screening tests for sphincter dysfunction. Endoscopic sphincterotomy is most likely to relieve symptoms in patients with a sphincter disorder or stenosis, although many patients continue to have some pain. In some cases, treatment with a calcium channel blocker, long-acting nitrate, phosphodiesterase inhibitor (eg, vardenafil), duloxetine, or tricyclic antidepressant or possibly injection of the sphincter with botulinum toxin may be beneficial. The rate

of psychosocial comorbidity with sphincter of Oddi dysfunction does not appear to differ from that of the general population. In refractory cases, surgical sphincteroplasty or removal of the cystic duct remnant may be considered.

► When to Refer

Patients with sphincter of Oddi dysfunction should be referred for diagnostic procedures.

Isherwood J et al. A systematic review of the aetiology and management of post cholecystectomy syndrome. *Surgeon*. 2019;17:33. [PMID: 29730174]

Miyatani H et al. Clinical course of biliary-type sphincter of Oddi dysfunction: endoscopic sphincterotomy and functional dyspepsia as affecting factors. *Ther Adv Gastrointest Endosc*. 2019;12:2631774519867184. [PMID: 31448369]

jaundice represents **Charcot triad** and denotes the classic picture of acute cholangitis. The addition of altered mental status and hypotension (**Reynolds pentad**) signifies acute suppurative cholangitis and is an endoscopic emergency. According to the Tokyo guidelines (2006), the diagnosis of acute cholangitis is established by the presence of either (1) the Charcot triad or (2) two elements of the Charcot triad plus laboratory evidence of an inflammatory response (eg, elevated white blood cell count, C-reactive protein) and/or elevated liver biochemical test levels, and/or imaging evidence of biliary dilatation or obstruction.

Hepatomegaly may be present in calculous biliary obstruction, and tenderness is usually present in the right upper quadrant and epigastrium. Bile duct obstruction lasting more than 30 days results in liver damage leading to cirrhosis. Hepatic failure with portal hypertension occurs in untreated cases. In a population-based study from Denmark, acute cholangitis was reported to be a marker of occult gastrointestinal cancer.

CHOLEDOCHOLITHIASIS & CHOLANGITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Often a history of biliary pain, which may be accompanied by jaundice.
- ▶ Occasional patients present with painless jaundice.
- ▶ Nausea and vomiting.
- ▶ Cholangitis should be suspected with fever followed by hypothermia and gram-negative shock, jaundice, and leukocytosis.
- ▶ Stones in bile duct most reliably detected by ERCP or EUS.

► General Considerations

About 15% of patients with gallstones have choledocholithiasis (bile duct stones). The percentage rises with age, and the frequency in elderly people with gallstones may be as high as 50%. Bile duct stones usually originate in the gallbladder but may also form spontaneously in the bile duct after cholecystectomy. The risk is increased twofold in persons with a juxtapapillary duodenal diverticulum. Symptoms and possible cholangitis result if there is obstruction.

► Clinical Findings

A. Symptoms and Signs

A history of biliary pain or jaundice may be obtained. Biliary pain results from rapid increases in bile duct pressure due to obstructed bile flow. The features that suggest the presence of a bile duct stone are (1) frequently recurring attacks of right upper abdominal pain that is severe and persists for hours, (2) chills and fever associated with severe pain, and (3) a history of jaundice associated with episodes of abdominal pain (Table 16–9). The combination of right upper quadrant pain, fever (and chills), and

B. Laboratory Findings

Acute obstruction of the bile duct typically produces a transient albeit striking increase in serum aminotransferase levels (often greater than 1000 units/L [20 mckat/L]). Bilirubinuria and elevation of the serum bilirubin are present if the bile duct remains obstructed; levels commonly fluctuate. Serum alkaline phosphatase levels rise more slowly. Not uncommonly, serum amylase elevations are present because of secondary pancreatitis. When extrahepatic obstruction persists for more than a few weeks, differentiation of obstruction from chronic cholestatic liver disease becomes more difficult. Leukocytosis is present in patients with acute cholangitis. Prolongation of the prothrombin time can result from the obstructed flow of bile to the intestine. In contrast to hepatocellular dysfunction, hypoprothrombinemia due to obstructive jaundice will respond to intravenous vitamin K, 10 mg, or water-soluble oral vitamin K (phytonadione), 5 mg, within 24–36 hours. In patients with acute calculous cholecystitis, predictors of concomitant choledocholithiasis are serum aminotransferase levels over three times the upper limit of normal, an alkaline phosphatase level above normal, a serum lipase over three times the upper limit of normal, a bilirubin of 1.8 mg/dL or more, and a bile duct diameter above 6 mm.

C. Imaging

Ultrasonography and CT may demonstrate dilated bile ducts, and radionuclide imaging may show impaired bile flow. EUS, helical CT, and magnetic resonance cholangiography are accurate in demonstrating bile duct stones and may be used in patients thought to be at intermediate risk for choledocholithiasis (age older than 55 years, cholecystitis, bile duct diameter greater than 6 mm on ultrasonography, serum bilirubin 1.8–4 mg/dL [30.78–68.4 mcmmol/L], elevated serum liver enzymes, or pancreatitis). A decision analysis has suggested that magnetic resonance cholangiography is preferable when the risk of bile duct stones is low (less than 40%), and EUS is preferable when the risk is intermediate (40–91%). ERCP (occasionally with

intraductal ultrasonography) or percutaneous transhepatic cholangiography (PTC) provides the most direct and accurate means of determining the cause, location, and extent of obstruction, but in patients at intermediate risk of choledocholithiasis, initial cholecystectomy with intraoperative cholangiography results in a shorter length of hospital stay, fewer bile duct investigations, and no increase in morbidity. If the likelihood that obstruction is caused by a stone is high (bile duct stone seen on ultrasonography, serum bilirubin greater than 4 mg/dL [68.4 mcmol/L], or acute cholangitis), ERCP with sphincterotomy and stone extraction or stent placement is the procedure of choice; meticulous technique is required to avoid causing acute cholangitis. Because the sensitivity of these criteria for choledocholithiasis is only 80%, it is not unreasonable for magnetic resonance cholangiography or EUS to be done before ERCP.

Differential Diagnosis

The most common cause of obstructive jaundice is a bile duct stone. Next in frequency are neoplasms of the pancreas, ampulla of Vater, or bile duct or an obstructed stent placed previously for decompression of an obstructing tumor. Extrinsic compression of the bile duct may result from metastatic carcinoma (usually from the gastrointestinal tract or breast) involving porta hepatis lymph nodes or, rarely, from a large duodenal diverticulum. Gallbladder cancer extending into the bile duct often presents as obstructive jaundice. Chronic cholestatic liver diseases (PBC, sclerosing cholangitis, drug-induced) must be considered. Hepatocellular jaundice can usually be differentiated by the history, clinical findings, and liver biochemical tests, but liver biopsy is necessary on occasion. Recurrent pyogenic cholangitis should be considered in persons from Asia (and occasionally elsewhere) with intrahepatic biliary stones (particularly in the left ductal system) and recurrent cholangitis.

Treatment

In general, bile duct stones, even small ones, should be removed, even in an asymptomatic patient. A bile duct stone in a patient with cholelithiasis or cholecystitis is usually treated by endoscopic sphincterotomy and stone extraction followed by laparoscopic cholecystectomy within 72 hours in patients with cholecystitis and within 2 weeks in those without cholecystitis. In select cases, laparoscopic cholecystectomy and ERCP can be performed in a single session. An alternative approach, which is also associated with a shorter duration of hospitalization in patients at intermediate risk for choledocholithiasis, is laparoscopic cholecystectomy and bile duct exploration.

For patients older than 70 years or poor-risk patients with cholelithiasis and choledocholithiasis, cholecystectomy may be deferred after endoscopic sphincterotomy because the risk of subsequent cholecystitis is low (although the risk of subsequent complications is lower when cholecystectomy is performed). ERCP with sphincterotomy, generally within 48 hours, should be performed before cholecystectomy in patients with gallstones and cholangitis, jaundice (serum total bilirubin greater than 4 mg/dL

[68.4 mcmol/L]), a dilated bile duct (greater than 6 mm), or stones in the bile duct seen on ultrasonography or CT. (Stones may ultimately recur in up to 12% of patients, particularly in older patients, when the bile duct diameter is 15 mm or greater or when brown pigment stones are found at the time of the initial sphincterotomy.) For bile duct stones 1 cm or more in diameter, endoscopic sphincterotomy followed by large balloon dilation has been recommended. Endoscopic balloon dilation of the sphincter of Oddi is otherwise reserved for patients with coagulopathy because the risk of bleeding is lower with balloon dilation than with sphincterotomy. Balloon dilation is not associated with a higher rate of pancreatitis than endoscopic sphincterotomy if adequate dilation for more than 1 minute is carried out, and it may be associated with a lower rate of stone recurrence. EUS-guided biliary drainage and PTC with drainage are second-line approaches if ERCP fails or is not possible. In patients with biliary pancreatitis that resolves rapidly, the stone usually passes into the intestine, and ERCP prior to cholecystectomy is not necessary if intraoperative cholangiography is planned.

Choledocholithiasis discovered at laparoscopic cholecystectomy may be managed via laparoscopic or, if necessary, open bile duct exploration or by postoperative endoscopic sphincterotomy. Operative findings of choledocholithiasis are palpable stones in the bile duct, dilatation or thickening of the wall of the bile duct, or stones in the gallbladder small enough to pass through the cystic duct. Laparoscopic intraoperative cholangiography (or intraoperative ultrasonography) should be done at the time of cholecystectomy in patients with liver enzyme elevations but a bile duct diameter of less than 5 mm; if a ductal stone is found, the duct should be explored. In the post-cholecystectomy patient with choledocholithiasis, endoscopic sphincterotomy with stone extraction is preferable to transabdominal surgery. Lithotripsy (endoscopic or external), peroral cholangioscopy (choledoscopy), or biliary stenting may be a therapeutic consideration for large stones. For the patient with a T tube and bile duct stone, the stone may be extracted via the T tube.

Postoperative antibiotics are not administered routinely after biliary tract surgery. Cultures of the bile are always taken at operation. If biliary tract infection was present preoperatively or is apparent at operation, ampicillin-sulbactam (3 g intravenously every 6 hours) or piperacillin-tazobactam (3.375 or 4.5 g intravenously every 6 hours) or a third-generation cephalosporin (eg, ceftriaxone, 1 g intravenously every 24 hours) is administered postoperatively until the results of sensitivity tests on culture specimens are available. A T-tube cholangiogram should be done before the tube is removed, usually about 3 weeks after surgery. A small amount of bile frequently leaks from the tube site for a few days.

Urgent ERCP with sphincterotomy and stone extraction (within 24–48 hours) is generally indicated for choledocholithiasis complicated by acute cholangitis and is preferred to surgery. Before ERCP, liver function should be evaluated thoroughly. The prothrombin time should be restored to normal by intravenous administration of vitamin K. For mild-to-moderately severe community-acquired acute cholangitis, ciprofloxacin (400 mg intravenously every 12 hours),

penetrates well into bile and is effective treatment, with metronidazole (500 mg intravenously every 6–8 hours) for anaerobic coverage. An alternative regimen is ampicillin-sulbactam (3 g intravenously every 6 hours). Regimens for patients with severe or hospital-acquired acute cholangitis, and those potentially infected with an antibiotic-resistant pathogen, include intravenous piperacillin-tazobactam (3.375 or 4 g every 6 hours) or a carbopenem such as meropenem (1 g intravenously every 8 hours). Aminoglycosides (eg, gentamicin 5–7 mg/kg intravenously every 24 hours) may be added in cases of severe sepsis or septic shock but should not be given for more than a few days because the risk of aminoglycoside nephrotoxicity is increased in patients with cholestasis. Regimens that include drugs active against anaerobes are required when a biliary-enteric communication is present.

Emergent decompression of the bile duct, generally by ERCP, is required for patients who are septic or fail to improve on antibiotics within 12–24 hours. Medical therapy alone is most likely to fail in patients with tachycardia, a serum albumin less than 3 g/dL (30 g/L), marked hyperbilirubinemia, a high serum ALT level, a high white blood cell count, and a prothrombin time greater than 14 seconds on admission. If sphincterotomy cannot be performed, the bile duct can be decompressed by a biliary stent or nasobiliary catheter. Once decompression is achieved, antibiotics are generally continued for at least another 3 days. Cholecystectomy can be undertaken after resolution of cholangitis, unless the patient remains unfit for surgery. Mortality from acute cholangitis has been reported to correlate with a high total bilirubin level, prolonged partial thromboplastin time, malnutrition, presence of a liver abscess, and unsuccessful ERCP.

► When to Refer

All symptomatic patients with choledocholithiasis should be referred.

► When to Admit

All patients with acute cholangitis should be hospitalized.

Chen H et al. Incidence and predictors of common bile duct stones in patients with acute cholecystitis: a systematic literature review and meta-analysis. *ANZ J Surg.* 2020;90:1598. [PMID: 31743951]

Discolo A et al. Outcomes following early versus delayed cholecystectomy performed for acute cholangitis. *Surg Endosc.* 2020;34:3204. [PMID: 31482348]

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BILIARY STRICTURE

Benign biliary strictures are the result of surgical (including liver transplantation) anastomosis or injury in about 95% of cases. The remainder of cases are caused by blunt external injury to the abdomen, pancreatitis, IgG₄-related disease, erosion of the duct by a gallstone, or prior endoscopic sphincterotomy.

Signs of injury to the duct may or may not be recognized in the immediate postoperative period. If complete occlusion has occurred, jaundice will develop rapidly; more often, however, a tear has been made accidentally in the duct, and the earliest manifestation of injury may be excessive or prolonged loss of bile from the surgical drains. Bile leakage resulting in a bile collection (biloma) may predispose to localized infection, which in turn accentuates scar formation and the ultimate development of a fibrous stricture.

Cholangitis is the most common complication of stricture. Typically, the patient experiences episodes of pain, fever, chills, and jaundice within a few weeks to months after cholecystectomy. Physical findings may include jaundice during an acute attack of cholangitis and right upper quadrant abdominal tenderness. Serum alkaline phosphatase is usually elevated. Hyperbilirubinemia is variable, fluctuating during exacerbations and usually remaining in the range of 5–10 mg/dL (85.5–171 mcmol/L). Blood cultures may be positive during an acute episode of cholangitis. Secondary biliary cirrhosis will inevitably develop if a stricture is not treated.

MRCP or multidetector CT is valuable in demonstrating the stricture and outlining the anatomy. ERCP is the first-line interventional approach and permits biopsy and cytologic specimens to exclude malignancy (in conjunction with EUS-guided fine-needle aspiration, an even more sensitive test for distal bile duct malignancy), sphincterotomy to allow a bile leak to close, and dilation (often repeated) and stent placement, thereby avoiding surgical repair in some cases. When ERCP is unsuccessful, dilation of a stricture may be accomplished by PTC or under EUS guidance. Placement of multiple plastic stents appears to be more effective than placement of a single stent. The use of fully covered self-expanding metal stents, which are more easily removed endoscopically than uncovered metal stents, as well as bioabsorbable stents, is an alternative to use of plastic stents and requires fewer ERCPs to achieve stricture resolution; stent migration may occur in 10% of cases. Uncovered metal stents, which often cannot be removed endoscopically, are generally avoided in benign strictures unless life expectancy is less than 2 years. Strictures related to chronic pancreatitis are more difficult than postsurgical strictures to treat endoscopically and may be best managed with a temporary covered metal stent. Following liver transplantation, endoscopic management is more successful for anastomotic than for nonanastomotic strictures. Results for nonanastomotic strictures may be improved with repeated dilations or the use of multiple plastic stents. Biliary strictures after live liver donor liver transplantation, particularly in patients with a late-onset (after 24 weeks) stricture or with intrahepatic biliary dilatation, are also challenging and require aggressive endoscopic therapy; in addition, the risk of post-ERCP pancreatitis appears to be increased.

When malignancy cannot be excluded with certainty, additional endoscopic diagnostic approaches may be considered—if available—including intraductal ultrasonography, peroral cholangioscopy, confocal laser endomicroscopy, optical coherence tomography, and fluorescence in situ hybridization. Differentiation from cholangiocarcinoma

may ultimately require surgical exploration in 20% of cases. Operative treatment of a stricture frequently necessitates performance of an end-to-end ductal repair, choledochojejunostomy, or hepaticojejunostomy to reestablish bile flow into the intestine.

► When to Refer

All patients with biliary stricture should be referred.

► When to Admit

Patients with acute cholangitis should be hospitalized.

Gerges C et al. Digital single-operator peroral cholangioscopy-guided biopsy sampling versus ERCP-guided brushing for indeterminate biliary strictures: a prospective, randomized, multicenter trial (with video). *Gastrointest Endosc*. 2020; 91:1105. [PMID: 31778656]

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PRIMARY SCLEROSING CHOLANGITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Most common in men aged 20–50 years.
- ▶ Often associated with ulcerative colitis.
- ▶ Progressive jaundice, itching, and other features of cholestasis.
- ▶ Diagnosis based on characteristic cholangiographic findings.
- ▶ At least 10% risk of cholangiocarcinoma.

► General Considerations

Primary sclerosing cholangitis is an uncommon disease thought to result from an increased immune response to intestinal endotoxins and characterized by diffuse inflammation of the biliary tract leading to fibrosis and strictures of the biliary system. From 60% to 70% of affected persons are male, usually 20–50 years of age (median age 41). The incidence is nearly 3.3 per 100,000 in Asian Americans, 2.8 per 100,000 in Hispanic Americans, and 2.1 per 100,000 in Blacks, with an intermediate (and increasing) incidence in Whites and a prevalence of 16.2 per 100,000 population (21 per 100,000 men and 6 per 100,000 women) in the United States.

Primary sclerosing cholangitis is closely associated with inflammatory bowel disease (more commonly ulcerative colitis than Crohn colitis), which is present in approximately two-thirds of patients with primary sclerosing cholangitis; however, clinically significant sclerosing cholangitis develops in only 1–4% of patients with ulcerative colitis. Smoking is associated with a decreased risk of primary sclerosing cholangitis in patients who also have inflammatory bowel disease. Coffee consumption is also associated with a decreased

risk of primary sclerosing cholangitis, and statin use is associated with improved outcomes in patients with primary sclerosing cholangitis. Women with primary sclerosing cholangitis may be more likely to have recurrent urinary tract infections and less likely to use hormone replacement therapy than healthy controls. Associations with cardiovascular disease and diabetes mellitus have been reported. Primary sclerosing cholangitis is associated with the histocompatibility antigens HLA-B8 and -DR3 or -DR4, and first-degree relatives of patients with primary sclerosing cholangitis have a fourfold increased risk of primary sclerosing cholangitis and a threefold increased risk of ulcerative colitis. A subset of patients with primary sclerosing cholangitis have increased serum IgG₄ levels and distinct HLA associations (with a poorer prognosis) but do not meet criteria for IgG₄-related sclerosing cholangitis. The diagnosis of primary sclerosing cholangitis may be difficult to make after biliary surgery.

► Clinical Findings

A. Symptoms and Signs

Primary sclerosing cholangitis presents as progressive obstructive jaundice, frequently associated with fatigue, pruritus, anorexia, and indigestion. Patients may be diagnosed in the presymptomatic phase because of an elevated alkaline phosphatase level or a subclinical phase based on abnormalities on magnetic resonance cholangiography despite normal liver enzyme levels. Complications of chronic cholestasis, such as osteoporosis, malabsorption of fat-soluble vitamins, and malnutrition, may occur late in the course. Risk factors for osteoporosis include older age, lower body mass index, and longer duration of inflammatory bowel disease. Esophageal varices on initial endoscopy are most likely in patients with a higher Mayo risk score based on age, bilirubin, albumin, and AST and a higher AST/ALT ratio, and new varices are likely to develop in those with a lower platelet count and higher bilirubin at 2 years. In patients with primary sclerosing cholangitis, ulcerative colitis is frequently characterized by rectal sparing and backwash ileitis.

B. Diagnostic Findings

The diagnosis of primary sclerosing cholangitis is generally made by MRCP, the sensitivity of which approaches that of ERCP. Characteristic cholangiographic findings are segmental fibrosis of bile ducts with saccular dilatations between strictures. Biliary obstruction by a stone or tumor should be excluded. Liver biopsy is not necessary for diagnosis when cholangiographic findings are characteristic. The disease may be confined to small intrahepatic bile ducts in about 15% of cases, in which case MRCP and ERCP are normal and the diagnosis is suggested by liver biopsy findings. These patients have a longer survival than patients with involvement of the large ducts and do not appear to be at increased risk for cholangiocarcinoma unless large-duct sclerosing cholangitis develops (which occurs in about 20% over 7–10 years). Liver biopsy may show characteristic periductal fibrosis (“onion-skinning”) and allows staging, which is based on the degree of fibrosis and which correlates with liver stiffness as measured by elastography. Perinuclear ANCA as well as antinuclear,

anticardiolipin, antithyroxoperoxidase, and anti-*Saccharomyces cerevisiae* antibodies and rheumatoid factor are frequently detected in serum.

Occasional patients have clinical and histologic features of both sclerosing cholangitis and autoimmune hepatitis. Cholangitis in IgG₄-related disease may be difficult to distinguish from primary sclerosing cholangitis and even cholangiocarcinoma, is associated with autoimmune pancreatitis (see Chronic Pancreatitis), and is responsive to corticosteroids. A serum IgG₄ level more than four times the upper limit of normal or an IgG₄:IgG₁ ratio of more than 0.24 strongly suggests IgG₄-related sclerosing cholangitis, but in up to one-third of cases, the serum IgG₄ level is normal. Primary sclerosing cholangitis must also be distinguished from idiopathic adulthood ductopenia (a rare disorder that affects young to middle-aged adults who manifest cholestasis resulting from loss of interlobular and septal bile ducts yet who have a normal cholangiogram; it is caused in some cases by a mutation in the canalicular phospholipid transporter gene *ABCB4*). Primary sclerosing cholangitis must also be distinguished from other cholangiopathies (including PBC; cystic fibrosis; eosinophilic cholangitis; AIDS cholangiopathy; histiocytosis X; allograft rejection; graft-versus-host disease; ischemic cholangiopathy [often with biliary “casts,” a rapid progression to cirrhosis, and a poor outcome] caused by hepatic artery thrombosis, shock, respiratory failure, or drugs [a similar entity has been described in patients with COVID]; intra-arterial chemotherapy; and sarcoidosis).

Complications

Cholangiocarcinoma may complicate the course of primary sclerosing cholangitis in up to 20% of cases (1.2% per year) and may be difficult to diagnose by cytologic examination or biopsy because of false-negative results. A serum CA 19-9 level above 100 units/mL is suggestive but not diagnostic of cholangiocarcinoma. Annual MRI with MRCP or right-upper-quadrant ultrasonography and, by some guidelines but not others, serum CA 19-9 testing (a level of 20 is the threshold for further investigation) are recommended for surveillance, with ERCP and biliary cytology if the results are suggestive of malignancy. MRCP is more sensitive than ultrasonography. PET and peroral cholangioscopy may play roles in the early detection of cholangiocarcinoma. Patients with ulcerative colitis and primary sclerosing cholangitis are at high risk (tenfold higher than ulcerative colitis patients without primary sclerosing cholangitis) for colorectal neoplasia. The risks of gallstones, cholecystitis, gallbladder polyps, and gallbladder carcinoma appear to be increased in patients with primary sclerosing cholangitis.

Treatment

Episodes of acute bacterial cholangitis may be treated with ciprofloxacin (750 mg twice daily orally or intravenously). Ursodeoxycholic acid in standard doses (10–15 mg/kg/day orally) may improve liver biochemical test results but does not appear to alter the natural history. However, withdrawal of ursodeoxycholic acid may result in worsening of liver biochemical test levels and increased pruritus, and

ursodeoxycholic acid in intermediate doses (17–23 mg/kg/day) has been reported to be beneficial.

Careful endoscopic evaluation of the biliary tract may permit balloon dilation of localized strictures, and repeated dilation of a dominant stricture may improve survival, although such patients have reduced survival compared with patients who do not have a dominant stricture. Short-term (2–3 weeks) placement of a stent in a major stricture also may relieve symptoms and improve biochemical abnormalities, with sustained improvement after the stent is removed, but may not be superior to balloon dilation alone; long-term stenting may increase the rate of complications such as cholangitis and is not recommended.

Cholecystectomy is indicated in patients with primary sclerosing cholangitis and a gallbladder polyp greater than 8 mm in diameter. In patients without cirrhosis, surgical resection of a dominant bile duct stricture may lead to longer survival than endoscopic therapy by decreasing the subsequent risk of cholangiocarcinoma. When feasible, extensive surgical resection of cholangiocarcinoma complicating primary sclerosing cholangitis may result in 5-year survival rates of greater than 50%. In patients with ulcerative colitis, primary sclerosing cholangitis is an independent risk factor for the development of colorectal dysplasia and cancer (especially in the right colon), and strict adherence to a colonoscopic surveillance program (yearly for those with ulcerative colitis and every 5 years for those without ulcerative colitis) is recommended. Whether treatment with ursodeoxycholic acid reduces the risk of colorectal dysplasia and carcinoma in patients with ulcerative colitis and primary sclerosing cholangitis is still uncertain. For patients with cirrhosis and clinical decompensation, liver transplantation is the treatment of choice; primary sclerosing cholangitis recurs in the graft in 30% of cases, with a possible reduction in the risk of recurrence when colectomy has been performed for ulcerative colitis before transplantation.

Prognosis

Survival of patients with primary sclerosing cholangitis averages 9–17 years, and up to 21 years in population-based studies. Adverse prognostic markers are older age, hepatosplenomegaly, higher serum bilirubin and AST levels, lower albumin levels, a history of variceal bleeding, a dominant bile duct stricture, and extrahepatic duct changes. Variceal bleeding is also a risk factor for cholangiocarcinoma. Patients in whom serum alkaline phosphatase levels decline by 40% or more (spontaneously, with ursodeoxycholic acid therapy, or after treatment of a dominant stricture) have longer transplant-free survival times than those in whom the alkaline phosphatase does not decline. Moreover, improvement in the serum alkaline phosphatase to less than 1.5 times the upper limit of normal is associated with a reduced risk of cholangiocarcinoma. Risk of progression can be predicted by three findings on MRI and MRCP: a cirrhotic appearance to the liver, portal hypertension, and enlarged perihepatic lymph nodes.

The Amsterdam-Oxford model has been proposed to predict transplant-free survival and is based on disease subtype (large- vs. small-duct involvement), age at diagnosis,

serum albumin, platelet count, serum AST, serum alkaline phosphatase, and serum bilirubin. Another promising scoring system is the UK-PSC risk score based on age, serum bilirubin, serum alkaline phosphatase, albumin, platelet count, presence of extrahepatic disease, and variceal hemorrhage. The PSC risk estimate tool (PREsTo) based on nine variables (bilirubin, albumin, alkaline phosphatase, platelets, AST, hemoglobin, sodium, patient age, and number of years since the diagnosis of primary sclerosing cholangitis) has been reported to accurately predict hepatic decompensation. Transplant-free survival can also be predicted by serum levels of markers of liver fibrosis—hyaluronic acid, tissue inhibitor of metalloproteinase-1, and propeptide of type III procollagen. Reduced quality of life is associated with older age, large-duct disease, and systemic symptoms. Maternal primary sclerosing cholangitis is associated with preterm birth and cesarean section delivery; risk of congenital malformations is not increased. Interestingly, patients with milder ulcerative colitis tend to have more severe primary cholangitis and a higher rate of liver transplantation. Actuarial survival rates with liver transplantation are as high as 72% at 5 years, but rates are much lower once cholangiocarcinoma has developed. Following transplantation, patients have an increased risk of nonanastomotic biliary strictures and—in those with ulcerative colitis—colon cancer, and the disease recurs in 25%. The retransplantation rate is higher than that for PBC. Patients who are unable to undergo liver transplantation will ultimately require high-quality palliative care (see Chapter 5).

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DISEASES OF THE PANCREAS

See Chapter 39 for Carcinoma of the Pancreas and Periampullary Area.

ACUTE PANCREATITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Abrupt onset of deep epigastric pain, often with radiation to the back.
- ▶ History of previous episodes, often related to alcohol intake.
- ▶ Nausea, vomiting, sweating, weakness.
- ▶ Abdominal tenderness and distention and fever.
- ▶ Leukocytosis, elevated serum amylase, elevated serum lipase.

► General Considerations

The annual incidence of acute pancreatitis ranges from 13 to 45 per 100,000 population and has increased since 1990. A majority of cases of acute pancreatitis are related to biliary tract disease (45%) (a passed gallstone, usually 5 mm or less in diameter) or heavy alcohol intake (20%), with worldwide variations. The exact pathogenesis is not known but may include edema or obstruction of the ampulla of Vater, reflux of bile into pancreatic ducts, and direct injury of pancreatic acinar cells by prematurely activated pancreatic enzymes. Among the numerous other causes or associations are (1) hyperlipidemias (chylomicronemia, hypertriglyceridemia, or both); (2) hypercalcemia; (3) abdominal trauma (including surgery); (4) medications (including azathioprine, mercaptopurine, asparaginase, pentamidine, didanosine, valproic acid, tetracyclines, dapsone, isoniazid, metronidazole, estrogen and tamoxifen [by raising serum triglycerides], sulfonamides, mesalamine, celecoxib, sulindac, leflunomide, thiazides, simvastatin, fenofibrate, enalapril, methyldopa, procainamide, sitagliptin, exenatide, possibly corticosteroids, and others); (5) vasculitis; (6) infections (eg, mumps, cytomegalovirus, HEV, *M avium intracellulare* complex, SARS-CoV-2); (7) peritoneal dialysis; (8) cardiopulmonary bypass, single- or double-balloon enteroscopy; and (9) ERCP. Medication-induced acute pancreatitis is generally dose-related and associated with worse outcomes than that due to other causes. In patients with pancreas divisum, a congenital anomaly in which the dorsal and ventral pancreatic ducts fail to fuse, acute pancreatitis may result from stenosis of the minor papilla with obstruction to flow from the accessory pancreatic duct, although concomitant genetic mutations, particularly in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, may actually account for acute pancreatitis in these patients. Acute pancreatitis may also result from an anomalous junction of the pancreaticobiliary duct (pancreaticobiliary malunion). Rarely, acute pancreatitis may be the presenting manifestation of a pancreatic or ampullary neoplasm. Celiac disease appears to be associated with an increased risk of acute and chronic pancreatitis. Apparently “idiopathic” acute pancreatitis is often caused by occult biliary microlithiasis but unlikely to be caused by sphincter of Oddi dysfunction involving the pancreatic duct. Between 15% and 25% of cases are truly idiopathic. Smoking, high dietary glycemic load, and abdominal adiposity increase the risk of pancreatitis, and older age and obesity increase the risk of a severe course; vegetable consumption, dietary fiber, and use of statins may reduce the risk of pancreatitis, and coffee drinking may reduce the risk of nonbiliary pancreatitis.

► Clinical Findings

A. Symptoms and Signs

Epigastric abdominal pain, generally abrupt in onset, is steady, boring, and severe and often made worse by walking and lying supine and better by sitting and leaning forward. The pain usually radiates into the back but may radiate to the right or left. Nausea and vomiting are usually

present. Weakness, sweating, and anxiety are noted in severe attacks. There may be a history of alcohol intake or a heavy meal immediately preceding the attack or a history of milder similar episodes or biliary pain in the past.

The upper abdomen is tender, most often without guarding, rigidity, or rebound. The abdomen may be distended, and bowel sounds may be absent with associated ileus. Fever of 38.4–39°C, tachycardia, hypotension (even shock), pallor, and cool clammy skin are present in severe cases. Mild jaundice may be seen. Occasionally, an upper abdominal mass due to the inflamed pancreas or a pseudocyst may be palpated. Acute kidney injury (usually prerenal azotemia) may occur early in the course of acute pancreatitis.

B. Laboratory Findings

Serum amylase and lipase are elevated—usually more than three times the upper limit of normal—within 24 hours in 90% of cases; their return to normal is variable depending on the severity of disease. Lipase remains elevated longer than amylase and is slightly more accurate for the diagnosis of acute pancreatitis. Leukocytosis (10,000–30,000/mcL [$10\text{--}30 \times 10^9/\text{L}$]), proteinuria, granular casts, glycosuria (10–20% of cases), hyperglycemia, and elevated serum bilirubin may be present. Blood urea nitrogen and serum alkaline phosphatase may be elevated and coagulation tests abnormal. An elevated serum creatinine level (greater than 1.8 mg/dL [149.94 mcmol/L]) at 48 hours is associated with the development of pancreatic necrosis. In patients with clear evidence of acute pancreatitis, a serum ALT level of more than 150 units/L (3 mkat/L) suggests biliary pancreatitis. A decrease in serum calcium may reflect saponification and correlates with severity of the disease. Levels lower than 7 mg/dL (1.75 mmol/L) (when serum albumin is normal) are associated with tetany and an unfavorable prognosis. Patients with acute pancreatitis caused by hypertriglyceridemia generally have fasting triglyceride levels above 1000 mg/dL (10 mmol/L) and often have other risk factors for pancreatitis; in some cases, the serum amylase is not elevated substantially because of an inhibitor in the serum of patients with marked hypertriglyceridemia that interferes with measurement of serum amylase. An early rise in the hematocrit value above 44% suggests hemoconcentration and predicts pancreatic necrosis. An elevated C-reactive protein concentration (greater than 150 mg/L [1500 mg/L]) at 48 hours suggests severe disease.

Other diagnostic tests that offer the possibility of simplicity, rapidity, ease of use, and low cost—including urinary trypsinogen-2, trypsinogen activation peptide, and carboxypeptidase B—are not widely available. In patients in whom ascites or a left pleural effusion develops, fluid amylase content is high. Electrocardiography may show ST-T wave changes.

C. Assessment of Severity

In addition to the individual laboratory parameters noted above, the severity of acute alcohol-associated pancreatitis can be assessed using several scoring systems (none of which has been shown to have high prognostic accuracy),

Table 16–10. Ranson criteria for assessing the severity of acute pancreatitis.

Three or more of the following predict a severe course complicated by pancreatic necrosis with a sensitivity of 60–80%	
Age over 55 years	
White blood cell count $> 16 \times 10^3/\text{mcL}$ ($> 16 \times 10^9/\text{L}$)	
Blood glucose $> 200 \text{ mg/dL}$ ($> 11 \text{ mmol/L}$)	
Serum lactic dehydrogenase $> 350 \text{ units/L}$ ($> 7 \text{ mkat/L}$)	
Aspartate aminotransferase $> 250 \text{ units/L}$ ($> 5 \text{ mkat/L}$)	
Development of the following in the first 48 hours indicates a worsening prognosis	
Hematocrit drop of more than 10 percentage points	
Blood urea nitrogen rise $> 5 \text{ mg/dL}$ ($> 1.8 \text{ mmol/L}$)	
Arterial Po_2 of $< 60 \text{ mm Hg}$ ($< 7.8 \text{ kPa}$)	
Serum calcium of $< 8 \text{ mg/dL}$ ($< 0.2 \text{ mmol/L}$)	
Base deficit over 4 mEq/L	
Estimated fluid sequestration of $> 6 \text{ L}$	
Mortality rates correlate with the number of criteria present	
Number of Criteria	Mortality Rate
0–2	1%
3–4	16%
5–6	40%
7–8	100%

including the **Ranson criteria** (Table 16–10). The **Sequential Organ Failure Assessment (SOFA)** score or **modified Marshall scoring system** can be used to assess injury to other organs, and the **Acute Physiology and Chronic Health Evaluation (APACHE II)** score is another tool for assessing severity. The severity of acute pancreatitis can also be predicted by the **Pancreatitis Activity Scoring System (PASS)** based on organ failure, intolerance to a solid diet, systemic inflammatory response syndrome, abdominal pain, and dose of intravenous morphine (or its equivalent). Another simple 5-point clinical scoring system (the **Bedside Index for Severity in Acute Pancreatitis**, or **BISAP**) based on blood urea nitrogen above 25 mg/dL (9 mmol/L), impaired mental status, systemic inflammatory response syndrome, age older than 60 years, and pleural effusion during the first 24 hours (before the onset of organ failure) identifies patients at increased risk for mortality. More simply, the presence of a systemic inflammatory response alone and an elevated blood urea nitrogen level on admission as well as a rise in blood urea nitrogen within the first 24 hours of hospitalization are independently associated with increased mortality; the greater the rise in blood urea nitrogen after admission, the greater the mortality rate. A model based on the change in serum amylase in the first 2 days after admission and the body mass index has been proposed. An early rise in serum levels of neutrophil gelatinase-associated lipocalin has also been proposed as a marker of severe acute pancreatitis. The absence of rebound abdominal tenderness or guarding, a normal hematocrit value, and a normal serum creatinine level (the “**harmless acute pancreatitis score**,” or **HAPS**)

predict a nonsevere course with 98% accuracy. The **revised Atlanta classification** of the severity of acute pancreatitis uses the following three categories: (1) **mild** disease is the absence of organ failure and local ([peri]pancreatic necrosis or fluid collections) or systemic complications; (2) **moderate** disease is the presence of transient (under 48 hours) organ failure or local or systemic complications, or both; and (3) **severe** disease is the presence of persistent (48 hours or more) organ failure. A similar “**determinant-based**” classification also includes a category of **critical** acute pancreatitis characterized by both persistent organ failure and infected peripancreatic necrosis.

D. Imaging

Plain radiographs of the abdomen may show gallstones (if calcified), a “sentinel loop” (a segment of air-filled small intestine most commonly in the left upper quadrant), the “colon cutoff sign”—a gas-filled segment of transverse colon abruptly ending at the area of pancreatic inflammation—or focal linear atelectasis of the lower lobes of the lungs with or without pleural effusions. Ultrasonography is often not helpful in diagnosing acute pancreatitis because of intervening bowel gas but may identify gallstones in the gallbladder. Unenhanced CT is useful for demonstrating an enlarged pancreas when the diagnosis of pancreatitis is uncertain, differentiating pancreatitis from other possible intra-abdominal catastrophes, and providing an initial assessment of prognosis but is often unnecessary early in the course (Table 16–11). Rapid-bolus intravenous contrast-enhanced CT following aggressive volume resuscitation is of particular value after the first 3 days of severe acute pancreatitis for identifying areas of necrotizing pancreatitis and assessing the degree of necrosis (although the use of intravenous contrast may increase the risk of complications of pancreatitis and of acute kidney injury and should be avoided when the serum creatinine level is above 1.5 mg/dL [124.95 μmol/L]). MRI appears to be a suitable alternative to CT. Perfusion CT on day 3 demonstrating areas of ischemia in the pancreas has been reported to predict the development of pancreatic necrosis. The presence of a fluid collection in the pancreas correlates with an increased mortality rate. CT-guided needle aspiration of areas of necrotizing pancreatitis after the

third day may disclose infection, usually by enteric organisms, which typically requires debridement; however, the false-negative rate is 25%. The presence of gas bubbles on CT implies infection by gas-forming organisms. EUS is useful in identifying occult biliary disease (eg, small stones, sludge, microlithiasis), which is present in a majority of patients with apparently idiopathic acute pancreatitis, and is indicated in persons over age 40 to exclude malignancy. ERCP is generally not indicated after a first attack of acute pancreatitis unless there is associated cholangitis or jaundice or a bile duct stone is known to be present, but EUS or MRCP should be considered, especially after repeated attacks of idiopathic acute pancreatitis. Following a single attack of idiopathic acute pancreatitis, a negative EUS examination predicts a low risk of relapse. In select cases, aspiration of bile for crystal analysis may confirm the suspicion of microlithiasis, and manometry of the pancreatic duct sphincter may detect sphincter of Oddi dysfunction as a cause of recurrent pancreatitis.

► Differential Diagnosis

Acute pancreatitis must be differentiated from an acutely perforated duodenal ulcer, acute cholecystitis, acute intestinal obstruction, leaking aortic aneurysm, renal colic, and acute mesenteric ischemia. Serum amylase may also be elevated in proximal intestinal obstruction, gastroenteritis, mumps not involving the pancreas (salivary amylase), and ectopic pregnancy and after administration of opioids and abdominal surgery. Serum lipase may also be elevated in many of these conditions.

► Complications

Intravascular volume depletion secondary to leakage of fluids into the pancreatic bed and to ileus with fluid-filled loops of bowel may result in prerenal azotemia and even acute tubular necrosis without overt shock. This sequence usually occurs within 24 hours of the onset of acute pancreatitis and lasts 8–9 days. Some patients require renal replacement therapy.

According to the revised Atlanta classification, fluid collections and necrosis may be acute (within the first 4 weeks)

Table 16–11. Severity index for acute pancreatitis.

CT Grade	Points	Pancreatic Necrosis	Additional Points	Severity Index ¹	Mortality Rate ²
A Normal pancreas	0	0%	0	0	0%
B Pancreatic enlargement	1	0%	0	1	0%
C Pancreatic inflammation and/or peripancreatic fat	2	< 30%	2	4	< 3%
D Single acute peripancreatic fluid collection	3	30–50%	4	7	6%
E Two or more acute peripancreatic fluid collections or retroperitoneal air	4	> 50%	6	10	> 17%

¹Severity Index = CT Grade Points + Pancreatic Necrosis Additional Points.

²Based on the Severity Index.

Adapted with permission from Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. Radiology. 2002; 223(3):603–13.

or chronic (after 4 weeks) and sterile or infected. Chronic collections, including pseudocysts and walled-off necrosis, are characterized by encapsulation. Sterile or infected necrotizing pancreatitis may complicate the course in 5–10% of cases and accounts for most of the deaths. The risk of infection does not correlate with the extent of necrosis. Pancreatic necrosis is often associated with fever, leukocytosis, and, in some cases, shock and is associated with organ failure (eg, gastrointestinal bleeding, respiratory failure, acute kidney injury) in 50% of cases. It may lead to complete transection of the pancreatic duct (disconnected pancreatic duct syndrome), which may result in recurrent fluid collections or persistent fistulae months or years after necrosis has resolved. Because infected pancreatic necrosis is often an indication for debridement, fine-needle aspiration of necrotic tissue under CT guidance should be performed (if necessary, repeatedly) for Gram stain and culture.

A serious complication of acute pancreatitis is acute respiratory distress syndrome (ARDS); cardiac dysfunction may be superimposed. It usually occurs 3–7 days after the onset of pancreatitis in patients who have required large volumes of fluid and colloid to maintain blood pressure and urinary output. Most patients with ARDS require intubation, mechanical ventilation, and supplemental oxygen.

Pancreatic abscess (also referred to as infected or suppurative pseudocyst) is a suppurative process characterized by rising fever, leukocytosis, and localized tenderness and an epigastric mass usually 6 or more weeks into the course of acute pancreatitis. The abscess may be associated with a left-sided pleural effusion or an enlarging spleen secondary to splenic vein thrombosis. In contrast to infected necrosis, the mortality rate is low following drainage.

Pseudocysts, encapsulated fluid collections with high amylase content, commonly appear in pancreatitis when CT is used to monitor the evolution of an acute attack. Pseudocysts that are smaller than 6 cm in diameter often resolve spontaneously. They most commonly are within or adjacent to the pancreas but can present almost anywhere (eg, mediastinal, retrorectal) by extension along anatomic planes. Multiple pseudocysts are seen in 14% of cases. Pseudocysts may become secondarily infected, necessitating drainage as for an abscess. Pancreatic ascites may present after recovery from acute pancreatitis as a gradual increase in abdominal girth and persistent elevation of the serum amylase level in the absence of frank abdominal pain. Marked elevations in ascitic protein (greater than 3 g/dL) and amylase (greater than 1000 units/L [20 mkat/L]) concentrations are typical. The condition results from disruption of the pancreatic duct or drainage of a pseudocyst into the peritoneal cavity.

Rare complications of acute pancreatitis include hemorrhage caused by erosion of a blood vessel to form a pseudoaneurysm and by colonic necrosis. Portosplenomesenteric venous thrombosis frequently develops in patients with necrotizing acute pancreatitis but rarely leads to complications. Other local complications include abdominal compartment syndrome, intestinal ischemia, and gastric outlet obstruction. Chronic pancreatitis develops in about 10% of cases of acute pancreatitis. Diabetes mellitus and exocrine pancreatic insufficiency may develop after acute pancreatitis.

► Treatment

A. Treatment of Acute Disease

1. Mild disease—In most patients, acute pancreatitis is a mild disease (“nonsevere acute pancreatitis”) that subsides spontaneously within several days. The pancreas is “rested” by a regimen of withholding food and liquids by mouth, bed rest, and, in patients with moderately severe pain or ileus and abdominal distention or vomiting, nasogastric suction. Goal-directed therapy with early aggressive fluid resuscitation (one-third of the total 72-hour fluid volume administered within 24 hours of presentation, 250–500 mL/h initially) may reduce the frequency of systemic inflammatory response syndrome and organ failure in this group of patients and appears to have the greatest benefit in patients with acute pancreatitis predicted to be mild in severity when started within 4 hours of the patient’s arrival at the hospital. Lactated Ringer solution may be preferable to normal saline; however, overly aggressive fluid resuscitation may lead to morbidity as well.

Pain is controlled with meperidine, up to 100–150 mg intramuscularly every 3–4 hours as necessary. In those with severe liver or kidney dysfunction, the dose may need to be reduced. Morphine had been thought to cause sphincter of Oddi spasm but is now considered an acceptable alternative and, given the potential side effects of meperidine, may even be preferable. Oral intake of fluid and foods can be resumed when the patient is largely free of pain and has bowel sounds (even if the serum amylase is still elevated). Clear liquids are given first (this step may be skipped in patients with mild acute pancreatitis), followed by gradual advancement to a low-fat diet, guided by the patient’s tolerance and by the absence of pain. Pain may recur on refeeding in 20% of patients.

Following recovery from acute biliary pancreatitis, laparoscopic cholecystectomy is generally performed, preferably during the same hospital admission, and is associated with a reduced rate of recurrent gallstone-related complications compared with delayed cholecystectomy. In selected cases endoscopic sphincterotomy alone may be done. In patients with recurrent pancreatitis associated with pancreas divisum, insertion of a stent in the minor papilla (or minor papilla sphincterotomy) may reduce the frequency of subsequent attacks, although complications of such therapy are frequent. In patients with recurrent acute pancreatitis attributed to pancreatic sphincter of Oddi dysfunction, biliary sphincterotomy alone is as effective as combined biliary and pancreatic sphincterotomy in reducing the frequency of recurrent acute pancreatitis, but chronic pancreatitis may still develop in treated patients. Hypertriglyceridemia with acute pancreatitis has been treated with combinations of insulin, heparin, apheresis, and hemofiltration, but the benefit of these approaches has not been proven.

2. Severe disease—In more severe pancreatitis—particularly necrotizing pancreatitis—there may be considerable leakage of fluids, necessitating large amounts of intravenous fluids (eg, 500–1000 mL/h for several hours, then 250–300 mL/h) to maintain intravascular volume. Risk factors for high levels of fluid sequestration include younger

age, alcohol etiology, higher hematocrit value, higher serum glucose, and systemic inflammatory response syndrome in the first 48 hours of hospital admission. Hemodynamic monitoring in an intensive care unit is required, and the importance of aggressive goal-directed intravenous hydration targeted to result in adequate urinary output, stabilization of blood pressure and heart rate, restoration of central venous pressure, and a modest decrease in hematocrit value cannot be overemphasized. Calcium gluconate must be given intravenously if there is evidence of hypocalcemia with tetany. Infusions of fresh frozen plasma or serum albumin may be necessary in patients with coagulopathy or hypoalbuminemia. With colloid solutions, the risk of ARDS may be increased. If shock persists after adequate volume replacement (including packed red cells), vasopressors may be required. For the patient requiring a large volume of parenteral fluids, central venous pressure and blood gases should be monitored at regular intervals.

Enteral nutrition via a nasojejunal or possibly nasogastric feeding tube is preferable to parenteral nutrition in patients who will otherwise be without oral nutrition for at least 7–10 days and reduces the risk of multiorgan failure and mortality when started within 48 hours of admission, but may not be tolerated in some patients with an ileus and does not reduce the rates of infection and death compared with the introduction of an oral diet after 72 hours. Parenteral nutrition (including lipids) should be considered in patients who have severe pancreatitis and ileus; glutamine supplementation appears to reduce the risk of infectious complications and mortality.

The routine use of antibiotics to prevent conversion of sterile necrotizing pancreatitis to infected necrosis is of no benefit and generally is not indicated in patients with less than 30% pancreatic necrosis. Imipenem (500 mg intravenously every 6 hours) or possibly cefuroxime (1.5 g intravenously three times daily, then 250 mg orally twice daily) administered for no more than 14 days to patients with sterile necrotizing pancreatitis has been reported in some studies to reduce the risk of pancreatic infection and mortality, but in general, prophylactic antibiotics are not recommended; meropenem and the combination of ciprofloxacin and metronidazole do not appear to reduce the frequency of infected necrosis, multiorgan failure, or mortality. When infected necrotizing pancreatitis is confirmed, imipenem or meropenem should be continued. Drug-resistant organisms are increasingly prevalent. In occasional cases, a fungal infection is found, and appropriate antifungal therapy should be prescribed.

The role of intravenous somatostatin in severe acute pancreatitis is uncertain, and octreotide is thought to have no benefit. A small study has suggested benefit from pentoxifylline. To date, probiotic agents have not been shown to reduce infectious complications of severe pancreatitis and may increase mortality.

NSAIDs (eg, indomethacin administered rectally) and aggressive hydration with lactated Ringer solution have been reported to reduce the frequency and severity of post-ERCP pancreatitis in persons at high risk, and rectal indomethacin is widely used, but studies of the benefit of indomethacin in unselected patients have yielded conflicting results.

Placement of a stent across the pancreatic duct or orifice has been shown to reduce the risk of post-ERCP pancreatitis by 60–80% and is a common practice.

B. Treatment of Complications and Follow-Up

A surgeon should be consulted in all cases of severe acute pancreatitis. If the diagnosis is in doubt and investigation indicates a strong possibility of a serious surgically correctable lesion (eg, perforated peptic ulcer), exploratory laparotomy is indicated. When acute pancreatitis is found unexpectedly, it is usually wise to close without intervention. If the pancreatitis appears mild and cholelithiasis or microlithiasis is present, cholecystectomy or cholecystostomy may be justified. When severe pancreatitis results from choledocholithiasis and jaundice (serum total bilirubin above 5 mg/dL [85.5 μmol/L]) or cholangitis is present, ERCP with endoscopic sphincterotomy and stone extraction is indicated. MRCP may be useful in selecting patients for therapeutic ERCP. Endoscopic sphincterotomy does not appear to improve the outcome of severe pancreatitis in the absence of cholangitis or jaundice.

Necrosectomy may improve survival in patients with necrotizing pancreatitis and clinical deterioration with multiorgan failure or lack of resolution by 4 weeks and is often indicated for infected necrosis, although a select group of relatively stable patients with infected pancreatic necrosis may be managed with antibiotics alone. The goal is to debride necrotic pancreas and surrounding tissue and establish adequate drainage. Outcomes are best if necrosectomy is delayed until the necrosis has organized, usually about 4 weeks after disease onset. A “step-up” approach in which nonsurgical endoscopic transluminal (transgastric or transduodenal) or percutaneous catheter drainage of walled-off pancreatic necrosis under radiologic guidance with subsequent open surgical necrosectomy if necessary has been shown to reduce mortality and resource utilization in select patients with necrotizing pancreatitis and confirmed or suspected secondary infection. In some cases, laparoscopic guidance (video-assisted retroperitoneal debridement) is an additional option, depending on local expertise. Lumen-apposing metal stents (LAMS) or double-pigtail plastic stents are used for endoscopic transluminal drainage, with removal of LAMS after 4 weeks to minimize the risk of complications. Treatment is labor intensive, and multiple procedures are often required, although costs and complication rates are lower than those for surgery. Peritoneal lavage has not been shown to improve survival in severe acute pancreatitis, in part because the risk of late septic complications is not reduced. Endoscopic or surgical interventions may be required for chronic disconnected pancreatic duct syndrome.

The development of a pancreatic abscess is an indication for prompt percutaneous or surgical drainage. Chronic pseudocysts require endoscopic, percutaneous catheter, or surgical drainage when infected or associated with persisting pain, pancreatitis, or bile duct obstruction. For pancreatic infections, imipenem, 500 mg every 8 hours intravenously, is a good choice of antibiotic because it achieves bactericidal levels in pancreatic tissue for most

causative organisms. Pancreatic duct leaks and fistulas may require endoscopic or surgical therapy.

► Prognosis

Mortality rates for acute pancreatitis have declined from at least 10% to around 5% since the 1980s, but the mortality rate for severe acute pancreatitis (more than three Ranson criteria; see Table 16–10) remains at least 20%, with rates of 10% and 25% in those with sterile and infected necrosis, respectively. Severe acute pancreatitis is predicted by features of the systemic inflammatory response on admission; a persistent systemic inflammatory response is associated with a mortality rate of 25% and a transient response with a mortality rate of 8%. Half of the deaths, usually from multiorgan failure, occur within the first 2 weeks. Multiorgan failure is associated with a mortality rate of at least 30%, and if it persists beyond the first 48 hours, a mortality rate of over 50%. Later deaths occur because of complications of infected necrosis. The risk of death doubles when both organ failure and infected necrosis are present. Moreover, hospital-acquired infections increase the mortality of acute pancreatitis, independent of severity. Readmission to the hospital for acute pancreatitis within 30 days may be predicted by a scoring system based on five factors during the index admission: eating less than a solid diet at discharge; nausea, vomiting, or diarrhea at discharge; pancreatic necrosis; use of antibiotics at discharge; and pain at discharge. Male sex, an alcohol etiology, and severe acute disease are risk factors. Recurrences are common (24%) in alcohol-associated pancreatitis, particularly in patients who smoke (40%), but can be reduced by repeated, regularly scheduled interventions to eliminate alcohol consumption and smoking after discharge from the hospital. A severe initial attack also increases the risk of recurrence and of subsequent exocrine pancreatic insufficiency. The risk of chronic pancreatitis following an episode of acute alcohol-associated pancreatitis is 8% in 5 years, 13% in 10 years, and 16% in 20 years, and the risk of diabetes mellitus is increased more than twofold over 5 years. Overall, chronic pancreatitis develops in 36% of patients with recurrent acute pancreatitis; alcohol use and smoking are principal risk factors. An association between a diagnosis of acute pancreatitis and long-term risk of pancreatic cancer has been reported.

► When to Admit

Nearly all patients with acute pancreatitis should be hospitalized.

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CHRONIC PANCREATITIS



ESSENTIALS OF DIAGNOSIS

- Chronic or intermittent epigastric pain, steatorrhea, weight loss, abnormal pancreatic imaging.
- A mnemonic for the predisposing factors of chronic pancreatitis is TIGAR-O: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive.

► General Considerations

The prevalence of chronic pancreatitis in the United States is 25–99 per 100,000 population with a peak in persons aged 46–55 years. Chronic pancreatitis occurs most often in patients with alcoholism (45–80% of all cases). The risk of chronic pancreatitis increases with the duration and amount of alcohol consumed, but pancreatitis develops in only 5–10% of heavy drinkers. Tobacco smoking is a risk factor for idiopathic chronic pancreatitis and has been reported to accelerate progression of alcohol-associated chronic pancreatitis. About 2% of patients with hyperparathyroidism develop pancreatitis. In tropical Africa and Asia, tropical pancreatitis, related in part to malnutrition, is the most common cause of chronic pancreatitis. By contrast, in Western societies, obesity can lead to pancreatic steatosis, which may lead ultimately to pancreatic exocrine and endocrine insufficiency and an increased risk of pancreatic cancer. A stricture, stone, or tumor obstructing the pancreas can lead to obstructive chronic pancreatitis. Autoimmune pancreatitis is associated with hypergammaglobulinemia (IgG_4 in particular), often with autoantibodies and other autoimmune diseases, and is responsive to corticosteroids. Affected persons are at increased risk for various cancers. Type 1 autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis, or simply autoimmune pancreatitis) is a multisystem disease, typically in a patient over age 60, characterized by lymphoplasmacytic infiltration and fibrosis on biopsy, associated bile duct strictures, retroperitoneal fibrosis, renal and salivary gland lesions, and a high rate of relapse after treatment. It is the pancreatic manifestation of IgG_4 -related disease. Type 2 ("idiopathic duct-centric chronic pancreatitis") affects the pancreas alone, typically in a patient aged 40–50 years, and is characterized by intense duct-centric lymphoplasmacytic infiltration on biopsy, lack of systemic IgG_4 involvement, an association with inflammatory bowel disease in 25% of cases, often a tumor-like mass, and a low rate of relapse after treatment. Between 10% and 30% of cases of chronic pancreatitis are idiopathic, with either early onset (median age 23) or late onset (median age 62). Genetic factors may predispose to chronic pancreatitis in some of these cases and include mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, the pancreatic secretory trypsin inhibitory gene (*PSTI*, also known as the serine protease inhibitor, *SPINK1*), the

chymotrypsin-C (*CTRC*) gene, and the genes for carboxypeptidase A1 (*CPA1*) and possibly uridine 5'-diphosphate glucuronosyltransferase (*UGT1A7*). Mutation of the cationic trypsinogen gene on chromosome 7 (serine protease 1, *PRSS1*) is associated with hereditary pancreatitis, transmitted as an autosomal dominant trait with variable penetrance. A useful mnemonic for the predisposing factors to chronic pancreatitis is TIGAR-O: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive.

The pathogenesis of chronic pancreatitis may be explained by the SAPE (sentinel acute pancreatitis event) hypothesis by which the first (sentinel) acute pancreatitis event initiates an inflammatory process that results in injury and later fibrosis ("necrosis-fibrosis"). In many cases, chronic pancreatitis is a self-perpetuating disease characterized by chronic pain or recurrent episodes of acute pancreatitis and ultimately by pancreatic exocrine or endocrine insufficiency (sooner in alcohol-associated pancreatitis than in other types). After many years, chronic pain may resolve spontaneously or as a result of surgery tailored to the cause of pain. Over 80% of adults develop diabetes mellitus within 25 years after the clinical onset of chronic pancreatitis.

► Clinical Findings

A. Symptoms and Signs

Persistent or recurrent episodes of epigastric and left upper quadrant pain are typical. The pain results in part from impaired inhibitory pain modulation by the central nervous system. Anorexia, nausea, vomiting, constipation, flatulence, and weight loss are common. During attacks, tenderness over the pancreas, mild muscle guarding, and ileus may be noted. Attacks may last only a few hours or as long as 2 weeks; pain may eventually be almost continuous. Steatorrhea (as indicated by bulky, foul, fatty stools) may occur late in the course.

B. Laboratory Findings

Serum amylase and lipase may be elevated during acute attacks; however, normal values do not exclude the diagnosis. Serum alkaline phosphatase and bilirubin may be elevated owing to compression of the bile duct. Glycosuria may be present. Excess fecal fat may be demonstrated on chemical analysis of the stool. Exocrine pancreatic insufficiency generally is confirmed by response to therapy with pancreatic enzyme supplements; the secretin stimulation test can be used if available (and has a high negative predictive value for ruling out early acute chronic pancreatitis), as can detection of decreased fecal chymotrypsin or elastase levels, although the latter tests lack sensitivity and specificity. Vitamin B₁₂ malabsorption is detectable in about 40% of patients, but clinical deficiency of vitamin B₁₂ and fat-soluble vitamins is rare. Accurate diagnostic tests are available for the major trypsinogen gene mutations, but because of uncertainty about the mechanisms linking heterozygous *CFTR* and *PSTI* mutations with pancreatitis, genetic testing for mutations in these two genes is recommended primarily in younger patients in whom the etiology of chronic

pancreatitis is unclear. Elevated IgG₄ levels, ANA, antibodies to lactoferrin and carbonic anhydrase II, and other autoantibodies are often found in patients with autoimmune pancreatitis (especially type 1). Pancreatic biopsy, if necessary, shows a lymphoplasmacytic infiltrate with characteristic IgG₄ immunostaining, which is also found in biopsy specimens of the major papilla, bile duct, and salivary glands, in type 1 autoimmune pancreatitis.

C. Imaging

CT or MRI is recommended as initial testing for diagnosis of chronic pancreatitis, although plain films show calcifications due to pancreaticolithiasis in 30% of affected patients. CT may show calcifications not seen on plain films as well as ductal dilatation and heterogeneity or atrophy of the gland. Occasionally, the findings raise suspicion of pancreatic cancer ("tumefactive chronic pancreatitis"). Secretin-enhanced MRCP may be considered in selected cases. When CT or MRI is inconclusive, EUS (with pancreatic tissue sampling) may be needed. Endoscopic ultrasonographic ("Rosemont") criteria for the diagnosis of chronic pancreatitis include hyperechoic foci with shadowing indicative of calculi in the main pancreatic duct and lobularity with honeycombing of the pancreatic parenchyma. ERCP is the most sensitive imaging study for chronic pancreatitis and may show dilated ducts, intraductal stones, strictures, or pseudocyst but is infrequently used for diagnosis alone; moreover, the results may be normal in patients with so-called minimal change pancreatitis. Histology is the gold standard for diagnosis when clinical suspicion is strong but imaging studies are inconclusive.

Characteristic imaging features of autoimmune pancreatitis include diffuse enlargement of the pancreas, a peripheral rim of hypoattenuation, and irregular narrowing of the main pancreatic duct. In the United States, the diagnosis of autoimmune pancreatitis is based on the HISORt criteria: histology, imaging, serology, other organ involvement, and response to corticosteroid therapy.

► Complications

Opioid addiction is common. Other frequent complications include often brittle diabetes mellitus, pancreatic pseudocyst or abscess, cholestatic liver enzymes with or without jaundice, bile duct stricture, exocrine pancreatic insufficiency, malnutrition, osteoporosis, and peptic ulcer. Pancreatic cancer develops in 4% of patients after 20 years; the risk may relate to tobacco and alcohol use. In patients with hereditary pancreatitis, the risk of pancreatic cancer rises after 50 years of age and reaches 19% by age 70 (see Chapter 39).

► Treatment

A. Medical Measures

A low-fat diet should be prescribed. Alcohol is forbidden because it frequently precipitates attacks. Opioids should be avoided if possible. Preferred agents for pain are acetaminophen, NSAIDs, and tramadol, along with

pain-modifying agents such as tricyclic antidepressants, selective serotonin reuptake inhibitors, and gabapentin or pregabalin. Exocrine pancreatic insufficiency is treated with pancreatic enzyme replacement therapy selected on the basis of high lipase activity (Table 16–12). A total dose of at least 40,000 units of lipase in capsules is given with each meal. Doses of 90,000 units or more of lipase per meal may be required in some cases. The tablets should be taken at the start of, during, and at the end of a meal. Concurrent administration of an H₂-receptor antagonist (eg, nizatidine, 150 mg orally twice daily), a proton pump inhibitor (eg, omeprazole, 20–60 mg orally daily), or sodium

bicarbonate (650 mg orally before and after meals) decreases the inactivation of lipase by acid and may thereby further decrease steatorrhea. In select cases of alcohol-associated pancreatitis and in cystic fibrosis, enteric-coated microencapsulated preparations may offer an advantage; however, in patients with cystic fibrosis, high-dose pancreatic enzyme replacement therapy has been associated with strictures of the ascending colon. Pain secondary to idiopathic chronic pancreatitis may be alleviated in some cases by the use of pancreatic enzyme replacement therapy (not enteric-coated preparations) or octreotide, 200 mcg subcutaneously three times daily, although some guidelines recommend against such therapy. Associated diabetes mellitus should be treated (see Chapter 27). Autoimmune pancreatitis is treated with prednisone 40 mg/day orally for 1–2 months, followed by a taper of 5 mg every 2–4 weeks. Nonresponse or relapse occurs in 45% of type 1 cases (particularly in those with concomitant IgG₄-associated cholangitis); rituximab is an effective induction and maintenance agent, and azathioprine or long-term low-dose corticosteroid use appears to reduce the risk of relapse.

Table 16–12. FDA-approved pancreatic enzyme (pancrelipase) preparations.

Product	Enzyme Content/Unit Dose, USP Units		
	Lipase	Amylase	Protease
Immediate-Release Capsules			
<i>Nonenteric-coated</i>			
VioKace 10,440	10,440	39,150	39,150
VioKace 20,880	20,880	78,300	78,300
Delayed-Release Capsules			
<i>Enteric-coated minimicrospheres</i>			
Creon 3000	3000	15,000	9500
Creon 6000	6000	30,000	19,000
Creon 12,000	12,000	60,000	38,000
Creon 24,000	24,000	120,000	76,000
Creon 36,000	36,000	180,000	114,000
<i>Enteric-coated minitablets</i>			
Ultresa 13,800	13,800	27,600	27,600
Ultresa 20,700	20,700	46,000	41,400
Ultresa 23,000	23,000	46,000	41,400
<i>Enteric-coated beads</i>			
Zenpep 3000	3000	16,000	10,000
Zenpep 5000	5000	27,000	17,000
Zenpep 10,000	10,000	55,000	34,000
Zenpep 15,000	15,000	82,000	51,000
Zenpep 20,000	20,000	109,000	68,000
Zenpep 25,000	25,000	136,000	85,000
<i>Enteric-coated microtablets</i>			
Pancreaze 4200	4200	17,500	10,000
Pancreaze 10,500	10,500	43,750	25,000
Pancreaze 16,800	16,800	70,000	40,000
Pancreaze 21,000	21,000	61,000	37,000
<i>Bicarbonate-buffered enteric-coated microspheres</i>			
Pertzye 8000	8000	30,250	28,750
Pertzye + 16,000	16,000	60,500	57,500

FDA, US Food and Drug Administration; USP, US Pharmacopeia.

B. Endoscopic and Surgical Treatment

Endoscopic therapy or surgery may be indicated in chronic pancreatitis to treat underlying biliary tract disease, ensure free flow of bile into the duodenum, drain persistent pseudocysts, treat other complications, eliminate obstruction of the pancreatic duct, attempt to relieve pain, or exclude pancreatic cancer. Liver fibrosis may regress after biliary drainage. Distal bile duct obstruction may be relieved by endoscopic placement of multiple plastic stents or a fully covered self-expandable metal stent in the bile duct. When obstruction of the duodenal end of the pancreatic duct can be demonstrated by ERCP, dilation or placement of such stents in the duct and pancreatic duct stone lithotripsy or surgical resection of the tail of the pancreas with implantation of the distal end of the duct by pancreaticojejunostomy may be performed. Endoscopic therapy is successful in about 50% of cases. In patients who do not respond to endoscopic therapy, surgery is successful in about 50%. When the pancreatic duct is diffusely dilated, anastomosis between the duct after it is split longitudinally and a defunctionalized limb of jejunum (modified Puestow procedure), in some cases combined with resection of the head of the pancreas (Beger or Frey procedure), is associated with relief of pain in 80% of cases. In advanced cases, subtotal or total pancreatectomy with islet autotransplantation may be considered as a last resort but has variable efficacy and causes pancreatic insufficiency and diabetes mellitus. Endoscopic or surgical (including laparoscopic) drainage is indicated for symptomatic pseudocysts and, in many cases, those over 6 cm in diameter. EUS may facilitate selection of an optimal site for endoscopic drainage. Pancreatic ascites or pancreaticopleural fistulas due to a disrupted pancreatic duct can be managed by endoscopic placement of a stent across the disrupted duct. Pancreatic sphincterotomy or fragmentation of stones in the pancreatic duct by lithotripsy and endoscopic removal of stones from the duct may relieve pain in selected patients. For patients with chronic pain and nondilated ducts, a percutaneous celiac plexus

nerve block may be considered under either CT or EUS guidance, with pain relief (albeit often short-lived) in approximately 50% of patients (see Chapter 5). A single session of radiation therapy to the pancreas has been reported to relieve otherwise refractory pain.

► Prognosis

Chronic pancreatitis often leads to disability and reduced life expectancy; pancreatic cancer is the main cause of death. The prognosis is best in patients with recurrent acute pancreatitis caused by a remediable condition, such as cholelithiasis, choledocholithiasis, stenosis of the sphincter of Oddi, or hyperparathyroidism, and in those with autoimmune pancreatitis. Medical management of hyperlipidemia, if present, may also prevent recurrent attacks of pancreatitis. The Chronic Pancreatitis Diagnosis Score based on pain, hemoglobin A_{1c} level, C-reactive protein level, body mass index, and platelet count has been shown to correlate with hospital admissions and number of hospital days. In alcohol-associated pancreatitis, pain relief is most likely when a dilated pancreatic duct can be decompressed. In patients with disease not amenable to decompressive surgery, addiction to opioids is a frequent outcome

of treatment. A poorer quality of life is associated with constant rather than intermittent pain, pain-related disability or unemployment, current smoking, and comorbidities.

► When to Refer

All patients with chronic pancreatitis should be referred for diagnostic and therapeutic procedures.

► When to Admit

- Severe pain.
- New jaundice.
- New fever.

Beyer G et al. Chronic pancreatitis. *Lancet*. 2020;396:499. [PMID: 32798493]

Gardner TB et al. ACG Clinical Guideline: chronic pancreatitis. *Am J Gastroenterol*. 2020;115:322. [PMID: 32022720]

Issa Y et al; Dutch Pancreatitis Study Group. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. *JAMA*. 2020;323:237. [PMID: 31961419]

Breast Disorders

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17

BENIGN BREAST DISORDERS

FIBROCYSTIC CONDITION



ESSENTIALS OF DIAGNOSIS

- ▶ Painful breast masses; often multiple and bilateral.
- ▶ Rapid fluctuation in mass size is common.
- ▶ Pain often worsens during premenstrual phase of cycle.
- ▶ Most common age is 30–50. Rare in postmenopausal women not receiving hormonal replacement.

General Considerations

Fibrocystic condition is the most frequent lesion of the breast. Although commonly referred to as “fibrocystic disease,” it does not, in fact, represent a pathologic or anatomic disorder. It is common in women 30–50 years of age but rare in postmenopausal women who are not taking hormonal replacement. Estrogen is considered a causative factor. There may be an increased risk in women who drink alcohol, especially women between 18 and 22 years of age. Fibrocystic condition encompasses a wide variety of benign histologic changes in the breast epithelium, some of which are found so commonly in normal breasts that they are probably variants of normal but have nonetheless been termed a “condition” or “disease.”

The microscopic findings of fibrocystic condition include cysts (gross and microscopic), papillomatosis, adenosis, fibrosis, and ductal epithelial hyperplasia. Although it has been thought that a fibrocystic condition increases the risk of breast cancer, *only the variants with a component of epithelial proliferation (especially with atypia), papillomatosis, or increased breast density on mammogram represent true risk factors.*

► Clinical Findings

A. Symptoms and Signs

Fibrocystic condition may produce an asymptomatic mass in the breast that is discovered by accident, but pain or tenderness often calls attention to it. Discomfort often occurs or worsens during the premenstrual phase of the cycle, at which time the cysts tend to enlarge. Fluctuations in size and rapid appearance or disappearance of a breast mass are common as are multiple or bilateral masses and serous nipple discharge. Patients will give a history of a transient lump in the breast or cyclic breast pain.

B. Diagnostic Tests

Mammography and ultrasonography should be used to evaluate a mass in a patient with fibrocystic condition. Ultrasonography alone may be used in women under 30 years of age; mammography may be helpful, but the breast tissue in young women is usually too radiodense to permit a worthwhile study. Ultrasonography is useful in differentiating a cystic mass from a solid mass, especially in women with dense breasts. Simple cysts are not worrisome and require no treatment or follow-up unless they are symptomatic and causing pain, in which case they may be aspirated. Ultrasonography can reliably distinguish fibroadenoma from carcinoma but not from a phyllodes tumor. Because a mass due to fibrocystic condition may be difficult to distinguish from carcinoma on the basis of clinical findings and imaging studies, *suspicious lesions should be biopsied.* Core needle biopsy, rather than fine-needle aspiration (FNA), is the preferable technique unless the lesion is cystic. Excisional biopsy is rarely necessary but should be done for lesions with atypia or where imaging and biopsy results are discordant. Surgery should be conservative, since the primary objective is to exclude cancer. Occasionally, FNA cytology will suffice. Simple mastectomy or extensive removal of breast tissue is rarely, if ever, indicated for fibrocystic condition.

► Differential Diagnosis

Pain, fluctuation in size, and multiplicity of lesions are the features consistent with fibrocystic condition and most helpful in differentiating it from carcinoma. If a dominant mass is present, the diagnosis of cancer should be assumed until disproven by imaging or biopsy. Final diagnosis depends on analysis of a biopsy specimen.

► Treatment

When the diagnosis of fibrocystic condition has been established by previous biopsy or is likely because the history is classic, aspiration of a discrete mass suggestive of a cyst is indicated to alleviate pain and, more importantly, to confirm the cystic nature of the mass. The patient is reexamined at intervals thereafter. If no fluid is obtained by aspiration, if fluid is bloody, if a mass persists after aspiration, or if at any time during follow-up a persistent or recurrent mass is noted, biopsy should be performed.

Breast pain associated with generalized fibrocystic condition is best treated by avoiding trauma and by wearing a good supportive brassiere during the night and day. Hormone therapy is not advisable because it does not cure the condition and has undesirable side effects. Danazol (100–200 mg orally twice daily), a synthetic androgen, is the only treatment approved by the US Food and Drug Administration (FDA) for patients with severe pain. This treatment suppresses pituitary gonadotropins, but androgenic effects (acne, edema, hirsutism) usually make this treatment intolerable; in practice, it is rarely used. Similarly, tamoxifen reduces some symptoms of fibrocystic condition, but because of its side effects, it is not useful for young women unless it is given to reduce the risk of cancer. Postmenopausal women receiving hormone replacement therapy may stop or change doses of hormones to reduce pain. Oil of evening primrose, a natural form of gamolenic acid, has been shown to decrease pain in 44–58% of users. The dosage of gamolenic acid is six capsules of 500 mg orally twice daily. Studies have also demonstrated a low-fat diet or decreasing dietary fat intake may reduce the painful symptoms associated with fibrocystic condition. Topical treatments such as nonsteroidal anti-inflammatory drugs are rarely of value.

The role of caffeine consumption in the development and treatment of fibrocystic condition is controversial. Some studies suggest that eliminating caffeine from the diet is associated with improvement while other studies refute the benefit. Many patients report relief of symptoms after giving up coffee, tea, and chocolate. Similarly, many women find vitamin E (400 international units daily) helpful; however, these observations remain anecdotal.

► Prognosis

Exacerbations of pain, tenderness, and cyst formation may occur at any time until menopause, when symptoms usually subside, except in patients receiving hormonal replacement. The patient should be advised to examine her own breasts regularly just after menstruation and to inform her

clinician if a mass appears. The risk of breast cancer developing in women with fibrocystic condition with a proliferative or atypical epithelial hyperplasia or papillomatosis is higher than that of the general population. These women should be monitored carefully with physical examinations and imaging studies.

Groen JW et al. Cyclic and non-cyclic breast pain: a systematic review on pain reduction, side effects, and quality of life for various treatments. *Eur J Obstet Gynecol Reprod Biol.* 2017; 219:74. [PMID: 29059585]

Qu P et al. Detection rate is not higher for women with BBD history in breast cancer screening. *J Public Health (Oxf).* 2019. [Epub ahead of print] [PMID: 31774529]

FIBROADENOMA OF THE BREAST

This common benign neoplasm occurs most frequently in young women, usually within 20 years after puberty. It is somewhat more frequent and tends to occur at an earlier age in Black women. Multiple tumors are found in 10–15% of patients.

The typical **fibroadenoma** is a round or ovoid, rubbery, discrete, relatively movable, nontender mass 1–5 cm in diameter. Clinical diagnosis in young patients is generally not difficult. In women over 30 years, fibrocystic condition of the breast and carcinoma of the breast must be considered. Cysts can be identified by aspiration or ultrasonography. Fibroadenoma does not normally occur after menopause but may occasionally develop after administration of hormones.

No treatment is usually necessary if the diagnosis can be made by core needle biopsy. Excision with pathologic examination of the specimen is performed if the diagnosis is uncertain or the lesion grows significantly. Cryoablation, or freezing of the fibroadenoma, appears to be a safe procedure if the lesion is a biopsy-proven fibroadenoma prior to ablation. Cryoablation is not appropriate for all fibroadenomas because some are too large to freeze or the diagnosis may not be certain. There is no obvious clinical advantage to cryoablation of a histologically proven fibroadenoma except that some patients may feel relief that a mass is gone. However, at times a mass of scar or fat necrosis replaces the mass of the fibroadenoma. Reassurance seems preferable. Distinguishing a large fibroadenoma from a phyllodes tumor based on needle biopsy results or imaging alone is usually not possible; histologic examination after excision is usually required. Presumed fibroadenomas larger than 3–4 cm should be excised to rule out phyllodes tumors.

Phyllodes tumor is a fibroadenoma-like tumor with cellular stroma that grows rapidly. It may reach a large size and, if inadequately excised, will recur locally. The lesion can be benign or malignant. If benign, phyllodes tumor is treated by local excision. The treatment of malignant phyllodes tumor is more controversial, but complete removal of the tumor with a margin of normal tissue avoids recurrence. Because these tumors may be large, total mastectomy is sometimes necessary. Lymph node dissection is not performed, since the sarcomatous portion of the tumor metastasizes to the lungs and not the lymph nodes.

- Co M et al. Mammary phyllodes tumour: a 15-year multicentre clinical review. *J Clin Pathol.* 2018;71:493. [PMID: 29146885]
- Erickson LA et al. Fibroadenoma of the breast. *Mayo Clin Proc.* 2020;95:2573. [PMID: 33153651]
- Rayzah M. Phyllodes tumors of the breast: a literature review. *Cureus.* 2020;12:e10288. [PMID: 32923300]

NIPPLE DISCHARGE

In order of decreasing frequency, the following are the most common causes of nipple discharge in the nonlactating breast: duct ectasia, intraductal papilloma, and carcinoma. The important characteristics of the discharge and other factors to be evaluated are listed in Table 17-1.

1. Discharge from a single duct—Spontaneous, unilateral, serous or serosanguineous discharge from a single duct is usually caused by an ectatic duct or an intraductal papilloma or, rarely, by an intraductal cancer. A mass may not be palpable. The involved duct may be identified by pressure at different sites around the nipple at the margin of the areola. Bloody discharge is suggestive of cancer but is more often caused by a benign papilloma in the duct. Cytologic examination may identify malignant cells, but negative findings do not rule out cancer, which is more likely in older women. In any case, the involved bloody duct—and a mass if present—should be excised. A ductogram (a mammogram of a duct after radiopaque dye has been injected), like cytology, is of limited value since excision of the suspicious ductal system is indicated regardless of findings. Ductoscopy, evaluation of the ductal system with a small scope inserted

through the nipple, has been attempted but is not effective management.

2. Discharge from multiple ducts—In premenopausal women, spontaneous multiple duct discharge, unilateral or bilateral, most noticeable just before menstruation, is often due to fibrocystic condition. Discharge may be green or brownish. Papillomatosis and ductal ectasia are usually detected only by biopsy. If a mass is present, it should be removed.

A milky discharge from multiple ducts in the nonlactating breast may occur from hyperprolactinemia. Serum prolactin levels should be obtained to search for a pituitary tumor. Thyroid-stimulating hormone (TSH) helps exclude causative hypothyroidism. Numerous antipsychotic medications and other medications may also cause a milky discharge that ceases on discontinuance of the medication.

Oral contraceptive agents or estrogen replacement therapy may cause clear, serous, or milky discharge from a single duct, but multiple duct discharge is more common. In the premenopausal woman, the discharge is more evident just before menstruation and disappears on stopping the medication. If it does not stop, is from a single duct, and is copious, exploration should be performed since this may be a sign of cancer.

A purulent discharge may originate in a subareolar abscess and require removal of the abscess and the related lactiferous sinus.

When localization of the discharge is not possible, no mass is palpable, and the discharge is nonbloody, the patient should be reexamined every 3 or 4 months for a year, and a mammogram and an ultrasound should be performed. Although most discharge is from a benign process, patients may find it annoying or disconcerting. To eliminate the discharge, proximal duct excision can be performed both for treatment and diagnosis.

Table 17-1. Characteristics of nipple discharge in the nonpregnant, nonlactating woman.

Finding	Significance
Serous	Most likely benign FCC, ie, duct ectasia
Bloody	More likely neoplastic—papilloma, carcinoma
Associated mass	More likely neoplastic
Unilateral	Either neoplastic or non-neoplastic
Bilateral	Most likely non-neoplastic
Single duct	More likely neoplastic
Multiple ducts	More likely FCC
Milky	Endocrine disorders, medications
Spontaneous	Either neoplastic or non-neoplastic
Produced by pressure at single site	Either neoplastic or non-neoplastic
Persistent	Either neoplastic or non-neoplastic
Intermittent	Either neoplastic or non-neoplastic
Related to menses	More likely FCC
Premenopausal	More likely FCC
Taking hormones	More likely FCC

FCC, fibrocystic condition.

Cetin K et al. Evaluation and management of pathological nipple discharges without using intraductal imaging methods. *Ir J Med Sci.* 2020;189:451. [PMID: 31631245]

Gupta D et al. Nipple discharge: current clinical and imaging evaluation. *AJR Am J Roentgenol.* 2021;216:330. [PMID: 33295815]

Zacharioudakis K et al. Can we see what is invisible? The role of MRI in the evaluation and management of patients with pathological nipple discharge. *Breast Cancer Res Treat.* 2019;178:115. [PMID: 31352554]

FAT NECROSIS

Fat necrosis is a rare lesion of the breast but is of clinical importance because it produces a mass (often accompanied by skin or nipple retraction) that is usually indistinguishable from carcinoma even with imaging studies. Fat necrosis can occur after trauma; after fat injections to augment breast size or fill defects after breast surgery; and after segmental resection, radiation therapy, or flap reconstruction following mastectomy.

The resultant mass may be confused with cancer. If untreated, the mass gradually disappears. If imaging is not typical of fat necrosis, the safest course is to obtain a biopsy. Core needle biopsy is usually adequate.

BREAST ABSCESS

During nursing, an area of redness, tenderness, and induration may develop in the breast. The organism most commonly found in these abscesses is *Staphylococcus aureus* (see Puerperal Mastitis, Chapter 19).

Infection in the nonlactating breast is rare. A subareolar abscess may develop in young or middle-aged women who are not lactating. These infections tend to recur after incision and drainage unless the area is explored during a quiescent interval, with excision of the involved lactiferous duct or ducts at the base of the nipple. In the nonlactating breast, inflammatory carcinoma must always be considered. Thus, incision and biopsy of any indurated tissue with a small piece of erythematous skin is indicated when suspected abscess or cellulitis in the nonlactating breast does not resolve promptly with antibiotics. Often needle or catheter drainage is adequate to treat an abscess, but surgical incision and drainage may be necessary.

O'Brien C et al. Breast abscess: not just a puerperal problem. *Breast J.* 2020;26:339. [PMID: 31544305]

Omranipour R et al. Mastitis, breast abscess, and granulomatous mastitis. *Adv Exp Med Biol.* 2020;1252:53. [PMID: 32816262]

DISORDERS OF THE AUGMENTED BREAST

At least 4 million American women have had breast implants. Breast augmentation is performed by placing implants under the pectoralis muscle or, less desirably, in the subcutaneous tissue of the breast. Most implants are made of an outer silicone shell filled with a silicone gel, saline, or some combination of the two. Capsule contraction or scarring around the implant develops in about 15–25% of patients, leading to a firmness and distortion of the breast that can be painful. Some require removal of the implant and surrounding capsule.

Implant rupture may occur in as many as 5–10% of women, and bleeding of gel through the capsule is noted even more commonly. Although silicone gel may be an immunologic stimulant, there is no increase in autoimmune disorders in patients with such implants. The FDA has advised symptomatic women with ruptured silicone implants to discuss possible surgical removal with their clinicians. However, women who are asymptomatic and have no evidence of rupture of a silicone gel prosthesis do not require removal of the implant. Women with symptoms of autoimmune illnesses often undergo removal, but no benefit has been shown.

Studies have failed to show any association between implants and an increased incidence of breast cancer. However, breast cancer may develop in a patient with an augmentation prosthesis, as it does in women without them. Detection in patients with implants may be more difficult because mammography is less able to detect early lesions. Mammography is better if the implant is subpectoral rather than subcutaneous. Local recurrence is usually cutaneous or subcutaneous and is easily detected by palpation. Rarely, lymphoma of the breast with silicone implants has been reported.

If a cancer develops in a patient with implants, it should be treated in the same manner as in women without

implants. Such women should be offered the option of mastectomy or breast-conserving therapy, which may require removal or replacement of the implant. Radiotherapy of the augmented breast often results in marked capsular contracture. Adjuvant treatments should be given for the same indications as for women who have no implants.

Mak JC et al. Complications in post-mastectomy immediate breast reconstruction: a ten-year analysis of outcomes. *Clin Breast Cancer.* 2020;20:402. [PMID: 32665188]

Marra A et al. Breast implant-associated anaplastic large cell lymphoma: a comprehensive review. *Cancer Treat Rev.* 2020;84:101963. [PMID: 31958739]

CARCINOMA OF THE FEMALE BREAST



ESSENTIALS OF DIAGNOSIS

- ▶ Risk factors: Age, nulliparity, childbirth after age 30, family history of breast cancer or deleterious mutations (*BRCA1*, *BRCA2*, or others), and personal history of breast cancer or some types of proliferative conditions.
- ▶ Early findings: Mammographic abnormalities and no palpable mass, or single, nontender, firm to hard mass with ill-defined margins.
- ▶ Later findings: Skin or nipple retraction; axillary lymphadenopathy; breast enlargement, erythema, edema, pain; fixation of mass to skin or chest wall.

Incidence & Risk Factors

Breast cancer will develop in *one of eight* American women. Next to skin cancer, breast cancer is the most common cancer in women; it is second only to lung cancer as a cause of death. In 2020, there were approximately 279,100 new cases and 42,690 deaths from breast cancer in the United States. Worldwide, breast cancer is diagnosed in approximately 2.2 million women, and about 684,996 die of breast cancer each year.

The most significant risk factor for the development of breast cancer is age. A woman's risk of breast cancer rises rapidly until her early 60s, peaks in her 70s, and then declines. A significant family history of breast or ovarian cancer imparts a high risk of developing breast cancer. Germline mutations in the *BRCA* family of tumor suppressor genes or other breast cancer susceptibility genes accounts for approximately 5–10% of breast cancer diagnoses and tend to cluster in certain ethnic groups, including women of Ashkenazi Jewish descent. Women with a mutation in the *BRCA1* gene, located on chromosome 17, have an estimated 85% chance of developing breast cancer in their lifetime. Other genes associated with an increased risk of breast and other cancers include *BRCA2* (associated with a gene on chromosome 13); ataxia-telangiectasia mutation (*ATM*), *BARD1*, *CHEK2*, *PALB2*, *RAD51D*; and mutation of the tumor suppressor gene *p53*. Primary care

clinicians should assess a woman's personal and family history for breast, ovarian, tubal or peritoneal cancer using a familial risk assessment tool (eg, <https://bcrisktool.cancer.gov>). Those with a positive result should receive genetic counseling in order to decide whether genetic testing is indicated.

Even when genetic testing fails to reveal a predisposing genetic mutation, women with a strong family history of breast cancer are at higher risk for development of breast cancer. Compared with a woman with no affected family members, a woman who has one first-degree relative with breast cancer has double the risk of developing breast cancer and a woman with two first-degree relatives with breast cancer has triple the risk of developing breast cancer. The risk is further increased for a woman whose affected family member was premenopausal at the time of diagnosis or had bilateral breast cancer. Lifestyle and reproductive factors also contribute to risk of breast cancer. Nulliparous women and women whose first full-term pregnancy occurred after the age of 30 have an elevated risk. Early menarche (under age 12) and late natural menopause (after age 55) are associated with an increase in risk, especially for hormone receptor-positive breast cancer. Combined oral contraceptive pills also appear to increase the risk of breast cancer, with longer use associated with higher risk. Several studies show that concomitant administration of progesterone and estrogen to postmenopausal women may increase the incidence of breast cancer, compared with the use of estrogen alone or with no hormone replacement treatment. Alcohol consumption, high dietary intake of fat, and lack of exercise may also increase the risk of breast cancer. Fibrocystic breast condition is also associated with an increased incidence of cancer but only when it is accompanied by proliferative changes, papillomatosis, atypical epithelial hyperplasia, or increased breast density on mammogram. A woman who had cancer in one breast is at increased risk for cancer developing in the other breast. In these women, a contralateral cancer develops at rate of 1% or 2% per year. Women with cancer of the uterine corpus have a risk of breast cancer significantly higher than that of the general population, and women with breast cancer have a comparably increased risk of endometrial cancer. Breast cancer tends to be diagnosed more frequently in women of higher socioeconomic status.

Women at greater than average risk for developing breast cancer (Table 17–2) should be identified by their clinicians and monitored carefully. Several risk assessment models have been validated to estimate a woman's risk of developing cancer. Women with genetic mutations in whom breast cancer develops may be treated in the same way as women who do not have mutations (ie, lumpectomy), though there is an increased risk of ipsilateral and contralateral breast cancer after lumpectomy for these women.

- Bahl M. Management of high-risk breast lesions. *Radiol Clin North Am.* 2021;59:29. [PMID: 33222998]
 Bray F et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394. [PMID: 30207593]

Jin J. JAMA patient page. Should I be tested for BRCA mutations? *JAMA.* 2019;322:702. [PMID: 31429898]

Lewin AA et al. Atypical ductal hyperplasia and lobular neoplasia: update and easing of guidelines. *AJR Am J Roentgenol.* 2020;214:265. [PMID: 31825261]

Minami CA et al. Menopausal hormone therapy and long-term breast cancer risk: further data from the Women's Health Initiative Trials. *JAMA.* 2020;324:347. [PMID: 32720989]

Sabiani L et al. How to manage BRCA mutation carriers? *Horm Mol Biol Clin Investig.* 2020;41:1868. [PMID: 32459193]

Siegel RL et al. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70:7. [PMID: 31912902]

Tung NM et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol.* 2020;38:2080. [PMID: 32243226]

US Preventive Services Task Force; Owens DK et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2019;322:652. [PMID: 31429903]

► Prevention

Multiple clinical trials have evaluated the use of selective estrogen receptor modulators (SERMs), including tamoxifen and raloxifene, or aromatase inhibitors for prevention of breast cancer in women with no personal history of breast cancer but at high risk for developing the disease. A network meta-analysis of six of these studies including 50,927 women demonstrated a 32% reduction in breast cancer incidence with the use of tamoxifen compared to placebo and a 47% reduction in risk of breast cancer with the use of an aromatase inhibitor compared to placebo. An increased risk of endometrial cancer, cataracts, and venous thromboembolic events has been associated with tamoxifen and a higher rate of fractures and musculoskeletal side effects are associated with aromatase inhibitors. While preventive agents have been shown to be effective at reducing the risk of breast cancer and saving costs, the use of this intervention by women has been relatively low, possibly due to the perceived risks and side effects of therapy.

Some women at high risk may consider prophylactic mastectomy or oophorectomy.

Table 17–2. Factors associated with increased risk of breast cancer (listed in alphabetical order).

Age	Older
Family history	Breast cancer in parent, sibling, or child (especially bilateral or premenopausal)
Genetics	<i>BRCA1</i> , <i>BRCA2</i> , or other unknown mutations
Menstrual history	Early menarche (under age 12) Late menopause (after age 55)
Previous medical history	Endometrial cancer Proliferative forms of fibrocystic disease Cancer in other breast
Race	White
Reproductive history	Nulliparous or late first pregnancy

- Graham D et al. Breast cancer risk-reducing medications. JAMA. 2020;324:310. [PMID: 32692388]
Shieh Y et al. Medications for primary prevention of breast cancer. JAMA. 2020;324:291. [PMID: 32692377]
US Preventive Services Task Force; Owens DK et al. Medication use to reduce risk of breast cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322:857. [PMID: 31479144]

and benefits (eg, early diagnosis), taking into consideration a patient's individual risk factors.

B. Imaging

1. Mammography—Mammography is the most reliable means of detecting breast cancer before a mass can be palpated. Most slowly growing cancers can be identified by mammography at least 2 years before reaching a size detectable by palpation.

Indications for mammography are as follows: (1) screening at regular intervals asymptomatic women at risk for developing breast cancer; (2) evaluating each breast when a diagnosis of potentially curable breast cancer has been made, and at regular intervals thereafter; (3) evaluating a questionable or ill-defined breast mass or other suspicious change in the breast; (4) searching for an occult breast cancer in women with metastatic disease in axillary nodes or elsewhere from an unknown primary; (5) screening women prior to cosmetic operations or prior to biopsy of a mass, to examine for an unsuspected cancer; (6) monitoring women with breast cancer who have been treated with breast-conserving surgery and radiation; and (7) monitoring the contralateral breast in women with breast cancer treated with mastectomy.

Calcifications are the most easily recognized mammographic abnormality. The most common findings associated with carcinoma of the breast are clustered pleomorphic microcalcifications. Such calcifications are usually at least five to eight in number, aggregated in one part of the breast and differing from each other in size and shape, often including branched or V- or Y-shaped configurations. There may be an associated mammographic mass density or, at times, only a mass density with no calcifications. Such a density usually has irregular or ill-defined borders and may lead to architectural distortion within the breast, but may be subtle and difficult to detect.

Patients with a dominant or suspicious mass on examination must undergo biopsy despite mammographic findings. The mammogram should be obtained prior to biopsy so that other suspicious areas can be noted and the contralateral breast can be evaluated. *Mammography is never a substitute for biopsy* because it may not reveal clinical cancer, especially in a very dense breast.

Communication and documentation among the patient, the referring clinician, and the interpreting physician are critical for high-quality screening and diagnostic mammography. The patient should be told about how she will receive timely results of her mammogram; that mammography does not "rule out" cancer; and that she may receive a correlative examination such as ultrasound at the mammography facility if referred for a suspicious lesion. She should also be aware of the technique and need for breast compression and that this may be uncomfortable. The mammography facility should be informed in writing by the clinician of abnormal physical examination findings. The Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guidelines strongly recommend that all mammography reports be communicated in writing to the patient and referring clinician. Legislation has been passed in a number of US states that requires imaging facilities to

► Early Detection of Breast Cancer

A. Screening Programs

Screening detects breast cancer before it has spread to the lymph nodes in about 80% of the women evaluated. This increases the chance of survival to greater than 85% at 5 years.

Substantial evidence supports the use of **routine screening mammography**; however, recommendations relating to timing and frequency vary by different agencies and countries. About one-third of the abnormalities detected on screening mammograms will be found to be malignant when biopsy is performed. The probability of cancer on a screening mammogram is directly related to the Breast Imaging Reporting and Data System (BIRADS) assessment, and workup should be performed based on this classification. The sensitivity of mammography varies from approximately 60% to 90%. This sensitivity depends on several factors, including patient age, breast density, tumor size, tumor histology (lobular versus ductal), location, and mammographic appearance. In young women with dense breasts, mammography is less sensitive than in older women with fatty breasts, in whom mammography can detect at least 90% of malignancies. Smaller tumors, particularly those without calcifications, are more difficult to detect, especially in dense breasts. The lack of sensitivity and the low incidence of breast cancer in young women have led to questions concerning the value of mammography for screening in women 40–50 years of age. The specificity of mammography in women under 50 years varies from about 30% to 40% for nonpalpable mammographic abnormalities to 85% to 90% for clinically evident malignancies. Guidelines from at least six separate organizations exist in the United States and each differs slightly, making it somewhat complex for clinicians and patients to navigate. While the American College of Radiology, American Medical Association, and National Comprehensive Cancer Network (NCCN) recommend starting mammography screening at age 40, the US Preventive Services Task Force (USPSTF) recommends starting screening at age 50. Most guidelines recommend annual screening; however, the American Cancer Society recommends decreasing the frequency of screening to every 1–2 years starting at age 55 years and the USPSTF recommends routine mammography be done no more than every 2 years beginning at age 50 years. It is generally agreed that mammography should continue until life expectancy is shorter than 7–10 years, although the USPSTF recommends stopping screening after age 74 years regardless of life expectancy. Thus, clinicians should have an informed discussion with patients about screening mammography regarding its potential risks (eg, false positives, overdiagnosis, radiation exposure)

report to patients the density of their breasts. This may prompt women with dense breasts to discuss with their clinician whether or not additional screening options would be appropriate in addition to mammogram.

2. Other imaging—MRI and ultrasound may be useful screening modalities in women who are at high risk for breast cancer but not for the general population. The *sensitivity* of MRI is much higher than mammography; however, the *specificity* is significantly lower and this results in multiple unnecessary biopsies. The increased sensitivity despite decreased specificity may be considered a reasonable trade-off for those at increased risk for developing breast cancer but not for normal-risk population. The NCCN guidelines recommend MRI in addition to screening mammography for high-risk women, including those with deleterious mutations, those who have a lifetime risk of breast cancer of at least 20%, and those with a personal history of lobular carcinoma *in situ* (LCIS).

Women who received radiation therapy to the chest in their teens or twenties are also known to be at high risk for developing breast cancer and screening MRI may be considered in addition to mammography. A Netherlands study (Dense Tissue and Early Breast Neoplasm Screening “DENSE”) involving over 40,000 women with extremely dense breast tissue demonstrated that the addition of annual MRI to screening mammography was associated with a lower rate of cancers being diagnosed in 2 years.

C. Clinical Breast Examination and Self-Examination

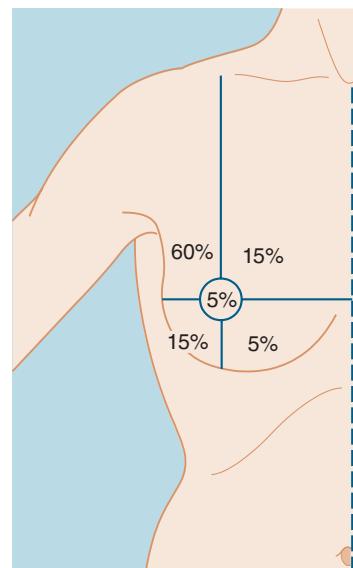
Breast self-examination has *not* been shown to improve survival. Because of the lack of strong evidence demonstrating value, the American Cancer Society no longer recommends monthly breast self-examination. Nonetheless, patients should recognize and report any breast changes to their clinicians as it remains an important facet of proactive care.

Destounis SV et al. Update on breast density, risk estimation, and supplemental screening. *AJR Am J Roentgenol.* 2020;214:296. [PMID: 31743049]

García-Albéniz X et al. Continuation of annual screening mammography and breast cancer mortality in women older than 70 years. *Ann Intern Med.* 2020;172:381. [PMID: 32092767]

Harkness EF et al. Risk-based breast cancer screening strategies in women. *Best Pract Res Clin Obstet Gynaecol.* 2020;65:3. [PMID: 31848103]

Hong S et al. Effect of digital mammography for breast cancer screening: a comparative study of more than 8 million Korean women. *Radiology.* 2020;294:247. [PMID: 31793847]



▲ **Figure 17-1.** Frequency of breast carcinoma at various anatomic sites.

the nipple; and redness, generalized hardness, enlargement, or shrinking of the breast. Rarely, an axillary mass or swelling of the arm may be the first symptom. Back or bone pain, jaundice, or weight loss may be the result of systemic metastases, but these symptoms are rarely seen on initial presentation.

The relative frequency of carcinoma in various anatomic sites in the breast is shown in Figure 17-1.

Inspection of the breast is the first step in physical examination and should be carried out with the patient sitting, arms at her sides and then overhead. Abnormal variations in breast size and contour, minimal nipple retraction, and slight edema, redness, or retraction of the skin can be identified (Figure 17-2). Asymmetry of the breasts and retraction or dimpling of the skin can often be accentuated by having the patient raise her arms overhead or press her hands on her hips to contract the pectoralis muscles. Axillary and supraclavicular areas should be



▲ **Figure 17-2.** Skin dimpling. (Used, with permission, from Armando E. Giuliano, MD.)

► Clinical Findings Associated with Early Detection of Breast Cancer

A. Symptoms and Signs

The presenting complaint in about 70% of patients with breast cancer is a lump (usually painless) in the breast. About 90% of these breast masses are discovered by the patient. Less frequent symptoms are breast pain; nipple discharge; erosion, retraction, enlargement, or itching of



▲ Figure 17–3. Paget disease. (Used, with permission, from Armando E. Giuliano, MD.)

thoroughly palpated for enlarged nodes with the patient sitting. Palpation of the breast for masses or other changes should be performed with the patient both seated and supine with the arm abducted. Palpation with a rotary motion of the examiner's fingers as well as a horizontal stripping motion has been recommended.

Breast cancer usually consists of a nontender, firm or hard mass with poorly delineated margins (caused by local infiltration). Very small (1–2 mm) erosions of the nipple epithelium may be the only manifestation of Paget disease of the breast (Figure 17–3). Watery, serous, or bloody discharge from the nipple is an occasional early sign but is more often associated with benign disease.

A lesion smaller than 1 cm in diameter may be difficult or impossible for the examiner to feel but may be discovered by the patient. The patient should always be asked to demonstrate the location of the mass. If the clinician fails to confirm the patient's suspicions and imaging studies are normal, the examination should be repeated in 2–3 months, preferably 1–2 weeks after the onset of menses. During the premenstrual phase of the cycle, increased innocuous nodularity may suggest neoplasm or may obscure an underlying lesion. If there is any question regarding the nature of an abnormality under these circumstances, the patient should be asked to return after her menses.

Metastases tend to first involve regional lymph nodes, which may be palpable. One or two movable, nontender, not particularly firm axillary lymph nodes 5 mm or less in diameter are frequently present and are generally of no significance. Firm or hard nodes larger than 1 cm are typical of metastases. Axillary nodes that are matted or fixed to skin or deep structures indicate advanced disease (at least stage III). If the examiner thinks that the axillary nodes are involved, that impression will be borne out by histologic section in about 85% of cases. The incidence of positive axillary nodes increases with the size of the primary tumor. Noninvasive cancers (*in situ*) do not metastasize. Metastases are present in about 30% of patients with clinically negative nodes.

In most cases, no nodes are palpable in the supraclavicular fossa. Firm or hard nodes of any size in this location

or just beneath the clavicle should be biopsied. Ipsilateral supraclavicular or infraclavicular nodes containing cancer indicate that the tumor is in an advanced stage (stage III or IV). Edema of the ipsilateral breast or arm, commonly caused by metastatic infiltration of regional lymphatics, is also a sign of advanced cancer.

B. Laboratory Findings

Liver or bone metastases may be associated with elevation of serum alkaline phosphatase. Hypercalcemia is an occasional important finding in advanced cancer of the breast. Serum tumor markers such as carcinoembryonic antigen (CEA) and CA 15-3 or CA 27-29 are *not* recommended for diagnosis of early lesions or for routine surveillance for recurrence after a breast cancer diagnosis.

C. Imaging

1. For lesions felt only by the patient—Ultrasonography is often valuable and mammography essential when an area is felt by the patient to be abnormal but the clinician feels no mass. MRI should not be used to rule out cancer because MRI has a false-negative rate of about 3–5%. Although lower than mammography, this false-negative rate cannot permit safe elimination of the possibility of cancer. False-negative results with imaging are more likely seen in infiltrating lobular carcinomas and ductal carcinoma *in situ* (DCIS) than invasive ductal carcinoma.

2. For metastatic lesions—For patients with suspicious symptoms or signs (bone pain, abdominal symptoms, elevated liver biochemical tests) or locally advanced disease (clinically abnormal lymph nodes or large primary tumors), staging scans are indicated prior to surgery or systemic therapy. Chest imaging with CT or radiographs may be done to evaluate for pulmonary metastases. Abdominal imaging with CT or ultrasound may be obtained to evaluate for liver metastases. Bone scans using ^{99m}Tc-labeled phosphates or phosphonates are more sensitive than skeletal radiographs in detecting metastatic breast cancer. Bone scanning has not proved to be of clinical value as a routine preoperative test in the absence of symptoms, physical findings, or abnormal alkaline phosphatase or calcium levels. The frequency of abnormal findings on bone scan parallels the status of the axillary lymph nodes on pathologic examination. Positron emission tomography (PET) scanning alone or combined with CT (PET-CT) may also be used for detecting soft tissue or visceral metastases in patients with locally advanced disease or with symptoms or signs of metastatic disease.

D. Diagnostic Tests

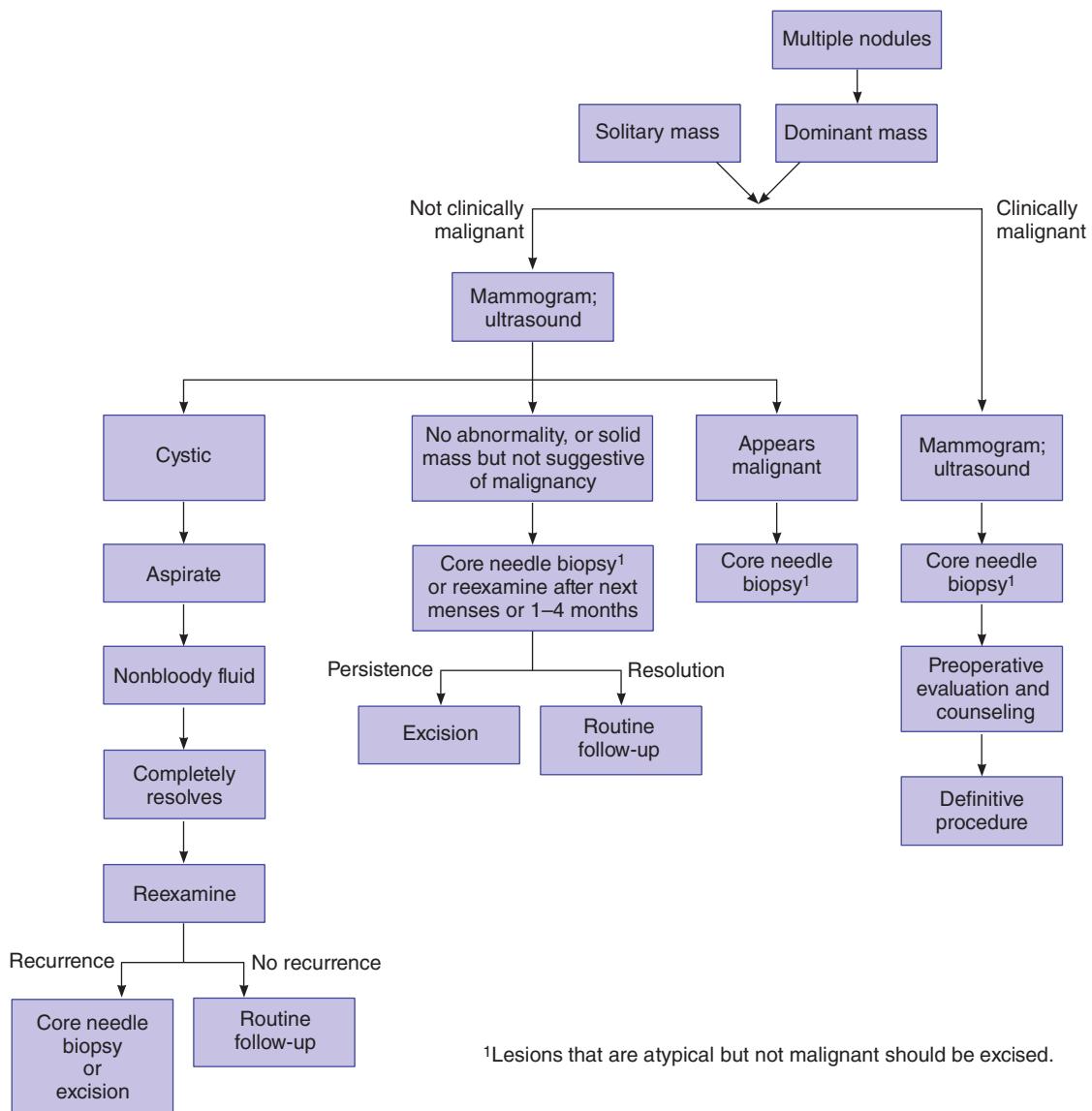
1. Biopsy—The diagnosis of breast cancer depends ultimately on examination of tissue or cells removed by biopsy. Treatment should never be undertaken without an unequivocal histologic or cytologic diagnosis of cancer. About 60% of lesions clinically thought to be cancer prove on biopsy to be benign, while about 30% of clinically benign lesions are found to be malignant. These findings demonstrate the fallibility of clinical judgment and the

necessity for biopsy. *The safest course is biopsy examination of all suspicious lesions found on physical examination or imaging, or both.*

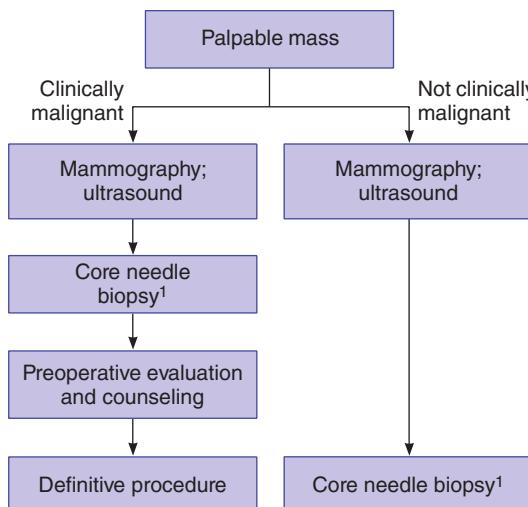
There is only one probable exception to the need for a histologic diagnosis of a breast mass: a nonsuspicious, presumably fibrocystic mass, in a premenopausal woman. Rather, these masses can be observed through one or two menstrual cycles. However, the mass must be biopsied if it does not completely resolve during this time and ultrasonographic findings show that it is not cystic or benign appearing (like a fibroadenoma or intramammary lymph node). Figures 17–4 and 17–5 present algorithms for management of breast masses in premenopausal and postmenopausal patients.

The simplest biopsy method is needle biopsy, either by aspiration of tumor cells (FNA cytology) or by obtaining a small core of tissue with a hollow needle (core needle biopsy). Core needle biopsy is preferable.

Core (large) needle biopsy removes a core of tissue with a large cutting needle for histologic examination and is the diagnostic procedure of choice for both palpable and image-detected abnormalities. Handheld biopsy devices make large-core needle (14-gauge) biopsy of a palpable mass easy and cost effective in the office with local anesthesia. As in the case of any needle biopsy, the main problem is sampling error due to improper positioning of the needle, giving rise to a false-negative test result. This is extremely unusual with image-guided biopsies.



▲ **Figure 17–4.** Evaluation of breast masses in premenopausal women. (Adapted, with permission, from Giuliano AE, Srour MK. Breast disease. In: Berek JS, Hacker NF [editors], *Berek & Hacker's Gynecologic Oncology*, 7th ed, Philadelphia: Wolters Kluwer, 2021.)



¹Lesions that are atypical but not malignant should be excised.

Figure 17–5. Evaluation of breast masses in postmenopausal women. (Adapted, with permission, from Giuliano AE, Srour MK. Breast disease. In: Berek JS, Hacker NF [editors], *Berek & Hacker's Gynecologic Oncology*, 7th ed, Philadelphia: Wolters Kluwer, 2021.)

Core needle biopsy allows the tumor to be tested for the expression of biological markers, such as estrogen receptor (ER), progesterone receptor (PR), and HER2.

FNA cytology is a technique whereby cells are aspirated with a small needle and examined cytologically. This technique can be performed easily with virtually no morbidity and is much less expensive than excisional or open biopsy. The main disadvantages are that it requires a pathologist skilled in the cytologic diagnosis of breast cancer and it is subject to sampling problems. Furthermore, noninvasive cancers usually cannot be distinguished from invasive cancers. The incidence of false-positive diagnoses is extremely low, perhaps 1–2%. The false-negative rate is as high as 10%. Most experienced clinicians would not leave a suspicious dominant mass in the breast even when FNA cytology is negative unless the clinical diagnosis, breast imaging studies, and cytologic studies were all in agreement, such as a fibrocystic lesion or fibroadenoma. Given the stated limitations, *FNA is not the modality of choice for sampling an abnormal breast mass and has been largely replaced by core needle biopsy*. FNA can be useful for biopsy of suspicious lymph nodes near the axillary vein.

Open biopsy under local anesthesia as a separate procedure prior to deciding upon definitive treatment has become less common with the increased use of core needle biopsy. Needle biopsy, when positive, offers a more rapid approach with less expense and morbidity, but when non-diagnostic it must be followed by open biopsy. It generally consists of an **excisional biopsy**, which is done through an incision with the intent to remove the entire abnormality, not simply a sample. Intraoperative frozen section examination of a breast biopsy has generally been abandoned unless there is a high clinical suspicion of malignancy in a

patient well prepared for the diagnosis of cancer and its treatment options.

2. Biopsy with ultrasound guidance—Ultrasound may show signs suggestive of carcinoma, such as an irregular mass or a mass within a cyst in the rare case of intracystic carcinoma. If a tumor is palpable and feels like a cyst, an 18-gauge needle can be used to aspirate the fluid and make the diagnosis of cyst. If a cyst is aspirated and the fluid is nonbloody, it does not have to be examined cytologically. If the mass does not recur, no further diagnostic test is necessary. Nonpalpable mammographic densities that appear benign should be investigated with ultrasound to determine whether the lesions are cystic or solid or have features suggestive of a malignancy. These may even be needle biopsied with ultrasound guidance.

3. Core needle biopsy with mammographic guidance ("stereotactic biopsy")—When a suspicious abnormality is identified by mammography alone and cannot be palpated by the clinician, the lesion should be biopsied under mammographic guidance. In the computerized stereotactic guided core needle technique, a biopsy needle is inserted into the lesion with mammographic guidance, and a core of tissue for histologic examination can then be examined.

Mammographic localization excisional biopsy is performed by obtaining a mammogram in two perpendicular views and placing a needle, hook-wire, or radioactive or radar-detectable seed localizer near the abnormality so that the surgeon can locate the lesion intraoperatively. After mammography confirms the position of the localizer in relation to the lesion, an incision is made and the localizer is identified. Often, the abnormality cannot even be palpated through the incision—as is the case with microcalcifications—and thus it is essential to obtain a mammogram of the specimen to document that the lesion was excised. Image-guided core needle biopsies have proved equivalent to mammographic localization biopsies. Core needle biopsy is preferable to mammographic localization for accessible lesions since an operation can be avoided. A metal clip should be placed after any image-guided core biopsy to facilitate finding the site of the lesion if subsequent treatment is necessary. Some atypical lesions such as atypical ductal hyperplasia or papilloma may require excision because they are associated with a malignancy in 15–25% of cases.

4. Other imaging modalities—Other modalities of breast imaging have been investigated for diagnostic purposes. Automated breast ultrasonography is useful in distinguishing cystic from solid lesions but should be used only as a supplement to physical examination and mammography. MRI is highly sensitive but not specific and should not be used for screening except in highly selective cases. For example, MRI is useful in differentiating scar from recurrence postlumpectomy and is valuable to screen high-risk women (eg, women with deleterious mutations). It may also be of value to examine for multicentricity when there is a known primary cancer; to examine the contralateral breast in women with cancer; to examine the extent of cancer, especially lobular carcinomas; or to determine the response to neoadjuvant chemotherapy. Moreover,

MRI-detected suspicious findings that are not seen on mammogram or ultrasound may be biopsied under MRI guidance. PET scanning does not appear useful in evaluating the breast itself but is useful to examine for distant metastases.

5. Cytology—Cytologic examination of nipple discharge or cyst fluid may be helpful on rare occasions. As a rule, mammography (or ductography) and breast biopsy are required when nipple discharge or cyst fluid is bloody or cytologically questionable.

► Differential Diagnosis

The most common lesions in the differential diagnosis of breast cancer are the following, in descending order of frequency: fibrocystic condition of the breast, fibroadenoma, intraductal papilloma, lipoma, and fat necrosis.

► Staging

The American Joint Committee on Cancer and the International Union Against Cancer have a joint TNM (tumor, regional lymph nodes, distant metastases) staging system for breast cancer (www.cancerstaging.org) (Table 17–3). The eighth edition is a landmark change in the TNM staging system because it adds biologic markers to modify the anatomic staging.

► Pathologic Types

Numerous pathologic subtypes of breast cancer can be identified histologically (Table 17–4).

Except for the *in situ* cancers, the histologic subtypes have only a slight bearing on prognosis when outcomes are compared after accurate staging. The noninvasive cancers by definition are confined by the basement membrane of the ducts and lack the ability to spread. Histologic parameters for invasive cancers, including lymphovascular invasion and tumor grade, have been shown to be of prognostic value. Immunohistochemical analysis for expression of hormone receptors and for overexpression of HER2 in the primary tumor offers prognostic and therapeutic information.

► Special Clinical Forms of Breast Cancer

A. Paget Carcinoma

Paget carcinoma is uncommon (about 1% of all breast cancers). Over 85% of cases are associated with an underlying invasive or noninvasive cancer, usually a well differentiated infiltrating ductal carcinoma or a DCIS. Gross nipple changes are often minimal, and a tumor mass may not be palpable.

Because the nipple changes appear innocuous, the diagnosis is frequently missed. The first symptom is often itching or burning of the nipple, with superficial erosion or ulceration. These are often diagnosed and treated as dermatitis or bacterial infection, leading to delay or failure in detection. The diagnosis is established by biopsy of the area of erosion. When the lesion consists of nipple changes only or an associated DCIS, the incidence of axillary metastases

is extremely low, and the prognosis is excellent. When a breast mass or invasive cancer is also present, the incidence of axillary metastases rises, with an associated marked decrease in prospects for cure by surgical or other treatment.

B. Inflammatory Carcinoma

This is the most malignant form of breast cancer and constitutes less than 3% of all cases. The clinical findings consist of a rapidly growing, sometimes painful mass that enlarges the breast. The overlying skin becomes erythematous, edematous, and warm. Often there is no distinct mass since the tumor diffusely infiltrates the involved breast. The inflammatory changes, often mistaken for an infection, are caused by carcinomatous invasion of the subdermal lymphatics, with resulting edema and hyperemia. If the clinician suspects infection but the lesion does not respond to antibiotics within 1–2 weeks, biopsy should be performed. Metastases tend to occur early and widely; while rarely deemed curable in the past, anti-HER2 therapy (if HER2 overexpressing or amplified), surgery, and chemotherapy have resulted in some long-term cures for patients with inflammatory carcinoma. Mastectomy is indicated when chemotherapy and radiation have resulted in clinical remission with no evidence of distant metastases. In these cases, residual disease in the breast may be eradicated. Sentinel node biopsy is not indicated due to the high false-negative rate.

► Breast Cancer Occurring During Pregnancy or Lactation

Breast cancer complicates up to one in 3000 pregnancies. Its incidence is increasing as women delay childbearing. The diagnosis is frequently delayed because physiologic changes in the breast may obscure the lesion and screening mammography is not done in young or pregnant women. Termination of pregnancy has not been shown to improve maternal prognosis. The decision whether to terminate the pregnancy must be made on an individual basis, taking into account the patient's wishes, the clinical stage of the cancer and overall prognosis, the gestational age of the fetus, and the potential for premature ovarian failure in the future with systemic therapy.

It is important for primary care and reproductive specialists to aggressively work up any breast abnormality discovered in a pregnant woman. Pregnancy (or lactation) is not a contraindication to operation or treatment, and therapy should be based on the stage of the disease as in the nonpregnant (or nonlactating) woman. Women with early-stage gestational breast cancer who choose to continue their pregnancy should undergo surgery to remove the tumor and systemic therapy if indicated. Often neoadjuvant systemic therapy may be given during pregnancy and the operation and radiation therapy delayed. Retrospective reviews of patients treated with anthracycline-containing regimens for gestational cancers (including leukemia and lymphomas) have established the relative safety of these regimens during pregnancy for both the patient and the fetus. Taxane-based and trastuzumab-based regimens have

Table 17–3. Abbreviated TNM staging for breast cancer.

Category	Criteria
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
T1–T1c	Tumor ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma
Regional Lymph Nodes (N)¹ Clinical (cN)	
cNX ²	Regional lymph nodes cannot be assessed (eg, previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi ³	Micrometastases (approximately 200 cells, > 0.2 mm, but none > 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)
Distant Metastasis (M)	
M0	No clinical or radiographic evidence of distant metastases; imaging studies not required to assign this category.
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no > 0.2 mm detected microscopically or by molecular techniques
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases > 0.2 mm

¹Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine-needle aspiration/core needle biopsy, respectively.

²The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.

³cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Used, with permission, of the American College of Surgeons. Amin MB, Edge SB, Greene FL et al (editors). AJCC Cancer Staging Manual, 8th ed. Springer New York, 2017.

Table 17–4. Histologic types of breast cancer.

Type	Frequency of Occurrence
Infiltrating ductal (not otherwise specified)	80–90%
Medullary	5–8%
Colloid (mucinous)	2–4%
Tubular	1–2%
Papillary	1–2%
Invasive lobular	6–8%
Noninvasive	4–6%
Intraductal	2–3%
Lobular in situ	2–3%
Rare cancers	< 1%
Juvenile (secretory)	
Adenoid cystic	
Epidermoid	
Sudoriferous	

not been evaluated extensively, however. Radiation therapy should be delayed until after delivery.

► Bilateral Breast Cancer

Bilateral breast cancer occurs in less than 5% of cases, but there is as high as a 20–25% incidence of later occurrence of cancer in the second breast. Bilaterality occurs more often in familial breast cancer, in women under age 50 years, and when there is a deleterious mutation. The incidence of second breast cancers increases directly with the length of time the patient is alive after her first cancer—about 1–2% per year. Tamoxifen or aromatase inhibitors decrease the risk of a contralateral hormone receptor-positive cancer.

In patients with breast cancer, mammography should be performed before primary treatment and at regular intervals thereafter to search for occult cancer in the opposite breast or conserved ipsilateral breast.

► Noninvasive Cancer

Noninvasive cancer can occur within the ducts (DCIS) or lobules (LCIS). DCIS tends to be unilateral and is believed to progress to invasive cancer if untreated. Invasive cancer will develop in the same breast in approximately 40–60% of women who have unresected DCIS. LCIS is generally agreed to be a marker of an increased risk of breast cancer rather than a direct precursor of breast cancer itself. In the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, LCIS is no longer considered a cancer. The probability of breast cancer (DCIS or invasive cancer in either breast) in a woman in whom LCIS has been diagnosed is estimated to be 1% per year. If LCIS is detected on core needle biopsy, an excisional biopsy without lymph node sampling may be performed to rule out DCIS or invasive cancer, but NCCN

guidelines suggest observation alone is satisfactory. The incidence of LCIS is rising, likely due to increased use of screening mammography. In addition, the rate of mastectomy after the diagnosis of LCIS is increasing in spite of the fact that mastectomy is only recommended in those patients who otherwise have an increased risk of breast cancer through family history, genetic mutation, or past exposure to thoracic radiation. Pleomorphic LCIS may behave more like DCIS and may be associated with invasive carcinoma. For this reason, pleomorphic LCIS should be surgically removed with clear margins.

The treatment of intraductal lesions is controversial. DCIS can be treated by wide excision with or without radiation therapy or with total mastectomy. Conservative management is advised in patients with small lesions amenable to lumpectomy. Patients in whom LCIS is diagnosed or who have received lumpectomy for DCIS may discuss chemoprevention (with hormonal blockade therapy) with their clinician, which is effective in reducing the risk of invasive breast cancer. Axillary metastases from in situ cancers should not occur unless there is an occult invasive cancer. Because a sentinel lymph node biopsy after mastectomy cannot be performed, it should be performed in a patient undergoing mastectomy for DCIS in case an invasive component is discovered.

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Wang Z et al. A large-cohort retrospective study of metastatic patterns and prognostic outcomes between inflammatory and non-inflammatory breast cancer. Ther Adv Med Oncol. 2020;12:1. [PMID: 32550867]

► Biomarkers & Gene Expression Profiling

Hormone receptor-positive tumors are ER (estrogen receptor)-positive or PR (progesterone receptor)-positive or both. Treatment with a hormonally targeted agent (anti-estrogen or anti-estrogen receptor) is an essential therapy for hormone receptor-positive breast cancer. Hormone receptor-negative cancers do not respond to endocrine treatments. Patients whose tumors are hormone receptor-positive tend to have a more indolent disease course than those whose tumors are hormone receptor-negative.

The *HER2* (*human epidermal growth factor receptor 2*) gene is an oncogene; breast cancer cells that overproduce the *HER2* gene (*HER2*-amplified or “*HER2*-positive” cancers) overproduce the growth-promoting protein *HER2*. *HER2*-positive breast cancer is generally more aggressive than breast cancer with normal *HER2* expression (*HER2*-negative breast cancer). Targeted therapies that block *HER2* have been shown to significantly improve outcomes for patients with *HER2*-positive disease.

Determining the ER, PR, and *HER2* status of the tumor at the time early breast cancer is diagnosed and, if possible, at the time of recurrence is critical, both to gauge a patient’s

prognosis and to determine the best treatment regimen. In addition to ER, PR, and HER2 status, other important prognostic factors include the rate at which tumor divides (assessed by an immunohistochemical stain for Ki67) and the grade and differentiation of the cells. These markers may be obtained on core biopsy or surgical specimens, but not reliably on FNA cytology. Individually these biomarkers are predictive and thus provide insight to guide appropriate therapy. Moreover, when combined, they provide useful information regarding risk of recurrence and prognosis in the curative setting.

In general, tumors that lack expression of HER2, ER, and PR (“**triple negative**”) have a higher risk of early recurrence and metastases and are associated with a worse survival compared with other types. Neither endocrine therapy nor HER2-targeted agents are useful for this type of breast cancer. Chemotherapy has been the primary treatment option for triple-negative breast cancer. In contrast, patients with early stage, hormone receptor-positive breast cancer may not benefit from the addition of chemotherapy to hormonally targeted treatments. Several molecular tests have been developed to assess risk of recurrence and to predict which patients are most likely to benefit from chemotherapy for early-stage disease. **Oncotype DX** (Genomic Health) evaluates the expression of 21 genes relating to ER, HER2, and proliferation in a tumor specimen and categorizes a patient’s risk of recurrence (recurrence score) as high, intermediate, or low risk. Patients in low- or intermediate-risk categories do not benefit from chemotherapy, especially when age 50 or over. This test is primarily indicated for ER-positive, lymph node-negative tumors, but a 2020 study (RxPONDER, NCT01272037) suggests that postmenopausal women with 1–3 positive lymph nodes with a recurrence score of less than 25 may not benefit from the use of chemotherapy.

MammaPrint (Agendia) is an FDA-approved 70-gene signature assay that is available for evaluating prognosis. This test classifies patients into good and poor prognostic groups to predict clinical outcome and may be used on patients with hormone receptor-positive or hormone receptor-negative breast cancer. American Society of Clinical Oncology (ASCO) guidelines indicate this assay may be best used to help determine whether chemotherapy may be safely withheld in patients with hormone receptor-negative, HER2-negative, node-positive breast cancer at high clinical risk. ASCO does not recommend using this assay in hormone receptor-negative or HER2-positive breast cancer. The eighth edition of the AJCC staging system incorporates genomic assays to provide a prognostic stage. Patients with low-risk genomic assays may be downstaged from their TNM stage. For example, a patient who has a TNM stage of II but has a low Oncotype Recurrence Score could be classified as having stage I disease per the eighth edition.

Sparano JA et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379:111. [PMID: 29860917]

Sparano JA et al. Development and validation of a tool integrating the 21-gene recurrence score and clinical-pathological features to individualize prognosis and prediction of chemotherapy benefit in early breast cancer. *J Clin Oncol.* 2021;39:557. [PMID: 33306425]

Wolff AC et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med.* 2018;142:1364. [PMID: 29846104]

► Curative Treatment

Most patients with early breast cancer can be cured. Treatment with a curative intent is advised for clinical stage I, II, and III disease (see Table 39–2). Patients with locally advanced (T3, T4) and even inflammatory tumors may be cured with multimodality therapy. When metastatic disease is diagnosed, palliation becomes the goal of therapy. Treatment with palliative intent is appropriate for all patients with stage IV disease and for patients with unresectable local cancers.

A. Choice and Timing of Primary Therapy

The extent of disease and its biologic aggressiveness are the principal determinants of the outcome of primary therapy. Clinical and pathologic staging help in assessing extent of disease (see Table 17–3), but each is imprecise. Other factors such as tumor grade, hormone receptor assays, HER2 amplification, and genomic assays are of prognostic and predictive value for benefits from systemic therapy but are not as relevant in determining the type of local therapy.

Controversy has surrounded the choice of primary therapy of stage I, II, and III breast carcinoma. Currently, the standard of care for stage I, stage II, and most stage III cancer is surgical resection followed by adjuvant radiation or systemic therapy, or both, when indicated. Neoadjuvant chemotherapy may shrink large tumors prior to surgery, making some patients who require mastectomy candidates for lumpectomy. (Neoadjuvant therapy is given before surgery, while adjuvant therapy is given after surgery in order to destroy remaining cancer cells.) In addition, in some cases of triple-negative and HER2-amplified breast cancer, the response to neoadjuvant therapy may determine the need for additional postoperative systemic therapy, which may result in improved survival. It is important for patients to understand all the surgical options, including reconstructive options, prior to having surgery. Patients with large primary tumors, inflammatory cancer, or palpably enlarged lymph nodes should have staging scans performed to rule out distant metastatic disease prior to definitive surgery. In general, adjuvant systemic therapy is started when the breast has adequately healed, ideally within 4–8 weeks after surgery. While no prospective studies have defined the appropriate timing of adjuvant chemotherapy, a single-institution study of over 6800 patients suggests that *systemic therapy should be started within 60 days of surgery*, especially in women with stage II or III

Kalinsky K et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy +/- chemotherapy in patients with 1-3 positive nodes, hormone receptor-positive and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007. San Antonio Breast Cancer Symposium 2020. Abstract GS3-00.

breast cancer, triple-negative breast cancer, or HER2-positive disease.

B. Surgical Resection

1. Breast-conserving therapy—Multiple, large, randomized studies including the Milan and NSABP trials show that disease-free and overall survival rates are similar for patients with stage I and stage II breast cancer treated with partial mastectomy (breast-conserving lumpectomy or “breast conservation”) plus axillary dissection followed by radiation therapy and for those treated by modified radical mastectomy (total mastectomy plus axillary dissection).

Tumor size is a major consideration in determining the feasibility of breast conservation. The NSABP lumpectomy trial randomized patients with tumors as large as 4 cm. To achieve an acceptable cosmetic result, the patient must have a breast of sufficient size to enable excision of a 4-cm tumor without considerable deformity. Therefore, large tumor size is only a relative contraindication. Subareolar tumors, also difficult to excise without deformity, are not contraindications to breast conservation. Oncoplastic techniques combining principles of plastic and reconstructive surgery with surgical oncologic principles are enabling resection of large tumors with excellent cosmetic results. Clinically detectable multifocality is a relative contraindication to breast-conserving surgery, as is fixation to the chest wall or skin or involvement of the nipple or overlying skin. The patient—not the surgeon—should be the judge of what is cosmetically acceptable. Given the relatively high risk of poor outcome after radiation, concomitant systemic sclerosis (scleroderma) is a contraindication to breast-conserving surgery. A history of prior therapeutic radiation to the ipsilateral breast or chest wall (or both) is also generally a contraindication for breast conservation, although accelerated partial breast irradiation may permit a second breast irradiation.

Axillary dissection is primarily used to properly stage cancer and plan radiation and systemic therapy. Intraoperative lymphatic mapping and sentinel node biopsy identify lymph nodes most likely to harbor metastases if present (Figure 17–6). **Sentinel node biopsy** is a proven alternative to axillary dissection in patients without clinical

evidence of axillary lymph node metastases. If sentinel node biopsy reveals no evidence of axillary metastases, it is highly likely that the remaining lymph nodes are free of disease and axillary dissection may be omitted. An important study from the American College of Surgeons Oncology Group randomized women with sentinel node metastases to undergo completion of axillary dissection or to receive no further axillary-specific treatment after lumpectomy; no difference in 10-year survival was found. *Omission of axillary dissection is acceptable for women with tumor-free sentinel nodes or those with involvement of one or two sentinel nodes who are treated with lumpectomy, whole breast irradiation, and adjuvant systemic therapy.*

Breast-conserving surgery with sentinel node biopsy and radiation is the preferred form of treatment for patients with early-stage breast cancer. Despite the numerous randomized trials showing no survival benefit of mastectomy over breast-conserving partial mastectomy with irradiation or of axillary dissection over sentinel node biopsy, these conservative procedures still appear to be underutilized.

2. Mastectomy—Modified radical mastectomy was previously the standard therapy for most patients with early-stage breast cancer. This operation removes the entire breast, overlying skin, nipple, and areolar complex usually with underlying pectoralis fascia with the axillary lymph nodes in continuity. The major advantage of modified radical mastectomy is that radiation therapy may not be necessary, although radiation may be used when lymph nodes are involved with cancer or when the primary tumor is 5 cm or larger. The disadvantage of mastectomy is the cosmetic and psychological impact associated with breast loss. Radical mastectomy, which removes the underlying pectoralis muscle, should be performed rarely, if at all. Axillary node dissection is not indicated for non-invasive cancers because nodal metastases are rarely present. Skin-sparing and nipple-sparing mastectomy is available but is not appropriate for all patients. Breast reconstruction, immediate or delayed, should be discussed with patients who choose or require mastectomy. Patients should have an interview with a reconstructive plastic surgeon to discuss options prior to making a decision regarding reconstruction. Time is well spent preoperatively in educating the patient and family about these matters. Skin-sparing mastectomies, including those with presentation of the nipple-areolar complex, are becoming more commonly used with excellent cosmetic and oncologic results.

C. Radiotherapy

Radiotherapy after breast-conserving surgery consists of 5–7 weeks of five daily fractions to a total dose of 5000–6000 cGy. Most radiation oncologists use a boost dose to the cancer location. Shorter fractionation schedules may be reasonable for women with low-risk, early-stage breast cancer. Guidelines by the American Society of Radiation Oncology (ASTRO) and the European Society for Radiotherapy (ESTRO) indicate that it is appropriate to discuss partial breast radiation for women over the age of 50 with node-negative, hormone receptor-positive, small (T1)



▲ **Figure 17–6.** Sentinel node. (Used, with permission, from Armando E. Giuliano, MD.)

tumors with surgical margins of at least 2 mm. Moreover, in women over the age of 70 with small (less than 2 cm), lymph node-negative, hormone receptor-positive cancers, radiation therapy may be avoided. The recurrence rates after intraoperative radiation, while low, appear significantly higher than postoperative whole breast radiation therapy. However, in all these situations, a balanced discussion with a radiation oncologist to weigh the risks and benefits of each approach is warranted.

Current studies suggest that radiotherapy after mastectomy may improve recurrence rates and survival in younger patients and those with tumors 5 cm or larger or positive lymph nodes.

Deli T et al. Hormone replacement therapy in cancer survivors—review of the literature. *Pathol Oncol Res.* 2020;26:63. [PMID: 30617760]

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Patel AU et al. Functional return after implant-based breast reconstruction: a prospective study of objective and patient-reported outcomes. *J Plast Reconstr Aesthet Surg.* 2020;73:850. [PMID: 31973982]

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Vicini FA et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet.* 2019;394:2155. [PMID: 31813636]

Whelan TJ et al; RAPID Trial Investigators. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet.* 2019;394:2165. [PMID: 31813635]

D. Adjuvant Systemic Therapy

Systemic therapy improves survival and is advocated for most patients with curable breast cancer. In practice, most medical oncologists use adjuvant chemotherapy for patients with either node-positive or higher-risk (eg, hormone receptor-negative or HER2-positive) node-negative breast cancer and use endocrine therapy for all hormone receptor-positive invasive breast cancer unless contraindicated. Prognostic factors other than nodal status that are used to determine the patient's risks of recurrence are tumor size, ER and PR status, nuclear grade, histologic type, proliferative rate, oncogene expression (Table 17–5), and patient's age and menopausal status. In general, systemic chemotherapy decreases the chance of recurrence by about 30%, hormonal modulation decreases the relative risk of recurrence by 40–50% (for hormone receptor-positive cancer), and HER2-targeted therapy decreases the relative risk of recurrence by approximately 40% (for HER2-positive cancer). Systemic chemotherapy is usually given sequentially, rather than concurrently with radiation.

Table 17–5. Prognostic factors for recurrence in node-negative breast cancer.

Prognostic Factors	Increased Recurrence	Decreased Recurrence
Size ¹	T3, T2	T1, T0
Hormone receptors (ER, PR)	Negative	Positive
Histologic grade	High	Low
S phase fraction	> 5%	< 5%
Lymphatic or vascular invasion	Present	Absent
HER2 oncogene amplification	High	Low
Epidermal growth factor receptor	High	Low
High Oncotype DX Recurrence Score or other genomic prognostic assays	High score	Low score

¹See Table 17–3 for TNM staging for breast cancer.

In terms of sequencing, typically chemotherapy is given before radiation and endocrine therapy is started concurrent with or after radiation therapy.

The long-term advantage of systemic therapy is well established. All patients with invasive hormone receptor-positive tumors should consider the use of hormone-modulating therapy. Most patients with HER2-positive tumors should receive trastuzumab-containing chemotherapy regimens. In general, adjuvant systemic chemotherapy should not be given to women who have small node-negative breast cancers with favorable histologic findings and tumor biomarkers. The ability to predict more accurately which patients with HER2-negative, hormone receptor-positive, lymph node-negative tumors should receive chemotherapy is improving with the advent of prognostic tools, such as Oncotype DX and MammaPrint (see Biomarkers and Gene Expression Profiling above). These validated tools enable clinicians to better select patients who can safely omit chemotherapy.

1. Chemotherapy—The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis involving over 28,000 women enrolled in 60 trials of adjuvant polychemotherapy versus no chemotherapy demonstrated a significant beneficial impact of chemotherapy on clinical outcome in non–stage IV breast cancer. This study showed that *adjuvant chemotherapy reduces the risk of recurrence and breast cancer-specific mortality in all women and women under the age of 50 derived the greatest benefit.*

A. ANTHRACYCLINE- AND CYCLOPHOSPHAMIDE-CONTAINING REGIMENS—On the basis of the superiority of anthracycline-containing regimens in metastatic breast cancer, both doxorubicin and epirubicin have been studied extensively in the adjuvant setting. Studies comparing Adriamycin (doxorubicin) and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) to cyclophosphamide-methotrexate-5-fluorouracil (CMF) have shown that treatments with anthracycline-containing regimens are at

least as effective as treatment with CMF. The EBCTCG analysis of over 14,000 patients comparing anthracycline-based regimens to CMF showed a small but statistically significant improved disease-free and overall survival with the use of anthracycline-based regimens. It should be noted, however, that most of these studies included a mixed population of patients with HER2-positive and HER2-negative breast cancer and were performed before the introduction of trastuzumab. Retrospective analyses of a number of these studies suggest that anthracyclines may be primarily effective in tumors with HER2 overexpression or alteration in the expression of topoisomerase IIa (the target of anthracyclines and close to the *HER2* gene). Given this, for HER2-negative, node-negative breast cancer, four cycles of AC or six cycles of CMF are probably equally effective.

B. TAXANES—Multiple trials of taxanes (paclitaxel and docetaxel) have been conducted to evaluate their use in combination with anthracycline-based regimens. The majority of these trials showed an improvement in disease-free survival and at least one showed an improvement in overall survival with the taxane-based regimen. A meta-analysis of taxane versus non-taxane anthracycline-based regimen trials showed an improvement in disease-free and overall survival for the taxane-based regimens. Several regimens have been reported including AC followed by paclitaxel (AC-P) or docetaxel (Taxotere) (AC-T), docetaxel concurrent with AC (TAC), 5-fluorouracil-epirubicine-cyclophosphamide (FEC)-docetaxel, and FEC-paclitaxel.

While it is generally agreed that *taxanes should be used for most patients receiving chemotherapy for early breast cancer, data relating to the benefits of anthracyclines are conflicting*; thus, a balanced discussion regarding the potential risks versus benefits of the addition of anthracyclines is warranted, especially in hormone receptor-positive disease.

C. DURATION AND DOSE OF CHEMOTHERAPY—The ideal duration of adjuvant chemotherapy still remains uncertain. However, based on the meta-analysis performed in the Oxford Overview (EBCTCG), the current recommendation is for 3–6 months of the commonly used regimens. Data suggest that the timing and sequencing of anthracycline-taxane-based chemotherapy may be important. Multiple trials beginning in the 1980s sought to demonstrate whether dose-intensification of adjuvant chemotherapy by shortening the intervals between cycles (“dose-dense”), or by giving chemotherapy at full dose sequentially rather than concurrently at reduced doses is associated with better outcomes. The EBCTCG meta-analysis included 37,298 patients treated on 26 trials and showed a significant 3.4% absolute decrease and 14% relative risk reduction in breast cancer recurrences with dose-intensification. Moreover, the absolute 10-year breast cancer mortality was improved by 2.4%. While impressive, the benefit of dose-intensification appeared to be strongest in node-positive disease. Its benefit, if any, in HER2-positive disease in the era of HER2-targeted therapy has not been validated. Additionally, the use of

dose-intensification in (non-anthracycline) taxane-based regimens has not been evaluated.

D. CHEMOTHERAPY SIDE EFFECTS—Chemotherapy side effects, which are discussed in Chapter 39, are generally well controlled.

2. Targeted therapy—Targeted therapy refers to agents that are directed specifically against a protein or molecule expressed uniquely on tumor cells or in the tumor microenvironment.

A. HER2 OVEREXPRESSION—Approximately 20% of breast cancers are characterized by amplification of the *HER2* oncogene leading to overexpression of the *HER2* oncoprotein. The poor prognosis associated with *HER2* overexpression has been drastically improved with the development of *HER2*-targeted therapy. Trastuzumab (Herceptin [H]), a monoclonal antibody that binds to *HER2*, is effective in combination with chemotherapy (AC-TH or TCH [docetaxel, carboplatin, trastuzumab]) in patients with *HER2*-overexpressing early breast cancer. Both AC-TH and TCH are FDA-approved for nonmetastatic, *HER2*-positive breast cancer. In these regimens, trastuzumab is given with chemotherapy and then continued beyond the course of chemotherapy with a goal, in general, to complete a full year. Neoadjuvant chemotherapy plus dual *HER2*-targeted therapy with trastuzumab and pertuzumab (also a *HER2*-targeted monoclonal antibody that prevents dimerization of *HER2* with *HER3* and has been shown to be synergistic in combination with trastuzumab) is a standard of care option available to patients with stage II/III *HER2*-positive breast cancer (see Neoadjuvant Therapy). Adjuvant pertuzumab in combination with trastuzumab is primarily restricted to patients with high-risk, node-positive disease. Neratinib, an orally bioavailable dual *HER1* (EGFR), *HER2* tyrosine kinase inhibitor, is FDA-approved as extended adjuvant therapy (to be given after completion of 1 year of trastuzumab). The phase 3 placebo-controlled EXTENET study demonstrated that neratinib improves invasive disease-free survival when given for 1 year after completion of a year of standard adjuvant trastuzumab-based therapy (median follow-up 5.2 years, stratified HR 0.73, 95% CI 0.57, 0.92, $P = 0.0083$). The benefit of neratinib appears to be restricted to those with tumor co-expression of hormone receptor(s). Neratinib is associated with gastrointestinal toxicity, most notably moderate to severe diarrhea in approximately 40% of patients who did not use antidiarrheal prophylaxis. Measures such as starting at a lower dose of neratinib and escalating as tolerated or using prophylactic colestipol or budesonide have been shown to mitigate this side effect in the CONTROL clinical trial (NCT02400476).

Patients who undergo neoadjuvant trastuzumab-based chemotherapy and have residual disease remaining at the time of surgery have a comparatively poor outcome compared to those who achieve a pathologic complete response. In the phase 3 randomized KATHERINE trial, 1486 patients with residual disease after standard neoadjuvant trastuzumab/taxane-based therapy (18% of whom also

received neoadjuvant pertuzumab) were randomized to receive the antibody-drug conjugate trastuzumab emtansine or standard trastuzumab for 14 cycles after surgery. Patients treated with trastuzumab emtansine had a statistically significantly improved 3-year invasive disease-free survival (88% vs 77%), associated with a 50% relative risk reduction. Adjuvant trastuzumab emtansine is FDA-approved for patients with residual disease after standard trastuzumab-containing neoadjuvant therapy.

Retrospective studies have shown that even small (stage T1a,b) *HER2*-positive tumors have a worse prognosis compared with same-sized *HER2*-negative tumors and may thus be appropriate for trastuzumab-based regimens.

Cardiomyopathy develops in a small but significant percentage (0.4–4%) of patients who receive trastuzumab-based regimens. For this reason, anthracyclines and trastuzumab are rarely given concurrently and cardiac function is monitored periodically throughout therapy.

B. ENDOCRINE THERAPY—Adjuvant hormone modulation therapy is highly effective in decreasing relative risk of recurrence by 40–50% and mortality by 25% in women with hormone receptor-positive tumors regardless of menopausal status.

(1) *Tamoxifen*—The traditional 5-year regimen of adjuvant estrogen-receptor antagonist/agonist tamoxifen was compared to a 10-year regimen in the Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial. Disease-free and overall survival were significantly improved in women who received 10 years of tamoxifen, particularly after year 10. Though these results are impressive, the clinical application of long-term tamoxifen use must be discussed with patients individually, taking into consideration risks of tamoxifen (such as secondary uterine cancers, venous thromboembolic events, and side effects that impact quality of life). Ovarian suppression in addition to tamoxifen has been shown to significantly improve 8-year disease-free survival (83.2% vs 78.9%) and 8-year overall survival (93.3% vs 91.5%) compared to tamoxifen alone in the randomized Suppression of Ovarian Function Trial (SOFT) study, though the benefits appeared to be seen primarily in chemotherapy-treated patients with higher risk disease.

(2) *Aromatase inhibitors*—AIs, including anastrozole, letrozole, and exemestane, reduce estrogen production and are also effective in the adjuvant setting for postmenopausal women. *AIs should not be used in a patient with functioning (premenopausal) ovaries since they do not block ovarian production of estrogen.* At least seven large randomized trials enrolling more than 24,000 postmenopausal patients with hormone receptor-positive nonmetastatic breast cancer have compared the use of AIs with tamoxifen or placebo as adjuvant therapy. All of these studies have shown small but statistically significant improvements in disease-free survival (absolute benefits of 2–6%) with the use of AIs. In addition, AIs have been shown to reduce the risk of contralateral breast cancers and to have fewer associated serious side effects (such as endometrial cancers and thromboembolic events) than tamoxifen. However, they are associated with accelerated bone loss and an increased risk of fractures as well as a musculoskeletal syndrome

characterized by arthralgias or myalgias (or both) in the majority of patients. The American Society of Clinical Oncology and the NCCN have recommended that *postmenopausal women with hormone receptor-positive breast cancer be offered an AI either initially or after tamoxifen therapy.* *HER2* status should not affect the use or choice of hormone therapy. A combined analysis of the SOFT and Tamoxifen and Exemestane Trial (TEXT) studies showed for the first time that exemestane plus ovarian suppression with triptorelin was associated with a reduced risk of relapse compared to tamoxifen, making this a viable adjuvant therapy option for *premenopausal* women with high-risk ER-positive breast cancers.

3. Bisphosphonates—Multiple randomized studies have evaluated the use of adjuvant bisphosphonates in addition to standard local and systemic therapy for early-stage breast cancer and have shown, in addition to improvement in bone density, a consistent reduction in the risk of metastatic recurrence in postmenopausal patients. A meta-analysis evaluating more than 18,000 women with early-stage breast cancer treated with bisphosphonates or placebo showed that bisphosphonates reduce the risk of cancer recurrence (especially in bone) and improve breast cancer-specific survival primarily in postmenopausal women. Side effects associated with bisphosphonate therapy include bone pain, fever, osteonecrosis of the jaw (rare, less than 1%), esophagitis or ulcers (for oral bisphosphonates), and kidney injury. Although the FDA has not yet approved the adjuvant use of bisphosphonates to reduce the risk of breast cancer recurrence, the 2017 jointly published guidelines of the Cancer Care Ontario and American Society of Clinical Oncology recommend that bisphosphonate use (zoledronic acid or clodronate) be considered in the adjuvant therapy plan for postmenopausal breast cancer patients. In addition, denosumab (another bone stabilizing medication), which is an antibody directed against receptor activator of nuclear factor kappa B ligand (RANK-L), was evaluated in two phase 3 adjuvant trials with discordant results. The “D-CARE” study randomized patients with early-stage breast cancer (all biologic subtypes) to receive denosumab or placebo and failed to demonstrate a reduction in breast cancer recurrences or deaths. It is speculated that one possible reason for this negative result may be due to the fact that premenopausal patients (who do not have a demonstrated metastatic recurrence benefit from bisphosphonates) were included in the study. In contrast, the ABCSG-18 trial restricted enrollment to postmenopausal women and did show an improvement in disease-free survival with denosumab.

4. Adjuvant therapy in older women—Data relating to the optimal use of adjuvant systemic treatment for women over the age of 65 are limited. Results from the EBCTCG overview indicate that while adjuvant chemotherapy yields a smaller benefit for older women compared with younger women, it still improves clinical outcomes. Moreover, individual studies do show that older women with higher risk disease derive benefits from chemotherapy. One study compared the use of oral chemotherapy (capecitabine) to

standard chemotherapy in older women and concluded that standard chemotherapy is preferred. Another study (USO TC vs AC) showed that women over the age of 65 derive similar benefits from the taxane-based regimen as women who are younger. The benefits of endocrine therapy for hormone receptor-positive disease appear to be independent of age. In general, decisions relating to the use of systemic therapy should take into account a patient's comorbidities and physiological age, more so than chronological age.

E. Neoadjuvant Therapy

The use of systemic therapy prior to resection of the primary tumor (neoadjuvant) is a standard option that in many cases should be discussed with patients prior to surgery. This enables the assessment of *in vivo* sensitivity of the tumor to the selected systemic therapy. Patients with hormone receptor-negative, triple-negative, or HER2-positive breast cancer are more likely to have a pathologic complete response (meaning no residual invasive cancer in the breast and sampled nodes at the time of surgery) to neoadjuvant chemotherapy than those with hormone receptor-positive breast cancer. A pathologic complete response at the time of surgery, especially in hormone receptor-negative tumors, is associated with improvement in event-free and overall survival. Neoadjuvant chemotherapy also increases the chance of breast conservation by shrinking the primary tumor in women who would otherwise need mastectomy for local control. Survival after neoadjuvant chemotherapy is similar to that seen with postoperative adjuvant chemotherapy.

1. HER2-positive breast cancer—Dual targeting of HER2 with two monoclonal antibodies, trastuzumab and pertuzumab, showed positive results in two phase 2 clinical trials in the neoadjuvant setting, the TRYphaena and the NEOSPHERE studies.

Based on these clinical trials, three regimens are FDA-approved in the HER2-positive neoadjuvant setting: docetaxel (T), cyclophosphamide (C), trastuzumab (H), and pertuzumab (P) (TCHP) for 6 cycles; 5-fluorouracil, epirubicin, cyclophosphamide (FEC) for 3 cycles followed by THP for 3 cycles; or THP for 4 cycles (followed by 3 cycles of postoperative FEC). After completing surgery, patients should resume HER2-targeted therapy. If there is residual disease, the standard of care is to give 14 cycles of trastuzumab emtansine based on the KATHERINE trial that showed a significantly improved invasive disease-free survival for patients who received trastuzumab emtansine if they had a non-pathologic complete response to neoadjuvant treatment. In the case of pathologic complete response, trastuzumab with or without pertuzumab is given to complete 1 year of total therapy with consideration for the use of neratinib as extended adjuvant therapy for high-risk (lymph node-positive, hormone receptor-positive) disease.

2. Hormone receptor-positive, HER2-negative breast cancer—Patients with hormone receptor-positive breast cancer have a lower chance of achieving a pathologic

complete response with neoadjuvant therapy than those patients with triple-negative or HER2-positive breast cancers. Studies indicate similar clinical response rates with neoadjuvant endocrine therapy compared to neoadjuvant chemotherapy. Typically, responses are not appreciated unless 4–6 or more months of therapy are given. Outside of the clinical trial setting, the use of neoadjuvant hormonal therapy is generally restricted to postmenopausal patients who are unable or unwilling to tolerate chemotherapy.

3. Triple-negative breast cancer—No targeted therapy has yet demonstrated meaningful improvements in long-term outcomes for patients with curable breast cancer that is lacking in HER2 amplification or hormone receptor expression. Neoadjuvant chemotherapy leads to pathologic complete response in up to 40–50% of patients with triple-negative breast cancer. Patients who achieve a pathologic complete response seem to have a similar prognosis to other breast cancer subtypes with pathologic complete response. However, those patients with residual disease at the time of surgery have a poor prognosis. Based on the theory that triple-negative breast cancers may be more vulnerable to DNA-damaging agents, several studies have evaluated whether the addition of platinum salts to a neoadjuvant chemotherapy regimen is beneficial in this disease subtype, several of which have shown improved outcomes (pathologic complete response and disease-free survival) with platinum use. Studies are ongoing to evaluate the pathologic complete response rates and long-term outcomes associated with incorporating platinums into standard chemotherapy regimens. One randomized phase 3 study, CREATE-X, indicated that the use of eight cycles of adjuvant capecitabine improved disease-free survival and overall survival in patients with residual disease after standard neoadjuvant therapy. This benefit was primarily observed in those with triple-negative breast cancer. As such, it has become a standard option available to patients who do not experience a complete response after neoadjuvant therapy. Immune checkpoint inhibitors have been evaluated in the neoadjuvant and adjuvant setting for triple-negative breast cancer. While some have shown an improvement in pathologic complete response rates when added to chemotherapy, none are yet FDA approved for this indication. Longer term outcomes, such as event-free survival, are awaited.

4. Timing of sentinel lymph node biopsy in neoadjuvant setting—There is considerable concern about the timing of sentinel lymph node biopsy, since the chemotherapy may affect cancer present in the lymph nodes. Several studies have shown that sentinel node biopsy can be done after neoadjuvant therapy. However, a large multicenter study, ACOSOG 1071, demonstrated a false-negative rate of 10.7%, well above the false-negative rate outside the neoadjuvant setting (less than 1–5%). If three nodes are removed and isotope and dye are used, the false-negative rate falls to an acceptable level. Some physicians recommend performing sentinel lymph node biopsy before administering the chemotherapy in order to avoid a false-negative result and to aid in planning subsequent radiation therapy. Others prefer to perform sentinel lymph node biopsy after

neoadjuvant therapy to avoid a second operation and assess post-chemotherapy nodal status. If a complete dissection is desired, this can be performed at the time of the definitive breast surgery. The SENTINA trial showed similarly poor results for sentinel node biopsy after neoadjuvant therapy. An effective approach for sentinel node biopsy for patients who had involved nodes pre-chemotherapy is to place a clip in the positive node and be sure to excise it at the time of sentinel node biopsy. No study has evaluated the survival impact of no axillary treatment for node-positive patients who become node-negative after neoadjuvant therapy. Important questions remain to be answered involving the use of neoadjuvant therapy, including which neoadjuvant agents to use, duration of treatment, and additional postoperative therapy.

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symptoms such as fatigue, change in appetite, abdominal pain, cough, dyspnea, or bone pain. Headaches, imbalance, vision changes, vertigo, and other neurologic symptoms may be signs of brain metastases. Triple-negative (ER-, PR-, HER2-negative) and HER2-positive tumors have a higher rate of brain metastases than hormone receptor-positive, HER2-negative tumors.

A. Radiotherapy and Bisphosphonates

Palliative radiotherapy may be advised for primary treatment of locally advanced cancers with distant metastases to control ulceration, pain, and other manifestations in the breast and regional nodes. Irradiation of the breast and chest wall and the axillary, internal mammary, and supraclavicular nodes should be undertaken in an attempt to cure locally advanced and inoperable lesions when there is no evidence of distant metastases. A small number of patients in this group are cured in spite of extensive breast and regional node involvement.

Palliative irradiation is of value also in the treatment of certain bone or soft-tissue metastases to control pain or avoid fracture. Radiotherapy is especially useful in the treatment of isolated bony metastases, chest wall recurrences, brain metastases and sometimes, in lieu of the preferred option of orthopedic surgery for acute spinal cord compression.

In addition to radiotherapy, bisphosphonate therapy has shown excellent results in delaying and reducing skeletal events in women with bony metastases. Pamidronate and zoledronic acid are FDA-approved intravenous bisphosphonates given for bone metastases or hypercalcemia of malignancy from breast cancer. Denosumab is FDA-approved for the treatment of bone metastases from breast cancer, with data showing that it reduced the time to first skeletal-related event (eg, pathologic fracture) compared to zoledronic acid.

Caution should be exercised when combining radiation therapy with chemotherapy because toxicity of either or both may be augmented by their concurrent administration. In general, *only one type of therapy should be given at a time* unless it is necessary to irradiate a destructive lesion of weight-bearing bone while the patient is receiving chemotherapy. Systemic therapy should be changed only if the disease is clearly progressing or if intolerable side effects have developed. This is especially difficult to determine for patients with destructive bone metastases, since changes in the status of these lesions are difficult to determine radiographically.

B. Targeted Therapy

1. Hormonally based therapy for metastatic disease—

The following therapies have all been shown to be effective in hormone receptor-positive metastatic breast cancer: administration of medications that block or downregulate estrogen receptors (such as tamoxifen or fulvestrant, respectively) or medications that block the synthesis of hormones (such as AIs); ablation of the ovaries, adrenals, or pituitary; and the administration of hormones (eg, estrogens, androgens, progestins); see Table 17–6. Because

► Palliative Treatment

Palliative treatments are aimed to manage symptoms, improve quality of life, and even prolong survival, without the expectation of achieving cure. Even with cure of the disease not expected, palliative treatments are appropriate for breast cancer metastatic to distant sites. In the United States, it is uncommon to have distant metastases at the time of diagnosis (*de novo* metastases). However, most patients who have a breast cancer recurrence after initial local and adjuvant therapy have metastatic rather than local (in breast) disease. Breast cancer most commonly metastasizes to the liver, lungs, and bone, causing

Table 17–6. Hormonal agents commonly used for management of metastatic breast cancer (listed in alphabetical order).

Medications	Action	Dose, Route, Frequency	Major Side Effects
Anastrozole (Arimidex)	AI	1 mg orally daily	Hot flushes, skin rashes, nausea and vomiting, bone loss
Exemestane (Aromasin)	AI	25 mg orally daily	Hot flushes, increased arthralgia/arthritis, myalgia, bone loss
Fulvestrant (Faslodex)	Steroidal estrogen receptor antagonist	500 mg intramuscularly days 1, 15, 29 and then monthly	Gastrointestinal upset, headache, back pain, hot flushes, pharyngitis, injection site pain
Goserelin (Zoladex)	Synthetic luteinizing hormone releasing analog	3.6 mg subcutaneously monthly	Arthralgias, blood pressure changes, hot flushes, headaches, vaginal dryness, bone loss
Letrozole (Femara)	AI	2.5 mg orally daily	Hot flushes, arthralgia/arthritis, myalgia, bone loss
Leuprorelin (Lupron)	Synthetic luteinizing hormone releasing analog	3.75 or 7.5 mg subcutaneously monthly	Arthralgias, blood pressure changes, hot flushes, headaches, vaginal dryness, bone loss
Megestrol acetate (Megace)	Progestin	40 mg orally four times daily	Fluid retention, venous thromboembolic events; rarely used except in very late stage, treatment-refractory disease
Tamoxifen citrate (Nolvadex)	SERM	20 mg orally daily	Hot flushes, uterine bleeding, thrombophlebitis, rash
Toremifene citrate (Fareston)	SERM	60 mg orally daily	Hot flushes, sweating, nausea, vaginal discharge, dry eyes, dizziness

AI, aromatase inhibitor; SERM, selective estrogen receptor modulator.

only 5–10% of women with ER-negative tumors respond, they should not receive endocrine therapy. Women within 1 year of their last menstrual period are arbitrarily considered to be premenopausal and should have surgical (bilateral oophorectomy) or chemical ovarian ablation (using a gonadotropin-releasing hormone [GnRH] analog such as leuprorelin [Lupron], goserelin [Zoladex], or triptorelin). Premenopausal women who have had chemical or surgical ovarian ablation are then eligible to receive the same hormonally targeted therapies that are available to postmenopausal women. Current guidelines indicate that sequential hormonal therapy is the preferred treatment for hormone receptor-positive metastatic breast cancer except in the rare case when disease is immediately threatening visceral organs.

A. FIRST-LINE TREATMENT OPTIONS—

(1) **Hormonally targeted agents**—Single-agent hormonally targeted therapy options include the pure estrogen receptor antagonist fulvestrant (500 mg intramuscularly days 1 and 15, then every month), tamoxifen (20 mg orally daily), or an AI (anastrozole, letrozole, or exemestane; all oral daily). The average time to progression associated with single agent first-line tamoxifen is 5–8 months and with AI is approximately 8–12 months. The side effect profile of AIs differs from tamoxifen. The main side effects of tamoxifen are nausea, skin rash, and hot flushes. Rarely, tamoxifen induces hypercalcemia in patients with bony metastases. Tamoxifen also increases the risk of venous thromboembolic events and uterine hyperplasia and cancer. The main side effects of AIs include hot flushes, vaginal dryness, and joint stiffness; however, osteoporosis and bone fractures

are significantly higher than with tamoxifen. Results from the phase 3 FALCON study (comparing first-line treatment with fulvestrant to anastrozole) showed that the use of first-line fulvestrant improves progression-free survival by almost 3 months (HR 0.79, 95% CI 0.637, 0.999, $P = 0.0486$) with the largest treatment effect observed in patients without visceral disease. Overall survival data are needed.

(2) **Hormonally targeted therapy plus cyclin dependent kinase inhibition**—Hormonally driven breast cancer may be particularly sensitive to inhibition of cell cycle regulatory proteins, called cyclin dependent kinases (CDK). Studies of three CDK inhibitors (palbociclib 125 mg daily, ribociclib 600 mg daily, and abemaciclib 150 mg twice daily) combined with an endocrine agent (AI or fulvestrant) all demonstrated a median progression-free survival of over 2 years; the longest median progression-free survival reported in metastatic ER-positive breast cancer to date. Similar progression-free survival benefits were achieved with ribociclib in younger women in the phase 3 randomized trial (MONALEESA-7) that exclusively enrolled premenopausal women (treated with goserelin to suppress ovarian function in combination with endocrine therapy). Collectively, clinical trials support the use of a **CDK4/6 inhibitor plus AI as the gold standard treatment in the first-line setting**. Importantly, these therapies yield objective response rates as good as or better than that seen with chemotherapy. All three agents are FDA-approved in the first-line setting in combination with endocrine therapy. Thus far, ribociclib is the only CDK4/6 inhibitor to report an overall survival benefit (in MONALEESA-3 and

MONALEESA-7) when added to endocrine therapy in patients who previously have not received endocrine therapy for metastatic disease (first-line setting). In general, CDK4/6 inhibitors are well tolerated, though monitoring patients for neutropenia (especially with ribociclib and palbociclib) and management of diarrhea (especially with abemaciclib) are necessary. Febrile neutropenia and infections are rare and use of growth factors is not required; however, palbociclib and ribociclib are given for 3 consecutive weeks, stopping for 1 week to allow white cell count to recover. Abemaciclib is given twice daily continuously (28-day cycles).

B. TREATMENT OPTIONS WHEN DISEASE PROGRESSES AFTER HORMONAL-BASED THERAPY

(1) *Fulvestrant plus CDK4/6 inhibitor*—Palbociclib, ribociclib, and abemaciclib have been evaluated in phase 3 trials (PALOMA-3, MONALEESA-3, MONARCH-2, respectively) in patients whose disease has progressed on prior endocrine therapy. All three have shown a significant improvement in median progression-free survival; ribociclib and abemaciclib have shown a significant improvement in overall survival when added to fulvestrant. Palbociclib, ribociclib, and abemaciclib are FDA approved in combination with fulvestrant for this indication and are the gold standard second-line regimen in patients who have not received a CDK4/6 inhibitor in the first-line setting. Abemaciclib is also FDA-approved as a single agent (200 mg orally twice daily) for patients with advanced ER-positive breast cancer who have received prior endocrine therapy and chemotherapy. There is no evidence to date that use of a CDK4/6 inhibitor benefits patients whose disease has progressed after therapy with a CDK4/6 inhibitor. Thus, at this time, use of any CDK4/6 inhibitor after disease progression on a CDK4/6 inhibitor is not appropriate outside of a clinical trial.

(2) *Secondary or tertiary hormonal therapy*—Patients who have disease progression following first-line endocrine-based therapy may be offered a different form of endocrine therapy. For example, if a patient has been treated with an AI as first-line therapy, fulvestrant or tamoxifen should be considered at the time of disease progression as second-line therapy.

(3) *Everolimus plus endocrine therapy*—Everolimus (Afinitor) is an oral inhibitor of the mammalian target of rapamycin (MTOR)—a protein whose activation has been associated with the development of endocrine resistance. A phase 3, placebo-controlled trial (BOLERO-2) evaluated the AI exemestane with or without everolimus in 724 patients with AI-resistant, hormone receptor-positive metastatic breast cancer and found that patients treated with everolimus had a significantly improved progression-free survival (7.8 months vs 3.2 months; HR, 0.45; 95% CI, 0.38–0.54; $P < 0.0001$) but no significant difference in overall survival. Everolimus has also been evaluated in combination with fulvestrant and shown to have similar improvements in progression-free survival compared to single agent fulvestrant. The main side effect of everolimus is stomatitis (mouth sores). This can be avoided, almost completely, by the prophylactic use of oral steroid mouthwash starting with cycle 1.

(4) *Phosphatidylinositol-3-kinase (PI3K) inhibitors plus endocrine therapy*—Approximately 40% of hormone receptor-positive breast cancers have activation of the PI3K-AKT-mTOR pathway, most commonly due to an activating mutation of PI3K on the PIK3CA gene. Alpelisib is FDA-approved for PIK3CA-mutated hormone receptor-positive breast cancer. Side effects of alpelisib include hyperglycemia, diarrhea, rash, and transaminitis.

2. HER2-targeted agents—For patients with HER2-positive tumors, trastuzumab plus chemotherapy significantly improves clinical outcomes, including survival compared to chemotherapy alone. Pertuzumab is an FDA-approved monoclonal antibody that targets the extracellular domain of HER2 at a different epitope than targeted by trastuzumab and inhibits receptor dimerization. Treatment with the combination of pertuzumab, trastuzumab, and docetaxel imparts a significantly longer progression-free and overall survival compared with treatment with docetaxel and trastuzumab and is the first-line gold standard for HER2-positive metastatic breast cancer. Trastuzumab emtansine (ado-trastuzumab emtansine) (Kadcyla) is an FDA-approved novel antibody-drug conjugate in which trastuzumab is stably linked to a derivative of maytansine, enabling targeted delivery of the cytotoxic chemotherapy to HER2-overexpressing cells. Trastuzumab emtansine is the second-line gold standard for HER2-positive metastatic breast cancer based on two phase 3 clinical trials (EMILIA and TH3ERESA) showing improved progression-free and overall survival compared to standard of care therapy.

In addition to pertuzumab, trastuzumab, and trastuzumab emtansine, there are six other HER2-targeted therapies approved for patients who have received two or more prior lines of therapy for advanced stage disease. The FDA-approved antibody-drug conjugate, trastuzumab deruxtecan (DS8201, TDxd), in which an HER2-targeted antibody is linked to a novel toxic payload (topoisomerase-I inhibitor), has demonstrated striking activity in heavily pretreated HER2-positive metastatic breast cancer. In a nonrandomized phase 2 trial (DESTINY-BREAST), the objective response rate was 60.9% and median progression-free survival was 16.4 months. The FDA provided accelerated approval for this medication in 2019. A novel HER2-selective oral tyrosine kinase inhibitor, tucatinib, has also been evaluated for HER2-positive metastatic breast cancer. This medication is of particular interest given its ability to penetrate the blood-brain barrier, potentially improving outcomes for those with brain metastases. A phase 3 trial (HER2CLIMB) compared capecitabine plus trastuzumab plus either tucatinib or placebo in patients with pretreated, HER2-positive advanced disease and demonstrated an improved progression-free survival in the overall population, improved progression-free survival in those with central nervous system metastases and, importantly, a significantly improved overall survival. These data led to the 2020 FDA approval of this agent in combination with trastuzumab and capecitabine. In 2020, the FDA also approved neratinib (in combination with capecitabine) and margetuximab, a monoclonal antibody similar to

trastuzumab that is designed to improve the antibody dependent cellular cytotoxicity mechanism of action when used with chemotherapy. Several other medications targeting *HER2* and its associated signaling pathways are in development, including trastuzumab duocarmazine, *HER2*-targeted bispecific antibodies, and *HER2*-targeted vaccines.

3. Targeting “triple-negative” breast cancer—Breast cancers lacking expression of the hormone receptors ER and PR and of *HER2* behave more aggressively and have traditionally been amenable only to therapy with cytotoxic chemotherapy. However, data support the use of immune modulation in the treatment of breast cancer. A novel therapy (atezolizumab) is FDA-approved for metastatic triple-negative breast cancer that is positive for PD-L1 expression. A phase 3 randomized trial (IMPASSION 130) demonstrated the anti-PD-L1 antibody atezolizumab significantly improved the median progression-free survival in the intent to treat population (7.2 months vs 5.5 months) and in the population with PD-L1-positive tumors (7.5 months vs 5.0 months) when added to nab-paclitaxel. While median overall survival was not significantly improved in the intent to treat population, there was almost a 10-month improvement in overall survival in patients with PD-L1-positive tumors (25.0 months vs 15.5 months). **These are the first results to demonstrate effectiveness of immune modulation therapy in breast cancer and have been practice changing.** In 2020, a second immune checkpoint inhibitor, pembrolizumab, was FDA approved in patients with PD-L1-positive disease in combination with chemotherapy (taxane or gemcitabine/carboplatin) based on results from the KEYNOTE 355 trial showing an improved median progression-free survival with the addition of this antibody to standard chemotherapy. Another therapy garnering attention for triple-negative disease is sacituzumab govitecan, an antibody-drug conjugate that delivers SN-38 (active metabolite of the chemotherapy irinotecan) to Trop-2 overexpressing breast cancer cells. This antibody-drug conjugate has demonstrated significant clinical activity in heavily pretreated triple-negative breast cancer, leading to its accelerated approval by the FDA in 2020. A phase 3 confirmatory trial, ASCENT, reported in 2020 demonstrated that sacituzumab govitecan (TRODELVY) is associated with a statistically significant improvement in progression-free and overall survival when compared to single-agent chemotherapy in patients with triple-negative breast cancer who had received at least two prior lines of standard chemotherapy for metastatic disease, making this the first antibody-drug conjugate approved for triple-negative breast cancer.

4. Targeting PARP in *BRCA1/2* mutation-associated breast cancer—Poly (adenosine diphosphate-ribose) polymerase (PARP) is an enzyme important in single-strand DNA repair. Patients who carry germline mutations in *BRCA1* or *BRCA2* have tumors with deficient double-strand DNA repair mechanisms. Experts have theorized that inhibiting PARP selectively kills *BRCA1/2*-mutated cancers. A phase 3 clinical trial (OlympiAD) that compared olaparib (an oral PARP inhibitor) to treatment

of physician’s choice (single-agent chemotherapy) demonstrated a significantly improved progression-free survival (7.0 months vs 4.2 months, HR 0.58; $P < 0.001$), an improved response rate, and a lower rate of adverse events than standard therapy. Talazoparib, a second PARP inhibitor, has also been shown to improve outcomes similarly in the phase 3 EMBRACA study. Both olaparib and talazoparib are FDA-approved for *BRCA*-mutated metastatic breast cancer as single agents.

C. Palliative Chemotherapy

Cytotoxic medications should be considered for the treatment of metastatic breast cancer (1) if life- or organ-threatening visceral metastases are present (especially brain, liver, or lymphangitic pulmonary), (2) if hormonal treatment is unsuccessful or the disease has progressed after an initial response to hormonal manipulation (for hormone receptor-positive breast cancer), or (3) if the tumor is ER-negative or *HER2*-positive. Prior adjuvant chemotherapy does not seem to alter response rates in patients who relapse. A number of chemotherapy medications (including vinorelbine, paclitaxel, docetaxel, gemcitabine, ixabepilone, carboplatin, cisplatin, capecitabine, albumin-bound paclitaxel, eribulin, and liposomal doxorubicin) may be used as single agents with first-line objective response rates ranging from 30% to 50%.

Combination chemotherapy yields statistically significantly higher response rates and progression-free survival rates, but has not been conclusively shown to improve overall survival rates compared with sequential single-agent therapy. Combinations that have been tested in phase 3 studies and have proven efficacy compared with single-agent therapy include capecitabine/docetaxel, gemcitabine/paclitaxel, and capecitabine/ixabepilone (see Tables 39–3 and 39–13). Various other combinations of medications have been tested in phase 2 studies, and a number of clinical trials are ongoing to identify effective combinations and to evaluate novel oral formulations of chemotherapy. Patients should be encouraged to participate in clinical trials given the number of promising targeted therapies in development. It is generally appropriate to treat willing patients with multiple sequential lines of therapy as long as they tolerate the treatment and as long as their performance status is good (eg, at least ambulatory and able to care for self, up out of bed more than 50% of waking hours).

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25–40% at 10 years. The use of biologic markers, such as ER, PR, grade, and HER2, helps identify high-risk tumor types as well as direct treatment used (see Biomarkers & Gene Expression Profiling). Gene analysis studies can predict disease-free survival for some subsets of patients. The eighth edition of the AJCC Staging Manual has incorporated these factors into staging, resulting in incorporation of biologic factors to predict outcome.

Five-year statistics do not accurately reflect the final outcome of therapy. The mortality rate of breast cancer patients exceeds that of age-matched normal controls for nearly 20 years. Thereafter, the mortality rates are equal, though deaths that occur among breast cancer patients are often directly the result of tumor.

In general, breast cancer appears to be somewhat more aggressive and associated with worse outcomes in younger than in older women, and this may be related to the fact that fewer younger women have ER-positive tumors. Disparities in treatment outcome for different racial and ethnic backgrounds have been reported by several studies. These differences appear to be not only due to different socioeconomic factors (and a resulting difference in access to health care) but also due to differences in the subtype of breast cancer diagnosed.

For those patients whose disease progresses despite treatment, some studies suggest supportive group therapy may improve survival. Especially as they approach the end of life, such patients will require meticulous palliative care (see Chapter 5).

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Follow-Up Care

After primary therapy, patients with breast cancer should be monitored long term in order to detect recurrences and to observe the opposite breast for a second primary carcinoma. Local and distant recurrences occur most frequently within the first 2–5 years, especially for hormone receptor-negative tumors. During the first 2 years, most patients should be examined every 6 months, then annually thereafter. Special attention is paid to the contralateral breast because a new primary breast malignancy will develop in 20–25% of patients. In some cases, especially in hormone receptor-positive breast cancer, metastases are dormant for long periods and may appear 20 years or longer after removal of the primary tumor. Although studies have failed to show an adverse effect of hormonal replacement in disease-free patients, it is rarely used after breast cancer treatment, particularly if the tumor was hormone receptor-positive. Even pregnancy

Table 17–7. Approximate survival of patients with breast cancer by TNM stage.

TNM Stage	5 Years	10 Years
0	95%	90%
I	85%	70%
IIA	70%	50%
IIB	60%	40%
IIIA	55%	30%
IIIB	30%	20%
IV	5–10%	2%
All	65%	30%

has not been associated with shortened survival of patients rendered disease free—yet many oncologists are reluctant to advise a young patient with breast cancer that it is safe to become pregnant. The use of estrogen replacement for conditions such as osteoporosis, vaginal dryness, and hot flushes may be considered for a woman with a history of breast cancer after discussion of the benefits and risks; however, it is not routinely recommended, especially given the availability of nonhormonal agents for these conditions (such as bisphosphonates and denosumab for osteoporosis).

A. Local Recurrence

The incidence of local recurrence correlates with tumor size, the presence and number of involved axillary nodes, the histologic type of tumor, the presence of skin edema or skin and fascia fixation with the primary tumor, and the type of definitive surgery and local irradiation. Local recurrence on the chest wall after total mastectomy and axillary dissection develops in as many as 8% of patients. When the axillary nodes are not involved, the local recurrence rate is less than 5%, but the rate is as high as 25% when they are heavily involved. A similar difference in local recurrence rate is noted between small and large tumors. Factors such as multifocal cancer, *in situ* tumors, lymphovascular invasion, positive resection margins, chemotherapy, and radiotherapy have an effect on local recurrence in patients treated with breast-conserving surgery. Adjuvant systemic therapy greatly decreases the rate of local recurrence. Genomic analysis with identification of high mutation scores also predicts local recurrence.

Chest wall recurrences usually appear within the first several years but may occur as late as 15 or more years after mastectomy. All suspicious nodules and skin lesions should be biopsied. Local excision or localized radiotherapy may be feasible if an isolated nodule is present. If lesions are multiple or accompanied by evidence of regional involvement in the internal mammary or supraclavicular nodes, the disease is best managed by radiation treatment of the entire chest wall including the parasternal, supraclavicular, and axillary areas as well as systemic therapy.

Local recurrence after mastectomy usually signals the presence of widespread disease and is an indication for studies to search for metastases. Distant metastases will develop within a few years in most patients with locally recurrent tumor after mastectomy. When there is no evidence of metastases beyond the chest wall and regional nodes, irradiation for cure after complete local excision should be attempted. After partial mastectomy, local recurrence does not have as serious a prognostic significance as after mastectomy. However, those patients in whom a recurrence develops have a worse prognosis than those who do not. It is speculated that the ability of a cancer to recur locally after radiotherapy is a sign of aggressiveness and resistance to therapy. Completion of the mastectomy should be done for local recurrence after partial mastectomy; some of these patients will survive for prolonged periods, especially if the breast recurrence is DCIS or occurs more than 5 years after initial treatment. Systemic chemotherapy or hormonal treatment should be used for

women in whom disseminated disease develops or those in whom local recurrence occurs. In rare cases, re-irradiation with accelerated partial breast techniques may be effective.

B. Breast Cancer Survivorship Issues

Given that most women with non-metastatic breast cancer will be cured, a significant number of women face survivorship issues stemming from either the diagnosis or the treatment of the breast cancer, or both. These challenges include psychological struggles, cognitive dysfunction (also called “chemo brain”), upper extremity lymphedema, weight management problems, cardiovascular issues, bone loss, postmenopausal side effects, and fatigue. One randomized study reported that survivors who received psychological intervention from the time of diagnosis had a lower risk of recurrence and breast cancer-related mortality. A randomized study in older, overweight cancer survivors showed that diet and exercise reduced the rate of self-reported functional decline compared with no intervention.

1. Edema of the arm—Significant edema of the arm occurs in about 10–30% of patients after axillary dissection with or without mastectomy. It occurs more commonly in obese women, in women who had radiotherapy, and in women who had postoperative infection. Partial mastectomy with radiation to the axillary lymph nodes is followed by chronic edema of the arm in 10–20% of patients. Sentinel lymph node dissection has proved to be an accurate form of axillary staging without the side effects of edema or infection. Judicious use of radiotherapy, with treatment fields carefully planned to spare the axilla as much as possible, can greatly diminish the incidence of edema, which will occur in only 5% of patients if no radiotherapy is given to the axilla after a partial mastectomy and lymph node dissection.

Late or secondary edema of the arm may develop years after treatment, as a result of axillary recurrence or infection in the hand or arm, with obliteration of lymphatic channels. When edema develops, a careful examination of the axilla for recurrence or infection is performed. Infection in the arm or hand on the dissected side should be treated with antibiotics, rest, and elevation. If there is no sign of recurrence or infection, the swollen extremity should be treated with rest and elevation. A mild diuretic may be helpful. If there is no improvement, a compressor pump or manual compression decreases the swelling, and the patient is then fitted with an elastic glove or sleeve. Most patients are not bothered enough by mild edema to wear an uncomfortable glove or sleeve and will treat themselves with elevation or manual compression alone. Rarely, edema may be severe enough to interfere with use of the limb. A prospective randomized study has shown that twice weekly progressive weight lifting improves lymphedema symptoms and exacerbations and improves extremity strength.

2. Breast reconstruction—Breast reconstruction is usually feasible after total or modified radical mastectomy. Reconstruction should be discussed with patients prior to

mastectomy, because it offers an important psychological focal point for recovery. Reconstruction is not an obstacle to the diagnosis of recurrent cancer. The most common breast reconstruction has been implantation of a silicone gel or saline prosthesis in the subpectoral plane between the pectoralis minor and pectoralis major muscles. Alternatively, autologous tissue can be used for reconstruction.

Autologous tissue flaps have the advantage of not feeling like a foreign body to the patient. The most popular autologous technique currently is reconstruction using abdominal tissue flaps. This includes the deep inferior epigastric perforator (DIEP) flap and the more traditional transrectus abdominis muscle (TRAM) flap. A latissimus dorsi flap can be swung from the back but offers less volume than the TRAM flap and thus often requires supplementation with an implant. Reconstruction may be performed immediately (at the time of initial mastectomy) or may be delayed until later, usually when the patient has completed adjuvant therapy. When considering reconstructive options, concomitant illnesses should be considered, since the ability of an autologous flap to survive depends on medical comorbidities. In addition, the need for radiotherapy may affect the choice of reconstruction as radiation may increase fibrosis around an implant or decrease the volume of a flap. Skin-sparing and nipple-sparing mastectomies with immediate reconstruction, when feasible, may afford superior cosmetic outcomes.

3. Risks of pregnancy—Clinicians are often asked to advise patients regarding the potential risk of future pregnancy after definitive treatment for early-stage breast cancer. *To date, no adverse effect of pregnancy on survival of women who have had breast cancer has been demonstrated.* When counseling patients, oncologists must take into consideration the patients' overall prognosis, age, comorbidities, and life goals.

In patients with inoperable or metastatic cancer (stage IV disease), induced abortion may be advisable because of the possible adverse effects of hormonal treatment, radiotherapy, or chemotherapy upon the fetus in addition to the expectant mother's poor prognosis.

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CARCINOMA OF THE MALE BREAST



ESSENTIALS OF DIAGNOSIS

- ▶ A painless lump beneath the areola in a man usually over 50 years of age.
- ▶ Nipple discharge, retraction, or ulceration may be present.
- ▶ Generally poorer prognosis than in women.

General Considerations

Breast cancer in men is a rare disease; the incidence is only about 1% of all breast cancer diagnoses. The average age at occurrence is about 70 years, and there may be an increased incidence of breast cancer in men with prostate cancer. As in women, hormonal influences are probably related to the development of male breast cancer. There is a high incidence of both breast cancer and gynecomastia in Bantu men, theoretically owing to failure of estrogen inactivation by associated liver disease. It is important to note that first-degree relatives of men with breast cancer are considered to be at high risk. This risk should be taken into account when discussing options with the patient and family. In addition, *BRCA2* mutations are common in men with breast cancer. Men with breast cancer, especially with a history of prostate cancer, should receive genetic counseling.

Clinical Findings

A painless lump, occasionally associated with nipple discharge, retraction, erosion, or ulceration, is the primary complaint. Examination usually shows a hard, ill-defined, nontender mass beneath the nipple or areola. Gynecomastia not uncommonly precedes or accompanies breast cancer in men. Nipple discharge is an uncommon presentation for breast cancer in men but is an ominous finding associated with carcinoma in nearly 75% of cases.

Breast cancer staging is the same in men as in women. Gynecomastia and metastatic cancer from another site (eg, prostate) must be considered in the differential diagnosis. Benign tumors are rare, and biopsy should be performed on all males with a defined breast mass.

Treatment

Treatment consists of modified radical mastectomy in operable patients, who should be chosen by the same criteria as women with the disease. Breast conserving therapy remains underutilized. Irradiation is the first step in treating localized metastases in the skin, lymph nodes, or skeleton that are causing symptoms. Examination of the cancer for hormone receptors and *HER2* overexpression is of value in determining adjuvant therapy. Over 95% of men have ER-positive tumors and less than 10% have overexpression of *HER2*. Androgen receptor is also commonly overexpressed in male breast cancer, though this does not

impact systemic therapy decisions. Adjuvant systemic therapy and radiation are used for the same indications as in breast cancer in women.

Because breast cancer in men is frequently hormone receptor positive, diagnosed late, and is a disseminated disease, endocrine therapy is of considerable importance in its management. Tamoxifen is the main medication for management of advanced breast cancer in men. Tamoxifen (20 mg orally daily) should be the initial treatment. There are few data regarding the use of AIs in men, but they are being used more frequently. Castration in advanced breast cancer is a successful measure and more beneficial than the same procedure in women but is rarely used. Objective evidence of regression may be seen in 60–70% of men with endocrine therapy for metastatic disease—approximately twice the proportion in women. Bone is the most frequent site of metastases from breast cancer in men (as in women), and endocrine therapy relieves bone pain in most patients so treated. The longer the interval between mastectomy and recurrence, the longer is the remission following treatment.

Chemotherapy should be administered for the same indications and using the same dosage schedules as for women with metastatic disease or for adjuvant treatment.

► Prognosis

A large population-based, international breast cancer study reported that after adjustment for prognostic features (age, stage, treatment), men have a similar relative survival stage for stage compared to women. For node-positive disease, 5-year survival is approximately 69%, and for node-negative disease, it is about 88%.

For those patients whose disease progresses despite treatment, meticulous efforts at palliative care are essential (see Chapter 5).

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18

Gynecologic Disorders

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PREMENOPAUSAL ABNORMAL UTERINE BLEEDING



ESSENTIALS OF DIAGNOSIS

- ▶ Accurate diagnosis of abnormal uterine bleeding (AUB) depends on appropriate categorization and diagnostic tests.
- ▶ The evaluation of AUB depends on the age and risk factors of the patient.
- ▶ Pregnancy should always be ruled out as a cause of AUB in reproductive age women.

► General Considerations

Normal menstrual frequency varies individually from 24 to 38 days with bleeding lasting an average of 5 days (range, 2–8 days), with a mean blood loss of 40 mL per cycle. AUB refers to menstrual bleeding of abnormal quantity, duration, or schedule. The International Federation of Gynecology and Obstetrics (FIGO) introduced the current classification system for AUB in 2011, which was then endorsed by the American College of Obstetrics and Gynecology. This classification system pairs AUB with descriptive terms denoting the bleeding pattern (ie, **heavy**, **light** and **menstrual**, **intermenstrual**) and etiology (the acronym PALM-COEIN standing for Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not yet classified). In adolescents, AUB often occurs as a result of persistent **anovulation** due to the immaturity of the hypothalamic-pituitary-ovarian axis. Once regular menses have been established during adolescence, **ovulatory dysfunction** AUB (AUB-O) accounts for most cases. AUB in women aged 19–39 years is often a result of pregnancy,

structural lesions, anovulatory cycles, use of hormonal contraception, or endometrial hyperplasia.

► Clinical Findings

A. Symptoms and Signs

The diagnosis depends on the following: (1) confirming uterine source of the bleeding; (2) excluding pregnancy and confirming patient is premenopausal; (3) ascertaining whether the bleeding pattern suggests regular ovulatory bleeding or anovulatory bleeding; (4) determining contribution of structural abnormalities (PALM), including risk for malignancy/hyperplasia; (5) identifying risk of medical conditions that may impact bleeding (eg, inherited bleeding disorders, endocrine disease, risk of infection); and (6) assessing contribution of current medications, including contraceptives or natural product supplements or combinations that may affect bleeding.

B. Laboratory Studies

A complete blood count, pregnancy test, and thyroid tests should be done. For adolescents with heavy menstrual bleeding and adults with a positive screening history, coagulation studies should be considered, since up to 18% of women with severe heavy menstrual bleeding have an underlying coagulopathy. Vaginal or urine samples should be obtained for polymerase chain reaction (PCR) or culture to rule out infectious causes. If indicated, cervical cytology should also be obtained.

C. Imaging

Transvaginal ultrasound is useful to assess for presence of fibroids, suspicion of adenomyosis, and to evaluate endometrial thickness. Sonohysterography or hysteroscopy may be used to diagnose endometrial polyps or subserous myomas. MRI is not a primary imaging modality for AUB but can more definitively diagnose submucous myomas and adenomyosis.

D. Endometrial Sampling

The purpose of endometrial sampling is to determine if hyperplasia or carcinoma is present. Sampling methods

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Table 18–1. Common gynecologic diagnostic procedures.

Colposcopy
Visualization of cervical, vaginal, or vulvar epithelium under 5–50 × magnification with and without dilute acetic acid to identify abnormal areas requiring biopsy. An office procedure.
Dilation & curettage (D&C)
Dilation of the cervix and curettage of the entire endometrial cavity, using a metal curette or suction cannula and often using forceps for the removal of endometrial polyps. Can usually be done in the office under local anesthesia or in the operating room under sedation or general anesthesia. D&C is often combined with hysteroscopy for improved sensitivity.
Endometrial biopsy
Blind sampling of the endometrium by means of a curette or small aspiration device without cervical dilation. Diagnostic accuracy similar to D&C. An office procedure performed with or without local anesthesia.
Endocervical curettage
Removal of endocervical epithelium with a small curette for diagnosis of cervical dysplasia and cancer. An office procedure performed with or without local anesthesia.
Hysterosalpingography
Injection of radiopaque dye through the cervix to visualize the uterine cavity and oviducts. Mainly used in investigation of infertility or to identify a space-occupying lesion.
Hysteroscopy
Visual examination of the uterine cavity with a small fiberoptic endoscope passed through the cervix. Curettage, endometrial ablation, biopsies of lesions, and excision of myomas or polyps can be performed concurrently. Can be done in the office under local anesthesia or in the operating room under sedation or general anesthesia. Greater sensitivity for diagnosis of uterine pathology than D&C.
Laparoscopy
Visualization of the abdominal and pelvic cavity through a small fiberoptic endoscope passed through a subumbilical incision. Permits diagnosis, tubal sterilization, and treatment of many conditions previously requiring laparotomy. General anesthesia is used.
Saline infusion sonohysterography
Introduction of saline solution into endometrial cavity with a catheter to visualize submucous myomas or endometrial polyps by transvaginal ultrasound. May be performed in the office with oral or local analgesia, or both.

and other gynecologic diagnostic procedures are described in Table 18–1. Polyps, endometrial hyperplasia and, occasionally, submucous myomas are identified on endometrial biopsy. Endometrial sampling should be performed in patients with AUB who are 45 years and older, or in younger patients with a history of unopposed estrogen exposure (including obesity or chronic ovulatory dysfunction) or failed medical management and persistent AUB.

► Treatment

Treatment for premenopausal patients with AUB depends on the etiology of the bleeding, determined by history, physical examination, laboratory findings, imaging, and endometrial sampling. Patients with AUB due to

submucosal myomas, thrombophilia, or pelvic (endometrial) neoplasms may require targeted therapy. A large proportion of premenopausal patients, however, have ovulatory dysfunction AUB (AUB-O).

Treatment for AUB-O should include consideration of potentially contributing medical conditions, such as thyroid dysfunction. Often AUB-O can be treated hormonally. For women amenable to using contraceptives, estrogen-progestin contraceptives and the 52-mg levonorgestrel-releasing intrauterine device (IUD) are both effective treatments. The choice between the two depends on whether any contraindications to these treatments exist as well as patient preference. High-dose oral or injectable progestin-only medications are also generally effective, but there is little consensus on optimal regimens, and they appear to be less effective than other medical therapies like the levonorgestrel IUD and tranexamic acid. Nonhormonal options include nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen or mefenamic acid, in the usual anti-inflammatory doses taken during menses, and tranexamic acid 1300 mg three times per day orally for up to 5 days. Both have been shown to decrease menstrual blood loss by about 40%, with tranexamic acid superior to NSAIDs in direct comparative studies.

Women who are experiencing heavier bleeding can be given a taper of any of the combination oral contraceptives (with 30–35 mcg of estrogen estradiol) to control the bleeding. There are several commonly used contraceptive dosing regimens, including three times daily for 1 or 2 days followed by two pills daily through day 5 and then one pill daily through day 20; after withdrawal bleeding occurs, pills are taken in the usual dosage for three cycles. In cases of heavy bleeding requiring hospitalization, intravenous conjugated estrogens, 25 mg every 4 hours for three or four doses, can be used to stop acute bleeding. This can be followed by oral conjugated estrogens, 2.5 mg daily, or ethinyl estradiol, 20 mcg orally daily, for 3 weeks, with the addition of medroxyprogesterone acetate, 10 mg orally daily for the last 10 days of treatment, or a combination oral contraceptive daily for 3 weeks. This will stabilize the endometrium and control the bleeding.

For women with ineffective results from medical management or who do not desire medical management, surgical options can be considered. Heavy menstrual bleeding due to structural lesions (eg, fibroids, adenomyosis, polyps) is the most common indication for surgery. Minimally invasive procedural options for fibroids include uterine artery embolization and focused ultrasound ablation. Surgical options include myomectomy or hysterectomy. For adenomyosis, the definitive treatment is hysterectomy. Polyps can often be excised hysteroscopically. For women without structural abnormalities, endometrial ablation has similar results compared to the levonorgestrel-releasing IUD in reducing menstrual blood loss. Hysteroscopic surgical approaches include endometrial ablation with laser photocoagulation or electrocautery. Nonhysteroscopic techniques include balloon thermal ablation, cryoablation, free-fluid thermal ablation, impedance bipolar radiofrequency ablation, and microwave ablation. The latter methods are well-adapted to outpatient therapy under local

anesthesia. While hysterectomy was used commonly in the past for bleeding unresponsive to medical therapy, the low risk of complications and the good short-term results of both endometrial ablation and levonorgestrel-releasing IUD make them attractive alternatives to hysterectomy.

► When to Refer

- If bleeding is not controlled with first-line therapy.
- If expertise is needed for a surgical procedure.

► When to Admit

If bleeding is uncontrollable with first-line therapy or the patient is not hemodynamically stable.

Bofill Rodriguez M et al. Cyclical progestogens for heavy menstrual bleeding. Cochrane Database Syst Rev. 2019;8:CD001016. [PMID: 31425626]

Bryant-Smith AC et al. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2018;4:CD000249. [PMID: 29656433]

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Singh S et al. SOGC Clinical Practice Guideline No. 292. Abnormal uterine bleeding in pre-menopausal women. J Obstet Gynaecol Can. 2018;40:e391. [PMID: 29731212]

Wouk N et al. Abnormal uterine bleeding in premenopausal women. Am Fam Physician. 2019;99:435. [PMID: 30932448]

used to measure endometrial thickness. An endometrial stripe measurement of 4 mm or less indicates a low likelihood of hyperplasia or endometrial cancer. If the endometrial thickness is greater than 4 mm, endometrial sampling is indicated. If there is focal thickening of the endometrium on ultrasound or persistent bleeding despite negative results on endometrial biopsy, guided sampling with hysteroscopy is more appropriate than random endometrial sampling.

► Treatment

Management options for simple endometrial hyperplasia without atypia include surveillance, oral contraceptives, or progestin therapy. Surveillance may be used if the risk of occult cancer or progression to cancer is low and the inciting factor (eg, anovulation) has been eliminated. Progestin therapy may include cyclic or continuous therapy (medroxyprogesterone acetate, 10–20 mg/day orally, or norethindrone acetate, 15 mg/day orally) or the use of a levonorgestrel-releasing IUD. Repeat sampling should be performed if symptoms recur. For complex hyperplasia without atypia, options include progestin therapy with scheduled repeat endometrial sampling or hysterectomy. Hysterectomy is indicated for endometrial hyperplasia with atypia (also called endometrial intraepithelial neoplasia) or carcinoma of the endometrium.

► When to Refer

- Expertise in performing ultrasonography is required.
- Endometrial hyperplasia with atypia is present.
- Hysteroscopy is indicated.

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LEIOMYOMA OF THE UTERUS (Fibroid Tumor)

ESSENTIALS OF DIAGNOSIS

- Irregular enlargement of the uterus (may be asymptomatic).
- Heavy or irregular uterine bleeding.
- Pelvic pain, dysmenorrhea, and pressure.

► General Considerations

Menopause is defined as 1 year without menstrual bleeding. The most common causes of postmenopausal bleeding are endometrial atrophy, endometrial proliferation or hyperplasia, endometrial or cervical cancer, and administration of estrogens without or with added progestin. Other causes include atrophic vaginitis, trauma, endometrial polyps, abrasion of the cervix associated with prolapse of the uterus, and blood dyscrasias.

► Diagnosis

The vulva and vagina should be inspected for areas of bleeding, ulcers, or neoplasms. Cervical cytology should be obtained, if indicated. Transvaginal sonography should be

Uterine leiomyomas are the most common benign neoplasm of the female genital tract. They are discrete, round, firm, often multiple, uterine tumors composed of smooth muscle and connective tissue. The most convenient classification is by anatomic location: (1) intramural, (2)

submucous, (3) subserous, and (4) cervical. Submucous myomas may become pedunculated and descend through the cervix into the vagina.

► Clinical Findings

A. Symptoms and Signs

In nonpregnant women, myomas are frequently asymptomatic. The two most common symptoms of uterine leiomyomas for which women seek treatment are AUB and pelvic pain or pressure. Occasionally, degeneration occurs, causing intense pain. Myomas that significantly distort the uterine cavity may affect pregnancy by interfering with implantation, rapidly distending in early pregnancy, or impairing uterine contractility postpartum.

B. Laboratory Findings

Iron deficiency anemia may result from blood loss.

C. Imaging

Ultrasonography will confirm the presence of uterine myomas and can be used sequentially to monitor growth. MRI can delineate intramural and submucous myomas accurately and is typically used prior to uterine artery embolization to determine fibroid size and location in relation to uterine blood supply. Hysterography or hysteroscopy can also confirm cervical or submucous myomas.

► Differential Diagnosis

Irregular myomatous enlargement of the uterus must be differentiated from the similar, but symmetric enlargement that may occur with pregnancy or adenomyosis. Subserous myomas must be distinguished from ovarian tumors. Leiomyosarcoma is an unusual tumor occurring in 0.5% of women operated on for symptomatic myomas. It is very rare under the age of 40 but increases in incidence thereafter.

► Treatment

A. Nonsurgical Measures

Women who have small asymptomatic myomas can be managed expectantly and evaluated annually. In patients wishing to defer surgical management, nonhormonal therapies (such as NSAIDs and tranexamic acid) have been shown to decrease menstrual blood loss. Women with heavy bleeding related to fibroids may respond to estrogen-progestin oral contraceptives or the levonorgestrel IUD, although an IUD cannot be used with a distorted cavity. Hormonal therapies, such as GnRH agonists, GnRH antagonists, and selective progesterone receptor modulators (eg, low-dose mifepristone and ulipristal acetate), have been shown to reduce myoma volume, uterine size, and menstrual blood loss. However, ulipristal acetate was withdrawn from the market in the European Union and Canada as of September 2020 due to rare reports of serious drug-induced liver injury. Additionally, selective progesterone receptor modulators are not approved for fibroid treatment in the United States.

B. Surgical Measures

Surgical intervention is based on the patient's symptoms, desire for future fertility or uterine preservation, and long-term treatment goals. A variety of surgical measures are available for the treatment of myomas: myomectomy (hysteroscopic, laparoscopic, or abdominal) and hysterectomy (vaginal, laparoscopy-assisted vaginal, laparoscopic, abdominal, or robotic). Submucous myomas may be amenable to hysteroscopic resection. Myomectomy is the surgical treatment of choice for women who wish to preserve fertility.

Because the risk of surgical complications increases with the increasing size of the myoma, preoperative reduction of myoma size is sometimes desirable prior to hysterectomy. GnRH analogs, such as depot leuprolide, 3.75 mg intramuscularly monthly, can be used preoperatively for 3- to 4-month periods to temporarily reduce the size of myomas and surrounding vascularity. GnRH analogs also can be used as a bridge to surgery in patients who are anemic. By stopping menses, patients may improve their hemoglobin level, perhaps decreasing their need for blood transfusion perioperatively.

Uterine artery embolization is a minimally invasive treatment for uterine fibroids. In uterine artery embolization, the goal is to block the blood vessels supplying the fibroids, causing them to shrink. Magnetic resonance-guided high-intensity focused ultrasound, myolysis/radiofrequency ablation, and laparoscopic or vaginal occlusion of uterine vessels are newer interventions with a smaller body of evidence.

► Prognosis

In women desiring future fertility, myomectomy can be offered, but patients should be counseled that recurrence is common, postoperative pelvic adhesions may impact fertility, and cesarean delivery may be necessary secondary to disruption of the myometrium. Approximately 80% of women have long-term improvement in symptoms following uterine artery embolization. Definitive surgical therapy (ie, hysterectomy) is curative.

► When to Refer

Refer to a gynecologist for treatment of symptomatic leiomyomata.

► When to Admit

For acute abdomen associated with an infarcted leiomyoma or for hemorrhage not controlled by outpatient measures.

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Chudnoff S et al. Ultrasound-guided transcervical ablation of uterine leiomyomas. Obstet Gynecol 2019;133:13. [PMID: 30531573]

Donnez J et al. The current place of medical therapy in uterine fibroid management. Best Pract Res Clin Obstet Gynaecol. 2018;46:57. [PMID: 29169896]

Manyonda I et al; FEMME Collaborative Group. Uterine-artery embolization or myomectomy for uterine fibroids. N Engl J Med. 2020;383:440. [PMID: 32726530]

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CERVICAL POLYPS



ESSENTIALS OF DIAGNOSIS

- ▶ Irregular or postcoital bleeding.
- ▶ Polyps visible in the cervical os on speculum examination.

► Clinical Findings

Cervical polyps commonly occur during the reproductive years, particularly after age 40, and are occasionally noted in postmenopausal women. The cause is not known, but inflammation may play an etiologic role. The principal symptoms are discharge and abnormal vaginal bleeding. However, abnormal bleeding should not be ascribed to a cervical polyp without sampling the endocervix and endometrium. The polyps are visible in the cervical os on speculum examination.

Cervical polyps must be differentiated from polypoid neoplastic disease of the endometrium, small submucous pedunculated myomas, large nabothian cysts, and endometrial polyps. Cervical polyps rarely contain foci of dysplasia (0.5%) or of malignancy (0.5%). Asymptomatic polyps in women under age 45 may be left untreated.

► Treatment

Cervical polyps can generally be removed in the office by avulsion with uterine packing forceps or ring forceps.

► When to Refer

- Polyp with a wide base.
- Inability to differentiate endocervical from endometrial polyp.

Budak A et al. Role of endometrial sampling in cases with asymptomatic cervical polyps. *J Gynecol Obstet Hum Reprod*. 2019;48:207. [PMID: 30660657]

PELVIC PAIN



ESSENTIALS OF DIAGNOSIS

- ▶ Determine if pain is acute or chronic.
- ▶ Categorize if pain is cyclic or continuous.
- ▶ Consider nongynecologic causes.

1. Primary Dysmenorrhea

Primary dysmenorrhea is menstrual pain associated with menstrual cycles in the absence of pathologic findings. Primary dysmenorrhea usually begins within 1–2 years after menarche and may become progressively more severe. The frequency of cases increases up to age 20 and then decreases with both increasing age and parity. Fifty percent to 75% of women are affected by dysmenorrhea at some time and 5–6% have incapacitating pain.

► Clinical Findings

Primary dysmenorrhea is low, midline, wave-like, cramping pelvic pain often radiating to the back or inner thighs. Cramps may last for 1 or more days and may be associated with nausea, diarrhea, headache, and flushing. The pain is produced by uterine vasoconstriction, anoxia, and sustained contractions mediated by prostaglandins. The pelvic examination is normal between menses; examination during menses may produce discomfort, but there are no pathologic findings.

► Treatment

NSAIDs (ibuprofen, ketoprofen, mefenamic acid, naproxen) and the cyclooxygenase (COX)-2 inhibitor (celecoxib) are generally helpful. The medication should be started 1–2 days before expected menses. Symptoms can be suppressed with use of combined hormonal contraceptives, depot-medroxyprogesterone acetate (DMPA), etonogestrel subdermal implant (Nexplanon), or the levonorgestrel-releasing IUD. Oral contraceptives taken continuously can be used to suppress menstruation completely and prevent dysmenorrhea. Other therapies that have shown some benefit include local heat, thiamine 100 mg/day orally, vitamin E 200 units/day orally, and high-frequency transcutaneous electrical nerve stimulation around the time of menses. These options may be offered to patients who desire nonhormonal therapy, although they have less supporting evidence.

2. Endometriosis

Endometriosis is an aberrant growth of endometrium outside of the uterus, particularly in the dependent parts of the pelvis and in the ovaries. Its principal manifestations are chronic pain and infertility. While retrograde menstruation is the most widely accepted cause, its pathogenesis and natural course are not fully understood. The overall prevalence in the United States is 6–10%.

► General Considerations

The clinical manifestations of endometriosis are variable and unpredictable in both presentation and course. Dysmenorrhea, chronic pelvic pain, and dyspareunia are among the well-recognized symptoms. A significant number of women with endometriosis, however, remain asymptomatic, and most women with endometriosis have a normal pelvic examination. However, in some women,

pelvic examination can disclose tender nodules in the cul-de-sac or rectovaginal septum, uterine retroversion with decreased uterine mobility, uterine tenderness, or adnexal mass or tenderness.

Endometriosis must be distinguished from pelvic inflammatory disease (PID), ovarian neoplasms, and uterine myomas. Bowel invasion by endometrial tissue may produce blood in the stool that must be distinguished from that produced by bowel neoplasm.

Imaging is useful mainly in the presence of a pelvic or adnexal mass. Transvaginal ultrasonography is the imaging modality of choice to detect the presence of deeply penetrating endometriosis of the rectum or rectovaginal septum; MRI should be reserved for equivocal cases of rectovaginal or bladder endometriosis. A definitive diagnosis of endometriosis is made only by histology of lesions removed at surgery.

► Treatment

A. Medical Treatment

Although there is no conclusive evidence that NSAIDs improve the pain associated with endometriosis, these agents are a reasonable option in appropriately selected patients. Medical treatment, using a variety of hormonal therapies, is effective in the amelioration of pain associated with endometriosis. Most of these regimens are designed to inhibit ovulation over 4–9 months and to lower hormone levels, thus preventing cyclic stimulation of endometriotic implants and inducing atrophy. The optimum duration of hormonal therapies is not clear, and their relative merits in terms of side effects and long-term risks and benefits show insignificant differences when compared with one another and even, in mild cases, with placebo. Commonly used medical regimens include the following:

1. Combined hormonal (estrogen-progestin) contraceptives are first-line treatment because they suppress ovulation, which may inhibit stimulation of endometriosis. Any of the combination oral contraceptives, the contraceptive patch, or the vaginal ring may be used continuously, which is preferred for treatment of endometriosis. Breakthrough bleeding can be treated with conjugated estrogens, 1.25 mg orally daily for 1 week, or estradiol, 2 mg daily orally for 1 week. Alternatively, a short hormone-free interval to allow a withdrawal bleed can be used whenever bothersome breakthrough bleeding occurs.
2. Progestins, specifically oral norethindrone acetate and subcutaneous DMPA, have been approved by the FDA for treatment of endometriosis-associated pain. The etonogestrel implant has also been shown to decrease endometriosis-related pain.
3. Intrauterine progestin, using the levonorgestrel-releasing IUD, has been shown to be effective in reducing endometriosis-associated pelvic pain and should be considered before surgery.
4. GnRH agonists are highly effective in reducing pain associated with endometriosis; however, they are not superior to other methods such as combined hor-

monal contraceptives as first-line therapy. The GnRH analog (such as long-acting injectable leuproide acetate, 3.75 mg intramuscularly monthly, used for 6 months) suppresses ovulation. Side effects of vasomotor symptoms and bone demineralization may be relieved by “add-back” therapy, such as conjugated equine estrogen, 0.625 mg orally daily, or norethindrone, 5 mg orally daily.

5. Danazol is an androgenic medication that has been used for the treatment of endometriosis-associated pain. It may be used for 4–6 months in the lowest dose necessary to suppress menstruation, usually 200–400 mg orally twice daily. However, danazol has a high incidence of androgenic side effects, including decreased breast size, weight gain, acne, and hirsutism, that are more severe than with other medications available.
6. Aromatase inhibitors (such as anastrozole or letrozole) in combination with conventional therapy have been evaluated with positive results in premenopausal women with endometriosis-associated pain and pain recurrence.
7. GnRH antagonists suppress pituitary gonadotropin production and create a hypoestrogenic state, like GnRH agonists, but they are effective immediately rather than requiring 7–14 days for GnRH suppression. Injectable and oral forms (eg, cetrorelix and elagolix, respectively) are available.

B. Surgical Measures

Surgical treatment of endometriosis—particularly extensive disease—is effective both in reducing pain and in promoting fertility. Laparoscopic ablation of endometrial implants significantly reduces pain. Ablation of implants and, if necessary, removal of ovarian endometriomas enhance fertility, although subsequent pregnancy rates are inversely related to the severity of disease. Women with disabling pain for whom childbearing is not a consideration can be treated definitively with hysterectomy plus bilateral salpingo-oophorectomy. In premenopausal women, hormone replacement may then be used to relieve vasomotor symptoms.

► Prognosis

There is little systematic research regarding either the progression of the disease or the prediction of clinical outcomes. The prognosis for reproductive function in early or moderately advanced endometriosis appears to be good with conservative therapy. Hysterectomy, with bilateral salpingo-oophorectomy, often is regarded as definitive treatment of endometriosis associated with intractable pelvic pain, adnexal masses, or multiple previous ineffective conservative surgical procedures. However, symptoms may recur even after hysterectomy and oophorectomy.

► When to Refer

Refer to a gynecologist for laparoscopic diagnosis or surgical treatment.

► When to Admit

Rarely necessary except for acute abdomen associated with ruptured or bleeding endometrioma.

3. Other Etiologies of Pelvic Pain

Additional causes of pelvic pain may include adenomyosis, fibroids, PID, malpositioned IUD, or other abnormalities of the pelvic organs, including the bowel or bladder.

► Clinical Findings

The history may be suggestive of the causes mentioned above. Physical examination may be useful to narrow the differential diagnosis.

► Diagnosis

Targeted physical examination may help identify the anatomic source of pelvic pain. PID should be considered in sexually active women with pelvic pain and examination findings of cervical motion tenderness, uterine, or adnexal tenderness without another explanation for the pain. Pelvic imaging is useful for diagnosing the presence of uterine fibroids or other anomalies. Adenomyosis (the presence of endometrial glands and stroma within the myometrium) may be detected with ultrasound or MRI. Laparoscopy may help diagnose endometriosis or other pelvic abnormalities not visualized by imaging.

► Treatment

Treatment should be directed at the underlying cause. For example, PID should be treated with antibiotics as described below. If pain symptoms are marked or prolonged or unresponsive to medical management, diagnostic laparoscopy may be warranted. Definitive surgery depends on the intra-operative findings and the underlying etiology. For example, adenomyosis may respond to the levonorgestrel-releasing IUD, uterine artery embolization, or hormonal approaches used to treat endometriosis, but if those are unsuccessful, hysterectomy remains the definitive treatment of choice for women for whom childbearing is not a consideration.

► When to Refer

- Standard therapy fails to relieve pain.
- Suspicion of pelvic pathology, such as endometriosis, leiomyomas, adenomyosis, or PID.

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Singh SS et al. Surgical outcomes in patients with endometriosis: a systematic review. *J Obstet Gynaecol Can*. 2020;42:881. [PMID: 31718952]

Vilasarag S et al. A practical guide to the clinical evaluation of endometriosis-associated pelvic pain. *J Minim Invasive Gynecol*. 2020;27:270. [PMID: 31669551]

PELVIC ORGAN PROLAPSE

► General Considerations

Pelvic organ prolapse, including cystocele, rectocele, and enterocele, are vaginal hernias commonly seen in multiparous women. **Cystocele** is a hernia of the bladder wall into the vagina, causing a soft anterior fullness. Cystocele may be accompanied by **urethrocele**, which is not a hernia but a sagging of the urethra following its detachment from the pubic symphysis during childbirth. **Rectocele** is a herniation of the terminal rectum into the posterior vagina, causing a collapsible pouch-like fullness. **Enterocèle** is a vaginal vault hernia containing small intestine, usually in the posterior vagina and resulting from a deepening of the pouch of Douglas. Two or all three types of hernia may occur in combination. The cause of pelvic organ prolapse is multifactorial. Risk factors include vaginal birth, genetic predisposition, advancing age, prior pelvic surgery, connective tissue disorders, and increased intra-abdominal pressure associated with obesity or straining associated with chronic constipation or coughing.

► Clinical Findings

Symptoms of pelvic organ prolapse may include a sensation of a bulge or protrusion in the vagina, urinary or fecal incontinence, constipation, sense of incomplete bladder or bowel emptying, and dyspareunia.

► Treatment

Treatment depends on the extent of prolapse; associated symptoms; impact on the patient's quality of life; the patient's age; and her desire for menstruation, pregnancy, and coitus.

A. General Measures

Supportive measures include a high-fiber diet and laxatives to improve constipation. Weight reduction in obese patients and limitation of straining and lifting are helpful. Pelvic muscle training (Kegel exercises) is a simple, noninvasive intervention that may improve pelvic function; it has demonstrated clear benefit for women with urinary or fecal symptoms, especially incontinence. Pessaries may reduce a

cystocele, rectocele, or enterocele and are helpful in women who do not wish to undergo surgery or who are poor surgical candidates.

B. Surgical Measures

The most common surgical procedure is vaginal or abdominal hysterectomy with additional attention to restoring apical support after the uterus is removed, with suspension either by vaginal uterosacral, sacrospinous fixation, or by abdominal sacral colpopexy. Since stress urinary incontinence and urinary retention may coexist with apical prolapse, women should be evaluated for these conditions prior to surgery. An anti-incontinence procedure may be done in conjunction with prolapse surgery if indicated. Surgical mesh placed transvaginally for pelvic organ prolapse repair was introduced into clinical practice in 2002, but in 2011 the FDA issued warnings about concerns for serious complications associated with this practice (including mesh erosion and pain). Use of these methods subsequently declined significantly. In April 2019, the US FDA withdrew its approval of surgical mesh for the indication of transvaginal repair of anterior compartment prolapse. Patients planning to have surgical repair of pelvic organ prolapse should discuss all treatment options with their clinician. Women who have received transvaginal mesh for the surgical repair of pelvic organ prolapse but who have no associated symptoms or complications should continue with their annual check-ups and other routine follow-up care. They should let their clinician know that they have a surgical mesh implant, especially if they plan to have another pelvic surgery or related medical procedure. In addition, they should notify their clinician if they develop symptoms such as persistent vaginal bleeding or discharge, pelvic or groin pain, or dyspareunia.

If a woman with symptomatic prolapse desires pregnancy, the same procedures for vaginal suspension can be performed without hysterectomy, though limited data on pregnancy outcomes or prolapse outcomes are available. Generally, surgical repair of pelvic organ prolapse is reserved until after completion of childbearing. For elderly women who do not desire coitus, colpocleisis, the partial obliteration of the vagina, is an effective and straightforward procedure. Uterine suspension with sacrospinous cervicocolpopexy may be an effective approach in older women who wish to avoid hysterectomy but preserve coital function.

► When to Refer

- Refer to urogynecologist or gynecologist for incontinence evaluation.
- Refer if nonsurgical therapy is ineffective.
- Refer for removal of mesh if symptoms develop.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 214: Pelvic organ prolapse. *Obstet Gynecol*. 2019;134:e126. [PMID: 31651832]

Carter P et al. Management of mesh complications following surgery for stress urinary incontinence or pelvic organ prolapse: a systematic review. *BJOG*. 2020;127:28. [PMID: 31541614]

Gluck O et al. Laparoscopic sacrocolpopexy: a comprehensive literature review on current practice. *Eur J Obstet Gynecol Reprod Biol*. 2020;245:94. [PMID: 31891897]

Hemming C et al. Surgical interventions for uterine prolapse and for vault prolapse: the two VUE RCTs. *Health Technol Assess*. 2020;24:1. [PMID: 32138809]

Ko KJ et al. Current surgical management of pelvic organ prolapse: strategies for the improvement of surgical outcomes. *Investig Clin Urol*. 2019;60:413. [PMID: 31692921]

PREMENSTRUAL SYNDROME

► General Considerations

The **premenstrual syndrome (PMS)** is a recurrent, variable cluster of troublesome physical and emotional symptoms that develop during the 5 days before the onset of menses and subside within 4 days after menstruation occurs. PMS intermittently affects about 40% of all premenopausal women, primarily those 25–40 years of age. In about 5–8% of affected women, the syndrome may be severe. Although not every woman experiences all the symptoms or signs at one time, many describe bloating, breast pain, headache, swelling, irritability, aggressiveness, depression, inability to concentrate, libido change, lethargy, and food cravings. When emotional or mood symptoms predominate, along with physical symptoms, and there is a clear functional impairment with work or personal relationships, the term "**premenstrual dysphoric disorder**" (PMDD) may be applied. The pathogenesis of PMS/PMDD is still uncertain, and current treatment methods are mainly empiric. The clinician should provide support for both the patient's emotional and physical distress, including the following:

1. Careful evaluation of the patient, with understanding, explanation, and reassurance.
2. Advice to keep a daily diary of all symptoms for 2–3 months, such as the Daily Record of Severity of Problems, to evaluate the timing and characteristics of her symptoms. If her symptoms occur throughout the month rather than in the 2 weeks before menses, she may have depression or other mental health diagnosis instead of or in addition to PMS.

► Treatment

For mild to moderate symptoms, a program of aerobic exercise; reduction of caffeine, salt, and alcohol intake; and use of alternative therapies, such as acupuncture and herbal treatments may be helpful, although these interventions remain unproven.

Medications that prevent ovulation, such as hormonal contraceptives, may lessen physical symptoms. These include continuous combined hormonal contraceptive methods (pill, patch, or vaginal ring) or GnRH agonist with "add-back" therapy (eg, conjugated equine estrogen, 0.625 mg orally daily, with medroxyprogesterone acetate, 2.5–5 mg orally daily).

When mood disorders predominate, several serotonin reuptake inhibitors have been shown to be effective in relieving tension, irritability, and dysphoria with few side

effects. First-line medication therapy includes serotonergic antidepressants (citalopram, escitalopram, fluoxetine, sertraline, venlafaxine) either daily or only on symptom days. There are limited data to support the use of calcium, vitamin D, and vitamin B₆ supplementation. There is insufficient evidence to support cognitive behavioral therapy.

Yonkers KA et al. Premenstrual disorders. Am J Obstet Gynecol. 2018;218:68. [PMID: 28571724]

MENOPAUSAL SYNDROME

See Chapter 26, Endocrine Disorders.

POLYCYSTIC OVARIAN SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Clinical or biochemical evidence of hyperandrogenism.
- ▶ Oligoovulation or anovulation.
- ▶ Polycystic ovaries on ultrasonography.

General Considerations

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of unknown etiology affecting 5–10% of reproductive age women. PCOS is characterized by chronic anovulation, polycystic ovaries, and hyperandrogenism. It is associated with hirsutism and obesity as well as an increased risk of diabetes mellitus, cardiovascular disease, and metabolic syndrome. Unrecognized or untreated PCOS is a risk factor for cardiovascular disease. The Rotterdam Criteria, endorsed by the National Institutes of Health, identify **hyperandrogenism, ovulatory dysfunction, and polycystic ovaries** as the key diagnostic features of the disorder in adult women; at least two of these features must be present for diagnosis.

Clinical Findings

PCOS often presents as a menstrual disorder (ranging from amenorrhea to heavy menstrual bleeding) and infertility. Skin disorders due to peripheral androgen excess, including hirsutism and acne, are common. Patients may also show signs of insulin resistance and hyperinsulinemia, and these women are at increased risk for early-onset type 2 diabetes mellitus and metabolic syndrome. Patients who do become pregnant are at increased risk for perinatal complications, such as gestational diabetes and preeclampsia. In addition, they have an increased long-term risk of endometrial cancer secondary to chronic exposure to unopposed estrogen.

Differential Diagnosis

Anovulation in the reproductive years may also be due to (1) premature ovarian failure (high FSH, low estradiol); (2) functional hypothalamic amenorrhea, often associated with

rapid weight loss or extreme physical exertion (low to normal FSH for age); (3) discontinuation of hormonal contraceptives (return to ovulation typically occurs within 90 days); (4) pituitary adenoma with elevated prolactin (galactorrhea may or may not be present); and (5) hyperthyroidism or hypothyroidism. To rule out other etiologies in women with suspected PCOS, serum FSH, LH, prolactin, and thyroid-stimulating hormone should be evaluated. Because of the high risk of insulin resistance and dyslipidemia, all women with suspected PCOS should have a hemoglobin A_{1C} and fasting glucose along with a lipid profile. Women with clinical evidence of androgen excess should have total testosterone, free (bioavailable) testosterone, and 17-hydroxyprogesterone measured. Women with stigmata of Cushing syndrome should have a 24-hour urinary free cortisol or a low-dose dexamethasone suppression test. Congenital adrenal hyperplasia and androgen-secreting adrenal tumors also tend to have high circulating androgen levels and anovulation with polycystic ovaries; these disorders must also be ruled out in women with presumed PCOS and high serum androgens.

Treatment

In obese patients with PCOS, weight reduction and exercise are often effective in reversing the metabolic effects and in inducing ovulation. For women who do not respond to weight loss and exercise, combined hormonal contraceptives are first-line treatment to manage hyperandrogenism and menstrual irregularities. Intermittent or continuous progestin therapy or a progestin-releasing IUD may be used for endometrial protection in women who cannot or choose not to use combined hormonal contraceptives. Metformin therapy may be used as a second-line therapy to improve menstrual function. Metformin has little or no benefit in the treatment of hirsutism, acne, or infertility. Contraceptive counseling should be offered to prevent unplanned pregnancy in case of a return of ovulatory cycles. For women who are seeking pregnancy and remain anovulatory, clomiphene, letrozole, or other medications can be used for ovarian stimulation (see section on Infertility below). Women with PCOS are at greater risk than normal women for twin gestation with ovarian stimulation.

If hirsutism does not improve after 6 months of treatment with combined hormonal contraceptives, an antiandrogen, such as spironolactone, may be added. Topical eflornithine cream applied to affected facial areas twice daily for 6 months may be helpful in most women. Hirsutism may also be managed with depilatory creams, electrolysis, and laser therapy. The combination of laser therapy and topical eflornithine may be particularly effective.

Weight loss, exercise, and treatment of unresolved metabolic derangements are important in preventing cardiovascular disease. Women with PCOS should be managed aggressively and should have regular monitoring of lipid profiles and glucose.

When to Refer

- If expertise in diagnosis is needed.
- If patient is infertile.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 194: Polycystic ovary syndrome. *Obstet Gynecol*. 2018;131:e157. [PMID: 29794677]

Gadalla MA et al. Medical and surgical treatment of reproductive outcomes in polycystic ovary syndrome: an overview of systematic reviews. *Int J Fertil Steril*. 2020;13:257. [PMID: 31710185]

Shi S et al. Letrozole and human menopausal gonadotropin for ovulation induction in clomiphene resistance polycystic ovary syndrome patients: a randomized controlled study. *Medicine (Baltimore)*. 2020;99:e18383. [PMID: 31977842]

A semen analysis should be completed to rule out a male factor for infertility (see Chapter 29).

B. Further Testing

1. Gross deficiencies of sperm (number, motility, or appearance) require a repeat confirmatory analysis.
2. A screening pelvic ultrasound and hysterosalpingography to identify uterine cavity or tubal anomalies should be performed. Hysterosalpingography is performed within 3 days following the menstrual period if structural abnormalities are suspected. This radiographic study will demonstrate uterine abnormalities (septa, polyps, submucous myomas) and tubal obstruction. Women who have had prior pelvic inflammation should receive doxycycline, 100 mg orally twice daily for 5 days.
3. Absent or infrequent ovulation requires additional laboratory evaluation. Elevated FSH and low estradiol and antimüllerian hormone levels indicate ovarian insufficiency. Patients with elevated prolactin levels should be evaluated for pituitary adenoma. Women over age 35 may require further assessment of **ovarian reserve**. A markedly elevated FSH (greater than 15–20 international units/L) on day 3 of the menstrual cycle suggests inadequate ovarian reserve. Although less widely used clinically, a clomiphene citrate challenge test, with measurement of FSH on day 10 after administration of clomiphene from days 5–9, can help confirm a diagnosis of diminished ovarian reserve. The number of antral follicles during the early follicular phase of the cycle can provide useful information about ovarian reserve and can confirm serum testing. An antimüllerian hormone level can be measured at any time during the menstrual cycle and is less likely to be affected by hormones.
4. If all the above testing is normal, **unexplained infertility** is diagnosed. In approximately 25% of women whose basic evaluation is normal, the first-line therapy is usually controlled ovarian hyperstimulation (usually with clomiphene citrate) and intrauterine insemination. IVF may be recommended as second-line therapy.

► Treatment

A. Medical Measures

Fertility may be restored by treatment of endocrine abnormalities, particularly hypothyroidism or hyperthyroidism. Women who are anovulatory as a result of low body weight or exercise may become ovulatory when they gain weight or decrease their exercise levels; conversely, obese women who are anovulatory may become ovulatory with loss of even 5–10% of body weight.

B. Surgical Measures

Excision of ovarian tumors or ovarian foci of endometriosis can improve fertility. Microsurgical relief of tubal obstruction due to salpingitis or tubal ligation will reestablish fertility in a significant number of cases, although with severe disease or proximal obstruction, IVF is preferable. Peritubal adhesions or endometriotic implants often can be treated via laparoscopy.

INFERTILITY

A couple is said to be infertile if pregnancy does not result after 1 year of normal sexual activity without contraception. Up to 20% of couples experience infertility at some point in their reproductive lives; the incidence of infertility increases with age, with a decline in fertility beginning in the early 30s and accelerating in the late 30s. The male partner contributes to about 40% of cases of infertility, and a combination of factors is common. The most recent data from the CDC National Survey of Family Growth noted that 12% of women in the United States aged 15–44 have impaired fecundity.

A. Initial Testing

During the initial interview, the clinician can present an overview of infertility and discuss an evaluation and management plan. Private consultations with each partner separately are then conducted, allowing appraisal of psychosexual adjustment without embarrassment or criticism. Pertinent details (eg, sexually transmitted infection history or prior pregnancies) must be obtained. The ill effects of cigarettes, alcohol, and other recreational drugs on male fertility should be discussed. Prescription medications that impair male potency and factors that may lead to scrotal hyperthermia, such as tight underwear or frequent use of saunas or hot tubs, should be discussed. The gynecologic history should include the menstrual pattern, the use and types of contraceptives, frequency and success of coitus, and correlation of intercourse with time of ovulation. The American Society for Reproductive Medicine provides patient information on the infertility evaluation and treatment (<https://www.reproductivefacts.org/topics/topics-index/infertility/>).

General physical and genital examinations are performed on the female partner. Basic laboratory studies include assessment of **ovarian reserve** (eg, antimüllerian hormone, and day 3 FSH and estradiol) and thyroid function tests. If the woman has regular menses with minimal symptoms, the likelihood of ovulatory cycles is very high. A luteal phase serum progesterone above 3 ng/mL establishes ovulation. Couples should be advised that coitus resulting in conception occurs during the 6-day window prior to the day of ovulation. Ovulation predictor kits have largely replaced basal body temperatures for predicting ovulation, but temperature charting may be used to identify most fertile days. Basal body temperature charts cannot predict ovulation; they can only retrospectively confirm that ovulation occurred.

In a male with a varicocele, sperm characteristics may be improved following surgical treatment. For men who have sperm production but obstructive azoospermia, trans-epidermal sperm aspiration or microsurgical epidermal sperm aspiration has been successful.

C. Induction of Ovulation

1. Clomiphene citrate—Clomiphene citrate stimulates gonadotropin release, especially FSH. It acts as a selective estrogen receptor modulator, similar to tamoxifen and raloxifene, and binds to the estrogen receptor. A low level of estrogen decreases the negative feedback on the hypothalamus, thereby increasing the release of FSH and LH. When FSH and LH are present in the appropriate amounts and timing, ovulation occurs.

After a normal menstrual period or induction of withdrawal bleeding with progestin, clomiphene 50 mg orally should be given daily for 5 days, typically on days 3–7 of the cycle. If ovulation does not occur, the clomiphene dosage is increased to 100 mg orally daily for 5 days. While doses of 150 mg may be used, doses greater than 100 mg do not appear to improve clinical pregnancy rates. The rate of ovulation following clomiphene treatment is approximately 80% in the absence of other infertility factors. The pregnancy rate is 30–40%, and twinning occurs in 5% of these pregnancies. Three or more fetuses are rare (less than 0.5% of cases). Pregnancy is most likely to occur within the first three ovulatory cycles, and unlikely to occur after cycle six. In addition, several studies have suggested a twofold to threefold increased risk of ovarian cancer with the use of clomiphene for more than 1 year, so treatment with clomiphene is usually limited to a maximum of six cycles.

2. Letrozole—The aromatase inhibitor letrozole appears to be at least as effective as clomiphene for induction of ovulation in women with PCOS. There is a reduced risk of multiple pregnancy, a lack of antiestrogenic effects, and a reduced need for ultrasound monitoring. The dose of letrozole is 2.5–7.5 mg daily, starting on day 3 of the menstrual cycle. In women who have a history of estrogen dependent tumors, such as breast cancer, letrozole is preferred over other agents because the estrogen levels with this medication are much lower.

3. Human menopausal gonadotropins (hMG) or recombinant FSH—hMG or recombinant FSH is indicated in cases of hypogonadotropism and most other types of anovulation resistant to clomiphene treatment. Because of the complexities, laboratory tests, and expense associated with this treatment, these patients should be referred to an infertility specialist.

D. Artificial Insemination in Azoospermia

If azoospermia is present, artificial insemination by a donor usually results in pregnancy, assuming female function is normal. The use of frozen sperm provides the opportunity for screening for sexually transmitted infections, including HIV infection.

E. Assisted Reproductive Technology (ART)

Couples who have not responded to traditional infertility treatments and those with occlusive tubal disease, severe endometriosis, oligospermia, and immunologic or unexplained infertility, may benefit from ART. All ART procedures involve ovarian stimulation to produce multiple oocytes, oocyte retrieval by transvaginal sonography-guided needle aspiration, and handling of the oocytes outside the body. With IVF, the eggs are fertilized in vitro and the embryos transferred to the uterus. Intracytoplasmic sperm injection allows fertilization with a single sperm. While originally intended for couples with male factor infertility, it is now used in two-thirds of all IVF procedures in the United States.

The chance of a multiple gestation pregnancy (ie, twins, triplets) is increased in all assisted reproductive procedures, increasing the risk of preterm delivery and other pregnancy complications. To minimize this risk, most infertility specialists recommend transferring only one embryo in appropriately selected patients with a favorable prognosis.

► Prognosis

The prognosis for conception and normal pregnancy is good if minor (even multiple) disorders can be identified and treated; it is poor if the causes of infertility are severe, untreatable, or of prolonged duration (over 3 years).

In the absence of identifiable causes of infertility, 60% of couples will achieve a spontaneous pregnancy within 3 years. Couples in which the woman is younger than 35 years who do not achieve pregnancy within 1 year of trying may be candidates for infertility treatment, and within 6 months for women age 35 years and older. Also, offering appropriately timed information about adoption is considered part of a complete infertility regimen.

► When to Refer

Refer to reproductive endocrinologist if ART is indicated, or surgery is required.

- American College of Obstetricians and Gynecologists. Committee Opinion No. 781: Infertility workup for the women's health specialist. *Obstet Gynecol*. 2019;133:e377. [PMID: 31135764]
Hodgson RM et al. Interventions for endometriosis-related infertility: a systematic review and network meta-analysis. *Fertil Steril*. 2020;113:374. [PMID: 32106991]
Merritt BA et al. Imaging of infertility, Part 1: Hysterosalpingograms to magnetic resonance imaging. *Radiol Clin North Am*. 2020;58:215. [PMID: 32044003]
Merritt BA et al. Imaging of infertility, Part 2: Hysterosalpingograms to magnetic resonance imaging. *Radiol Clin North Am*. 2020;58:227. [PMID: 32044004]
Shi S et al. Letrozole and human menopausal gonadotropin for ovulation induction in clomiphene resistance polycystic ovary syndrome patients: a randomized controlled study. *Medicine (Baltimore)*. 2020;99:e18383. [PMID: 31977842]

CONTRACEPTION & FAMILY PLANNING

Unintended pregnancies are a worldwide problem but disproportionately impact developing countries. From 2010 to 2014, it is estimated that 44% of pregnancies worldwide were unintended and 56% of them resulted in an abortion.

In developed regions, the unintended pregnancy rate fell by 30% compared to 1990–1994, whereas it fell by only 16% in developing regions over this time frame. It is important for primary care providers to educate their patients about the benefits of contraception and to provide options that are appropriate and desirable for the patient.

1. Oral Contraceptives

A. Combined Oral Contraceptives

1. Efficacy and methods of use—Combined oral contraceptives have a perfect use failure rate of 0.3% and a typical use failure rate of 8%. Their primary mode of action is suppression of ovulation. The pills can be initially started on the first day of the menstrual cycle, the first Sunday after the onset of the cycle, or on any day of the cycle. If started more than 5 days after the first day of the cycle, a backup method should be used for the first 7 days. If an active pill is missed at any time, and no intercourse occurred in the past 5 days, two pills should be taken immediately, and a backup method should be used for 7 days. If intercourse occurred in the previous 5 days, emergency contraception should be offered. A backup method should be used for 7 days.

2. Benefits of oral contraceptives—Noncontraceptive benefits of oral contraceptives include lighter menses and improvement of dysmenorrhea, decreased risk of ovarian and endometrial cancer, and improvement in acne. Functional ovarian cysts are less likely with oral contraceptive use. There is also a beneficial effect on bone mass.

3. Selection of an oral contraceptive—Any of the combination oral contraceptives containing 35 mcg or less of ethinyl estradiol or 3 mg of estradiol valerate are suitable for most women. There is some variation in potency of the various progestins in the pills, but there are essentially no clinically significant differences for most women among the progestins in the low-dose pills. There is insufficient evidence that triphasic oral contraceptives provide any benefit compared to monophasic oral contraceptives in terms of effectiveness, bleeding patterns, or discontinuation rates. Therefore, monophasic pills are recommended as a first choice for women starting oral contraceptive use. Women who have acne or hirsutism may benefit from treatment with desogestrel, drospirenone, or norgestimate, since they are the least androgenic. Pills are typically packaged in 21- or 28-day cyclic regimens but may be taken continuously to allow the user to decide if and when she has a withdrawal bleed. Studies have not shown any significant risk from long-term amenorrhea in patients taking continuous oral contraceptives. The low-dose oral contraceptives commonly used in the United States are listed in Table 18–2.

4. Drug interactions—Several medications interact with oral contraceptives potentially decreasing their efficacy, typically by causing induction of microsomal enzymes in the liver. Some commonly prescribed medications in this category are phenytoin, phenobarbital (and other barbiturates), primidone, topiramate, carbamazepine, rifampin, and St. John's wort. Women taking these medications should use another means of contraception for maximum safety.

Antiretroviral medications, specifically ritonavir-boosted protease inhibitors, may significantly decrease the efficacy of combined oral contraceptives. Other antiretrovirals, such as nonnucleoside reverse transcriptase inhibitors, have smaller effects on oral contraceptive efficacy.

5. Contraindications and adverse effects—Oral contraceptives have been associated with many adverse effects; they are contraindicated with some conditions and should be used with caution in others (Table 18–3).

A. Myocardial infarction—The risk of heart attack is higher with use of oral contraceptives in certain populations, but the risk attributable to oral contraceptives is low in reproductive age women. Cigarette smoking, obesity, hypertension, diabetes mellitus, or hypercholesterolemia increases the risk. Smokers over age 35 and women with other cardiovascular risk factors should use other non-estrogen-containing methods of birth control.

B. Thromboembolic disease—A three- to five-fold increased rate of venous thromboembolism is found in oral contraceptive users, but the absolute risk is very low (5–6 per 100,000 woman-years compared to a rate of 50–300 per 100,000 pregnancies). Several studies have reported a two-fold increased risk in women using oral contraceptives containing the progestins, gestodene (not available in the United States), drospirenone, or desogestrel, compared with women using oral contraceptives with levonorgestrel and norethindrone. Women in whom thromboembolism develops should stop using oral contraceptives, as should those at increased risk for thromboembolism associated with surgery, fracture, serious injury, hypercoagulable condition, or immobilization. Women with a known thrombophilia should not use estrogen-containing contraceptives.

C. Cerebrovascular disease—Overall, a small increased risk of hemorrhagic stroke and subarachnoid hemorrhage and a somewhat greater increased risk of thrombotic stroke have been found; smoking, hypertension, and age over 35 years are associated with increased risk. Women should stop using estrogen-containing contraceptives if such warning symptoms as severe headache, blurred or lost vision, or other transient neurologic disorders develop.

D. Carcinoma—There is no increased risk of breast cancer in women aged 35–64 who are current or former users of oral contraceptives. Women with a family history of breast cancer or women who started oral contraceptive use at a young age are not at increased risk. Combination oral contraceptives reduce the risk of endometrial carcinoma by 40% after 2 years of use and 60% after 4 or more years of use. The risk of ovarian cancer is reduced by 30% with pill use for less than 4 years, by 60% with pill use for 5–11 years, and by 80% with use for 12 or more years. Oral contraceptives have been associated with the development of benign hepatocellular adenomas and peliosis hepatitis (blood-filled cavities) (but not focal nodular hyperplasia or hepatocellular carcinoma); hepatocellular adenomas may rarely cause rupture of the liver, hemorrhage, and death. The risk of hepatocellular adenoma increases with higher dosage, longer duration of use, and older age.

Table 18–2. Commonly used low-dose oral contraceptives (listed within each group in order of increasing estrogen dose).

Name	Progestin	Estrogen (Ethinyl Estradiol)	Cost per Month ¹
Combination			
Alesse ^{2,3}	0.1 mg levonorgestrel	20 mcg	\$35.20
Loestrin 1/20 ²	1 mg norethindrone acetate	20 mcg	\$28.65
Mircette ²	0.15 mg desogestrel	20 mcg	\$59.98
Yaz ²	3 mg drospirenone	20 mcg	\$67.87
Loestrin 21 1.5/30 ²	1.5 mg norethindrone acetate	30 mcg	\$26.67
Low Ogestrel ²	0.3 mg norgestrel	30 mcg	\$30.52
Levora ²	0.15 mg levonorgestrel	30 mcg	\$30.92
Desogen ²	0.15 mg desogestrel	30 mcg	\$34.33
Yasmin ²	3 mg drospirenone	30 mcg	\$76.72
Brevicon ² , Modicon ²	0.5 mg norethindrone	35 mcg	\$32.17
Demulen 1/35 ²	1 mg ethynodiol diacetate	35 mcg	\$29.88
Ortho-Novum 1/35 ²	1 mg norethindrone	35 mcg	\$29.47
Ortho-Cyclen ²	0.25 mg norgestimate	35 mcg	\$32.23
Gildagia ²	0.4 mg norethindrone	35 mcg	\$44.84
Combination: Extended-Cycle			
LoSeasonique (91-day cycle) ²	0.10 mg levonorgestrel (days 1–84)/0 mg levonorgestrel (days 85–91)	20 mcg (84 days)/10 mcg (7 days)	\$88.53
Amethyst (28-day pack)	90 mcg levonorgestrel	20 mcg	\$59.40
Seasonique (91-day cycle) ²	0.15 mg levonorgestrel (days 1–84)/0 mg levonorgestrel (days 85–91)	30 mcg (84 days)/10 mcg (7 days)	\$66.95
Triphasic			
Estrostep ²	1 mg norethindrone acetate (days 1–5) 1 mg norethindrone acetate (days 6–12) 1 mg norethindrone acetate (days 13–21)	20 mcg 30 mcg 35 mcg	\$141.81
Cyclessa ²	0.1 mg desogestrel (days 1–7) 0.125 mg desogestrel (days 8–14) 0.15 mg desogestrel (days 15–21)	25 mcg	\$33.64
Tri-Lo-Estarrylla	0.18 mg norgestimate (days 1–7) 0.215 mg norgestimate (days 8–14) 0.25 mg norgestimate (days 15–21)	25 mcg	\$61.56
Trivora ^{2,3}	0.05 mg levonorgestrel (days 1–6) 0.075 mg levonorgestrel (days 7–11) 0.125 mg levonorgestrel (days 12–21)	30 mcg 40 mcg 30 mcg	\$27.48
Ortho-Novum 7/7/7 ^{2,3}	0.5 mg norethindrone (days 1–7) 0.75 mg norethindrone (days 8–14) 1 mg norethindrone (days 15–21)	35 mcg	\$32.17
Tri Estarrylla ^{2,3}	0.18 mg norgestimate (days 1–7) 0.215 mg norgestimate (days 8–14) 0.25 mg norgestimate (days 15–21)	35 mcg	\$39.32
Tri-Noriny ^{1,3}	0.5 mg norethindrone (days 1–7) 1 mg norethindrone (days 8–16) 0.5 mg norethindrone (days 17–21)	35 mcg	\$39.35
Progestin-Only Pill			
Ortho Micronor ^{2,3}	0.35 mg norethindrone to be taken continuously	None	\$39.54
Slynd	4 mg drospirenone (days 1–24)	None	\$194.00

¹Average wholesale price (AWP) for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Redbook (electronic version), IBM Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

²Generic equivalent available.

³Multiple other brands available.

Table 18–3. Contraindications to use of combined hormonal contraceptives.

Absolute contraindications
Pregnancy
Thrombophlebitis or thromboembolic disorders (past or present)
Stroke or coronary artery disease (past or present)
Cancer of the breast (known or suspected)
Undiagnosed abnormal vaginal bleeding
Estrogen-dependent cancer (known or suspected)
Hepatocellular adenoma (past or present)
Uncontrolled hypertension
Diabetes mellitus with vascular disease
Age ≥ 35 and smoking ≥ 15 cigarettes daily
Known thrombophilia
Migraine with aura
Active hepatitis
Surgery or orthopedic injury requiring prolonged immobilization
Relative contraindications
Migraine without aura
Hypertension
Heart or kidney disease
Diabetes mellitus
Gallbladder disease
Cholestasis during pregnancy
Sickle cell disease (S/S or S/C type)
Lactation

E. HYPERTENSION—Oral contraceptives may cause hypertension in some women; the risk is increased with longer duration of use and older age. Women in whom hypertension develops while using oral contraceptives should use other non-estrogen-containing contraceptive methods. However, with regular blood pressure monitoring, non-smoking women with well-controlled mild hypertension may use oral contraceptives.

F. HEADACHE—Migraine or other vascular headaches may occur or worsen with pill use. If severe or frequent headaches develop while using this method, it should be discontinued. Women with migraine headaches *with aura* should not use oral contraceptives due to the increased risk of stroke.

G. LACTATION—Combined oral contraceptives can impair the quantity and quality of breast milk. While it is preferable to avoid the use of combination oral contraceptives during lactation, the effects on milk quality are small and are not associated with developmental abnormalities in infants. Combination oral contraceptives should be started no earlier than 6 weeks postpartum to allow for establishment of lactation. Progestin-only pills, levonorgestrel implants, and DMPA are alternatives with no adverse effects on milk supply.

H. OBESITY—Obese and overweight women have generally been excluded from oral contraceptive trials until recently. Obesity is an independent risk factor for thromboembolic complications. However, it is important that obese women are not denied effective contraception as a result of concerns about oral contraceptive complications or efficacy. Current evidence suggests that efficacy is

similar for overweight and obese women as for normal-weight individuals.

I. OTHER DISORDERS—Depression may occur or be worsened with oral contraceptive use. Fluid retention may occur. Patients who had cholestatic jaundice during pregnancy may develop it while taking birth control pills.

6. Minor side effects—Nausea and dizziness may occur in the first few months of pill use. Spotting or breakthrough bleeding between menstrual periods may occur; this may be helped by switching to a pill of slightly greater estrogen potency. Missed menstrual periods may occur, especially with low-dose pills. A pregnancy test should be performed if pills have been skipped or an expected menstrual period is missed. Fatigue and decreased libido can occur. Chloasma may occur, as in pregnancy, and is increased by exposure to sunlight.

B. Progestin Minipill

1. Efficacy and methods of use—A formulation containing 0.35 mg of norethindrone alone is available in the United States. The efficacy is similar to that of combined oral contraceptives but is highly dependent on consistent use (eg, taking the pill within the same 3-hour window every day). A progestin-only pill containing drospirenone was approved by the FDA in the United States in 2019, and a desogestrel-only pill is available in several countries outside the United States. The minipill is believed to prevent conception by causing thickening of the cervical mucus to make it hostile to sperm, by causing alteration of ovum transport (which may account for the slightly higher rate of ectopic pregnancy with these pills), and by causing inhibition of implantation. Ovulation is inhibited inconsistently with this method. The minipill is begun on the first day of a menstrual cycle and then taken continuously for as long as contraception is desired; there is no “placebo week.”

2. Advantages—The low dose of progestin and absence of estrogen make the minipill safe for women with contraindications to estrogen therapy. Because estrogen may decrease initial milk production during lactation, the progestin minipill is an ideal choice for breastfeeding women. It also is often tried by women who want minimal doses of hormones and by patients who are over age 35. The minipill lacks the cardiovascular side effects of combination pills.

3. Complications and contraindications—There are few contraindications to the minipill (ie, malabsorptive disease, current or past ischemic heart disease, and history of stroke). Minipill users often have bleeding irregularities (eg, prolonged flow, spotting, or amenorrhea); such patients may need regular pregnancy tests if there is a concern about contraceptive effectiveness. Many of the absolute contraindications and relative contraindications listed in Table 18–3 apply to the minipill; however, the contraceptive benefit of the minipill may outweigh the risks for patients who smoke, who are over age 35, or who have conditions such as superficial or deep venous thrombosis or known thromboembolic disorders or diabetes mellitus with vascular disease. Minor side effects of combination oral contraceptives such as mild headache may also occur with the minipill.

Bastianelli C et al. Pharmacodynamics of combined estrogen-progestin oral contraceptives: 4. Effects on uterine and cervical epithelia. *Expert Rev Clin Pharmacol.* 2020;13:163. [PMID: 31975619]

Bearak J et al. Global, regional, and subregional trends in unintended pregnancy and its outcomes from 1990 to 2014: estimates from a Bayesian hierarchical model. *Lancet Glob Health.* 2018;6:e380. [PMID: 29519649]

Serfaty D. Update on contraceptive contraindications. *J Gynecol Obstet Hum Reprod.* 2019;48:297. [PMID: 30796985]

Shufelt C et al. Hormonal contraception in women with hypertension. *JAMA.* 2020;324:1451. [PMID: 32955577]

2. Contraceptive Injections & Implants (Long-Acting Progestins)

The injectable progestin depot-medroxyprogesterone acetate (**DMPA**) is approved for contraceptive use in the United States. There has been extensive worldwide experience with this method over the past 3 decades. The medication is given as a deep intramuscular injection of 150 mg every 3 months and has a contraceptive efficacy of 99.7%. A subcutaneous preparation, containing 104 mg of DMPA is also available in the United States. Common side effects include irregular bleeding, amenorrhea, weight gain, and headache. It is associated with bone mineral loss that is reversible after discontinuation of the method. Users commonly have irregular bleeding initially and subsequently develop amenorrhea. Ovulation may be delayed after its discontinuation. Contraindications are similar to those for the minipill.

A single-rod, subdermal progestin implant, etonogestrel (**Nexplanon**), is approved for use in the United States. Nexplanon is a 40-mm by 2-mm rod containing 68 mg of the progestin etonogestrel that is inserted in the inner aspect of the nondominant arm. It is approved for use for 3 years, but data suggest it maintains effectiveness through 5 years. Hormone levels drop rapidly after removal, and there is no delay in the return of fertility. In clinical trials, the pregnancy rate was 0.0% with 3 years of use. The side effect profile is similar to the minipill and DMPA. Irregular bleeding has been the most common reason for discontinuation.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 206: Use of hormonal contraception in women with coexisting medical conditions. 2019;133:e128. [PMID: 30681544]

Bahamondes L et al. Long-acting reversible contraceptive (LARCs) methods. *Best Pract Res Clin Obstet Gynaecol.* 2020;66:28. [PMID: 32014434]

Dianat S et al. Side effects and health benefits of depot medroxyprogesterone acetate: a systematic review. *Obstet Gynecol.* 2019;133:332. [PMID: 30633132]

Espay E et al. Barriers and solutions to improve adolescent intrauterine device access. *J Pediatr Adolesc Gynecol.* 2019;32:S7. [PMID: 31585618]

Horvath S et al. From uptake to access: a decade of learning from ACOG LARC program. *Am J Obstet Gynecol.* 2020;222:S866. [PMID: 31794720]

3. Other Combined Hormonal Contraceptives

A **transdermal contraceptive patch** containing norelgestromin (150 mcg) and ethinyl estradiol (20 mcg) and measuring 20 cm² is available. The patch is applied to the

lower abdomen, upper torso, or buttock once a week for 3 consecutive weeks, followed by 1 week without the patch. It appears that the average steady-state concentration of ethinyl estradiol with the patch is approximately 60% higher than with a 35-mcg pill. However, there is currently no evidence for an increased incidence of estrogen-related side effects. The mechanism of action, side effects, and efficacy are similar to those associated with oral contraceptives, although compliance may be better. However, discontinuation due to side effects is more frequent.

A **contraceptive vaginal ring** that releases 120 mcg of etonogestrel and 15 mcg of ethinyl estradiol daily (Nuva-ring) is available. The ring is soft and flexible and is placed in the upper vagina for 3 weeks, removed, and replaced 1 week later, or can be removed and replaced after 4 weeks for continuous cycling, similar to oral contraceptives. The 1-year reusable seegersterone acetate/ethinyl estradiol vaginal ring (Annovera) was approved by the US FDA in 2018. The ring is worn for 3 weeks and removed for 1 week, and that pattern is repeated for a total of 13 cycles. The efficacy, mechanism of action, and systemic side effects of combined hormonal vaginal rings are similar to those associated with oral contraceptives. Ring users may experience increased vaginal discharge.

4. Intrauterine Devices

In the United States, the following IUDs are available: the levonorgestrel-releasing **Mirena**, **Liletta**, **Kyleena**, and **Skyla** IUDs and the copper-bearing **TCu380A (Paragard)**. The mechanism of action of the copper IUD is thought to involve either spermicidal or inhibitory effects on sperm capacitation and transport. The levonorgestrel-containing IUDs also cause thickening of cervical mucus, prevent endometrial thickening, and can inhibit ovulation. IUDs are not abortifacients.

Skyla is FDA approved for use for 3 years, Kyleena for 5 years, Mirena and Liletta for 6 years, and the TCu380A for 10–12 years. These hormone-containing IUDs have the advantage of reducing cramping and menstrual flow. Mirena is FDA approved for the treatment of heavy menstrual bleeding.

The IUD is an excellent contraceptive method for most women. The devices are highly effective, with failure rates similar to those achieved with surgical sterilization. IUDs may be used in nulliparous women and adolescents. Women who are not in mutually monogamous relationships should (also) use condoms for protection from sexually transmitted diseases. Levonorgestrel-containing IUDs may have a protective effect against upper tract infection similar to that of oral contraceptives.

A. Insertion

Insertion can be performed at any time during the menstrual cycle if pregnancy can be reasonably excluded. There is growing evidence to suggest that IUDs can be safely inserted in the immediate postabortal and postpartum periods.

Both types of IUDs (levonorgestrel-releasing and copper bearing) may be inserted up to 48 hours after vaginal delivery, or prior to closure of the uterus at the time of cesarean section. Insertion immediately following abortion is acceptable if there is no sepsis and if follow-up insertion

Table 18–4. Contraindications to IUD use.

Absolute contraindications
Pregnancy
Acute or subacute pelvic inflammatory disease or purulent cervicitis
Significant anatomic abnormality of uterus
Unexplained uterine bleeding
Wilson disease or copper allergy (copper IUD)
Breast cancer (levonorgestrel IUD)
Cervical, endometrial, or gestational trophoblastic neoplasia
Relative contraindications
Active liver disease (levonorgestrel IUD)
Menorrhagia or severe dysmenorrhea (copper IUD)

IUD, intrauterine device.

a month later will not be possible; otherwise, it is wise to wait until 4 weeks postabortion. NSAIDs given as premedication may be helpful.

B. Contraindications and Complications

Contraindications to use of IUDs are outlined in Table 18–4.

1. Pregnancy—A copper-containing IUD can be inserted within 5 days following a single episode of unprotected midcycle coitus as a **postcoital contraceptive**. An IUD should not be inserted into a pregnant uterus. If pregnancy occurs as an IUD failure, there is a greater chance of spontaneous abortion if the IUD is left in situ (50%) than if it is removed (25%). Women using an IUD who become pregnant should have the IUD removed if the string is visible. It can be removed at the time of abortion if that is desired. If the string is not visible and the patient wants to continue the pregnancy, she should be informed of the increased risk of miscarriage, infection, preterm birth, and abruption. She should be informed that any flu-like symptoms such as fever, myalgia, headache, or nausea warrant immediate medical attention for possible septic abortion.

Since the risk of ectopic pregnancy is increased in IUD users who become pregnant with an IUD in situ, clinicians should search for adnexal masses in early pregnancy and should always check the products of conception for placental tissue following abortion.

2. Pelvic infection—There is an increased risk of pelvic infection during the first month following insertion; however, prophylactic antibiotics are not recommended at the time of insertion since they do not appear to decrease this risk. The subsequent risk of pelvic infection appears to be primarily related to the risk of acquiring sexually transmitted infections. Infertility rates do not appear to be increased among women who have previously used the currently available IUDs. At the time of insertion, women with an increased risk of sexually transmitted diseases should be screened for gonorrhea and *Chlamydia*. Women with a history of recent or recurrent pelvic infection are not good candidates for an IUD.

3. Heavy menstrual bleeding or severe dysmenorrhea

The copper IUD can cause heavier menstrual periods, bleeding between periods, and more cramping, so it is

generally not suitable for women who already suffer from these problems. Alternatively, the hormone-releasing IUD Mirena has been approved by the FDA to treat heavy menstrual bleeding. NSAIDs are also helpful in decreasing bleeding and pain in IUD users.

4. Complete or partial expulsion—Spontaneous expulsion of the IUD occurs in up to 10% of women during the first year of use. Any IUD should be removed if the body of the device can be seen or felt in the cervical os.

5. Missing IUD strings—If the transcervical tail cannot be seen, this may signify unnoticed expulsion, perforation of the uterus with abdominal migration of the IUD, or simply retraction of the string into the cervical canal or uterus owing to movement of the IUD or uterine growth with pregnancy. Once pregnancy is ruled out, the clinician may probe for the IUD with sterile sound or forceps designed for IUD removal. If the IUD cannot be detected, pelvic ultrasound will demonstrate if the IUD is intrauterine. Alternatively, obtain anteroposterior and lateral radiographs of the pelvis to evaluate for an extrauterine IUD. If the IUD is in the abdominal cavity, it should generally be removed by laparoscopy or laparotomy. Perforations of the uterus are less likely if insertion is performed slowly, with meticulous care taken to follow directions applicable to each type of IUD.

Averbach SH et al. Expulsion of intrauterine devices after postpartum placement by timing of placement, delivery type, and intrauterine device type: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;223:177. [PMID: 32142826]

De Nadai MN et al. Intracervical block for levonorgestrel-releasing intrauterine system placement among nulligravid women: a randomized double-blind controlled trial. *Am J Obstet Gynecol*. 2020;222:245. [PMID: 31541635]

Mazza D et al. Increasing long-acting reversible contraceptives: the Australian Contraceptive Choice Project (ACCORD) cluster randomized trial. *Am J Obstet Gynecol*. 2020;222:S921. [PMID: 31837291]

5. Diaphragm & Cervical Cap

The **diaphragm (with contraceptive jelly)** is a safe and effective contraceptive method with features that make it acceptable to some women and not others. Failure rates range from 6% to 16%, depending on the motivation of the woman and the care with which the diaphragm is used. The advantages of this method are that it has no systemic side effects and gives significant protection against pelvic infection and cervical dysplasia as well as pregnancy. The disadvantages are that it must be inserted near the time of coitus and that pressure from the rim predisposes some women to cystitis after intercourse.

The **cervical cap (with contraceptive jelly)** is similar to the diaphragm but fits snugly over the cervix only (the diaphragm stretches from behind the cervix to behind the pubic symphysis). The cervical cap is more difficult to insert and remove than the diaphragm. The main advantages are that it can be used by women who cannot be fitted for a diaphragm because of a relaxed anterior vaginal wall or by women who have discomfort with or in whom

repeated bladder infections develop with the diaphragm. However, failure rates are 9% (perfect use) and 16% (typical use) in nulliparous women and 26% (perfect use) and 32% (typical use) in parous women.

Because of the small risk of toxic shock syndrome, a cervical cap or diaphragm should not be left in the vagina for over 24 hours, nor should these devices be used during the menstrual period.

6. Contraceptive Foam, Cream, Film, Sponge, Jelly, & Suppository

These products are available without prescription, are easy to use, and have typical failure rates of 10–22%. All contain the spermicide nonoxynol-9, which also has some viricidal and bactericidal activity. Nonoxynol-9 does not appear to adversely affect the vaginal colonization of hydrogen peroxide-producing lactobacilli. The FDA requires products containing nonoxynol-9 to include a warning that the products do not protect against HIV or other sexually transmitted diseases and that use of these products can irritate the vagina and rectum and may increase the risk of HIV acquisition from an infected partner. A different on-demand vaginal contraceptive, a vaginal pH regulator gel containing lactic acid–citric acid–potassium bitartrate (commercial name Phexxi), was FDA approved for use in the United States in 2020. The supporting clinical trial estimated 27.5 pregnancies per 100 woman-years.

Phexxi—a nonhormonal contraceptive gel. *Med Lett Drugs Ther.* 2020;62:129. [PMID: 32970042]

7. Condom

The male condom of latex, polyurethane or animal membrane affords protection against pregnancy—equivalent to that of a diaphragm and spermicidal jelly; latex and polyurethane (but not animal membrane) condoms also offer protection against many sexually transmitted diseases, including HIV. When a spermicide, such as vaginal foam, is used with the condom, perfect use failure rate is approximately 2% and typical use, 15%. The disadvantages of condoms are dulling of sensation and spillage of semen due to tearing, slipping, or leakage with detumescence of the penis.

Two female condoms, one made of polyurethane and the other of synthetic nitrile, are available in the United States. The reported failure rates range from 5% to 21%; the efficacy is comparable to that of the diaphragm. These are the only female-controlled method that offers significant protection against both pregnancy and sexually transmitted diseases.

Beksinska M et al. Male and female condoms: their key role in pregnancy and STI/HIV prevention. *Best Pract Res Clin Obstet Gynaecol.* 2020;66:55. [PMID: 32007451]

8. Contraception Based on Awareness of Fertile Periods

These methods are most effective when the couple restricts intercourse to the post-ovular phase of the cycle or uses a barrier method at other times. Well-instructed, motivated

couples may be able to achieve low pregnancy rates with fertility awareness methods. Examples of some of these include monitoring cervical mucus changes, basal body temperature fluctuations, and menstrual cycle calculations to avoid having intercourse on fertile days. However, properly done randomized clinical trials comparing the efficacy of most of these methods with other contraceptive methods do not exist.

9. Emergency Contraception

Emergency contraception can be used to decrease the risk of pregnancy after intercourse but before the establishment of pregnancy. These methods should be started as soon as possible and within 120 hours after unprotected coitus: (1) Levonorgestrel, 1.5 mg orally as a single dose (available in the United States prepackaged as Plan B and available over-the-counter [OTC] for women aged 17 years and older), has a 1–2% failure rate when taken within 72 hours. It remains efficacious up to 120 hours after intercourse, though less so compared with earlier use. (2) If the levonorgestrel regimen is not available, a combination oral contraceptive containing ethinyl estradiol and levonorgestrel given twice in 12 hours may be used. At least 20 brands of pills may be used in this way. For specific dosages and instructions for each pill brand, consult “not-2-late” at <http://ec.princeton.edu/>. Used within 72 hours, the failure rate of these regimens is approximately 3%, but antinausea medication is often necessary. (3) Ulipristal acetate, a selective progesterone receptor modulator, taken orally as a single 30 mg dose, has been shown to be more effective than levonorgestrel, especially when used between 72 and 120 hours, particularly among overweight and obese women. It is available by prescription in the United States but was withdrawn from the market in the European Union and Canada in 2020 due to rare reports of serious drug-induced liver injury. Patients should wait 5 days after taking ulipristal to start or restart a hormonal contraceptive method. (4) Copper IUD insertion within 5 days after one episode of unprotected midcycle coitus will also prevent pregnancy. Copper IUD use for emergency contraception is the most effective available method, with first cycle pregnancy rates of 0.1%. All victims of sexual violence should be offered emergency contraception.

Information on clinics or individual clinicians providing emergency contraception in the United States may be obtained by calling 1-888-668-2528.

Goldstuck ND et al. The efficacy of intrauterine devices for emergency contraception and beyond: a systemic review update. *Int J Womens Health.* 2019;11:471. [PMID: 31686919]

Shen J et al. Interventions for emergency contraception. *Cochrane Database Syst Rev.* 2019;1:CD001324. [PMID: 30661244]

Upadhyia KK; Committee on Adolescence. Emergency contraception. *Pediatrics.* 2019;144:e20193149. [PMID: 31740497]

10. Sterilization

In the United States, sterilization is the most popular method of birth control for couples who want no more children. Although sterilization is reversible in some

instances, reversal surgery for both women and men is costly, complicated, and not always successful. Therefore, patients should be counseled carefully before sterilization and should view the procedure as permanent.

Female sterilization procedures include laparoscopic bipolar electrocoagulation, salpingectomy, plastic ring application on the uterine tubes, or minilaparotomy with tubal resection. Salpingectomy may be preferred for the added benefit of decreasing ovarian cancer risk. The advantages of laparoscopy are minimal postoperative pain, small incisions, and rapid recovery. The advantages of minilaparotomy are that it can be performed with standard surgical instruments under local or general anesthesia. However, there is more postoperative pain and a longer recovery period. The cumulative 10-year failure rate for all methods combined is 1.85%, varying from 0.75% for postpartum partial salpingectomy and laparoscopic unipolar coagulation to 3.65% for spring clips; this fact should be discussed with women preoperatively. Some studies have found an increased risk of menstrual irregularities as a long-term complication of tubal ligation, but findings in different studies have been inconsistent. A method of trans-cervical sterilization, Essure, involving placement of an expanding nickel-titanium microcoil into the proximal uterine tube under hysteroscopic guidance, was approved by the FDA in 2002. However, as of 2018, Essure was no longer marketed due to concerns related to complications and side effects reported by users.

Male sterilization by vasectomy is a safe, simple procedure in which the vas deferens is severed and sealed through a scrotal incision under local anesthesia. Long-term follow-up studies on vasectomized men show no excess risk of cardiovascular disease. Despite past controversy, there is no definite association of vasectomy with prostate cancer.

► When to Refer

Refer to experienced clinicians for etonogestrel subdermal (Nexplanon) insertion, IUD insertion, tubal occlusion or ligation, therapeutic abortion, or vasectomy.

ACOG Practice Bulletin No. 208 Summary: Benefits and risks of sterilization. *Obstet Gynecol*. 2019;133:592. [PMID: 30801465]
Mercier RJ et al. Expedited scheduling of interval tubal ligation: a randomized controlled trial. *Obstet Gynecol*. 2019;134:1178. [PMID: 31764727]

Zamorano AS et al. Postpartum salpingectomy: a procedure whose time has come. *Am J Obstet Gynecol*. 2019;220:8. [PMID: 30591122]

11. Abortion

Since the legalization of abortion in the United States in 1973, the related maternal mortality rate has fallen markedly because illegal and self-induced abortions have been replaced by safer medical procedures. Abortions in the first trimester of pregnancy are performed by vacuum aspiration under local anesthesia or with medical regimens. Dilatation and evacuation, a variation of vacuum aspiration is generally used in the second trimester. Techniques utilizing

intra-amniotic instillation of hypertonic saline solution or various prostaglandins regimens, along with medical or osmotic dilators are occasionally used after 18 weeks. Several medical abortion regimens using mifepristone and multiple doses of misoprostol have been reported as being effective in the second trimester. Overall, legal abortion in the United States has a mortality rate of less than 1:100,000. Rates of morbidity and mortality rise with length of gestation. In the United States, more than 60% of abortions are performed before 9 weeks, and more than 90% are performed before 13 weeks' gestation; only 1.2% are performed after 20 weeks. If abortion is chosen, every effort should be made to encourage the patient to seek an early procedure. In the United States, while numerous state laws limiting access to abortion and a federal law banning a rarely used variation of dilation and evacuation have been enacted, abortion remains legal and available until fetal viability (definition varies by state), under *Roe v. Wade*.

Complications resulting from abortion include retained products of conception (often associated with infection and heavy bleeding), uterine perforation, and unrecognized ectopic pregnancy. Immediate analysis of the removed tissue for placenta can exclude or corroborate the diagnosis of ectopic pregnancy. Women who have fever, bleeding, or abdominal pain after abortion should be examined; use of broad-spectrum antibiotics and reaspiration of the uterus are frequently necessary. Hospitalization is advisable if postabortal endometritis requires administration of intravenous antibiotics. Complications following illegal abortion often need emergency care for hemorrhage, septic shock, or uterine perforation.

Prophylactic antibiotics are recommended prior to surgical abortion; for example, a single dose of doxycycline 200 mg orally can be given 1 hour before the procedure. Rh immune globulin should be given to all Rh-negative women following abortion. Contraception should be thoroughly discussed, and contraceptive supplies or pills provided at the time of abortion. There is growing evidence to support the safety and efficacy of immediate postabortal insertion of IUDs.

Mifepristone (RU 486) is approved by the FDA as an oral abortifacient at a dose of 200 mg orally on day 1, followed by misoprostol 800 mcg buccally 24–48 hours later. The WHO recommended regimen includes mifepristone orally followed by misoprostol vaginally, sublingually, or buccally. These combinations are 93% successful in terminating pregnancies of up to 70 days' gestation with few complications. There is a 5–10% risk of incomplete abortion requiring curettage and approximately 1% risk of requiring intervention for excessive bleeding. Overall, the risk of uterine infection is lower with medical than with surgical abortion.

Baiju N et al. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. *BJOG*. 2019;126:1536. [PMID: 31471989]

Mark KS et al. Risk of complication during surgical abortion in obese women. *Am J Obstet Gynecol*. 2018;218:238. [PMID: 29074080]

Schmidt-Hansen M et al. Follow-up strategies to confirm the success of medical abortion of pregnancies up to 10 weeks' gestation: a systematic review with meta-analyses. Am J Obstet Gynecol. 2020;222:551. [PMID: 31715147]

FEMALE SEXUAL DYSFUNCTION

► General Considerations

Female sexual dysfunction is a common problem. Depending on the questions asked, surveys have shown that from 35% to 98% of women report sexual concerns. Questions related to sexual functioning should be asked as part of the routine medical history. Three helpful questions to broach the topic are “Are you currently involved in a sexual relationship?,” “With men, women, or both?,” and “Do you have any sexual concerns or any pain with sex?” If the woman is not involved in a sexual relationship, she should be asked if there are any concerns that are contributing to a lack of sexual behavior. If a history of sexual dysfunction is elicited, a complete history of factors that may affect sexual function should be taken. These factors include her reproductive history (including pregnancies and mode of delivery) as well as history of infertility, sexually transmitted infection, rape or sexual violence, gynecologic or urologic disorders, endocrine abnormalities (such as diabetes mellitus or thyroid disease), neurologic problems, cardiovascular disease, psychiatric disease, and current prescription and over-the-counter medication use. A detailed history of the specific sexual dysfunction should be elicited, and a gynecologic examination should focus on findings that may contribute to sexual complaints.

► Etiology

A. Disorders of Sexual Desire

Sexual desire in women is a complex and poorly understood phenomenon. Emotion is a key factor. Relationship conflict, fear or anxiety related to previous sexual encounters, or history of sexual abuse or violence may contribute to a lack of desire. Physical factors such as chronic illness, fatigue, depression, and specific medical disorders (such as diabetes mellitus, thyroid disease, or adrenal insufficiency) may also contribute. Menopause and attitudes toward aging may play a role. In addition, sexual desire may be influenced by other sexual dysfunction, such as arousal disorders, dyspareunia, or anorgasmia.

B. Sexual Arousal Disorders

Sexual arousal disorders may be both subjective and objective. Sexual stimulation normally leads to genital vasocongestion and lubrication. Some women may have a physiologic response to sexual stimuli but may not subjectively feel aroused because of factors such as distractions; negative expectations; anxiety; fatigue; depression; or medications, such as SSRIs or oral contraceptives. Other women with vaginal atrophy may lack both a subjective and physiologic response to sexual stimuli.

C. Orgasmic Disorders

In spite of subjective and physiologic arousal, women may experience a marked delay in orgasm, diminished sensation of an orgasm, or anorgasmia. The etiology of orgasmic disorders is complex and typically multifactorial, but the cause of a particular patient's orgasmic disorder is usually amenable to treatment.

D. Sexual Pain Disorders

Dyspareunia (female sexual pain) is defined as recurrent or persistent genital pain that is provoked by sexual contact. **Vulvodynia** is a frequent cause of dyspareunia in premenopausal women. It is defined as vulvar pain of at least 3 months' duration without an identifiable cause. The discomfort may be experienced as either constant or intermittent, focal or diffuse, and spontaneous or provoked. There are generally no physical findings, except a subset of patients may have vulvar erythema.

Vaginismus is defined as recurrent or persistent involuntary spasm of the musculature of the lower third of the vagina that interferes with sexual intercourse, resulting from fear, pain, sexual violence, or a negative attitude toward sex, and causing marked distress or interpersonal difficulty. Other medical causes of sexual pain may include vulvovaginitis; vulvar disease, including lichen planus, lichen sclerosus, and lichen simplex chronicus; and pelvic disease, such as endometriosis or chronic PID; or vaginal atrophy.

► Treatment

A. Disorders of Sexual Desire

In the absence of specific medical disorders, arousal or orgasmic disorders or dyspareunia, the focus of therapy is psychological. Cognitive behavioral therapy, sexual therapy, and couples therapy may all play a role. Success with pharmacologic therapy, particularly the use of dopamine agonists or testosterone with estrogen, has been reported, but data from large long-term clinical trials are lacking.

B. Sexual Arousal Disorders

As with disorders of sexual desire, arousal disorders may respond to psychological therapy. The phosphodiesterase inhibitors used in men do not appear to benefit the majority of women with sexual arousal disorders. However, there is some evidence to suggest a role for sildenafil in women with sexual dysfunction due to multiple sclerosis, type 1 diabetes mellitus, spinal cord injury, and antidepressant medications if other established approaches fail.

Flibanserin (Addyi), an antidepressant, was approved by the FDA in August 2015 as an effective treatment of hypoactive sexual desire disorder in premenopausal women; however, it must be used long term to be effective and has significant risks that require specific certifications of providers and pharmacies for dispensation to patients in the United States. While this medication remains available, it is not commonly prescribed.

C. Orgasmic Disorders

For many women, counseling or sex therapy may be adequate treatment. There is an FDA-cleared vacuum device that increases clitoral blood flow and may improve the likelihood of orgasm.

D. Sexual Pain Disorders

Specific medical disorders, such as endometriosis, vulvovaginitis, vulvar dermatoses, or vaginal atrophy, should be treated as outlined in other sections of this chapter.

Vaginismus may be treated initially with sexual counseling and education on anatomy and sexual functioning. The patient can be instructed in self-dilation, using a lubricated finger or dilators of graduated sizes. Before coitus (with adequate lubrication) is attempted, the patient—and then her partner—should be able to easily and painlessly introduce two fingers into the vagina. Penetration should never be forced, and the woman should always be the one to control the depth of insertion during dilation or intercourse. Injection of botulinum toxin has been used successfully in refractory cases.

Since the cause of vulvodynia is unknown, management is difficult. Few treatment approaches have been subjected to methodologically rigorous trials. A variety of topical agents have been tried, although only topical anesthetics (eg, estrogen cream and a compounded mixture of topical amitriptyline 2% and baclofen 2% in a water washable base) have been useful in relieving vulvodynia. Useful oral medications include tricyclic antidepressants, such as amitriptyline in gradually increasing doses from 10 mg/day to 75–100 mg/day; various SSRIs; and anticonvulsants, such as gabapentin, starting at 300 mg three times daily and increasing to 1200 mg three times daily. Biofeedback and physical therapy, with a physical therapist experienced with the treatment of vulvar pain, have been shown to be helpful. Surgery—usually consisting of vestibulectomy—has been useful for women with introital dyspareunia. See also Chapter e6.

► When to Refer

- When symptoms or concerns persist despite first-line therapy.
- For expertise in surgical procedures.

Clayton AH et al. Female sexual dysfunction. *Med Clin North Am*. 2019;103:681. [PMID: 31078200]

Kingsberg SA et al. Bremelanotide for the treatment of hypoactive sexual desire disorder: two randomized phase 3 trials. *Obstet Gynecol*. 2019;134:899. [PMID: 31599840]

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Rogers RG et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the assessment of sexual health of women with pelvic floor dysfunction. *Int Urogynecol J*. 2018;29:647. [PMID: 29577166]

SEXUAL VIOLENCE



ESSENTIALS OF DIAGNOSIS

- The legal definition of rape varies by state and geographic location. The term “sexual violence” is used by the CDC and will be used in this discussion. It can be committed by a stranger, but more commonly the assailant is known to the victim, including a current or former partner or spouse (a form of intimate partner violence [IPV]).
- All victims of sexual violence should be offered emergency contraception.
- The large number of individuals affected, the enormous health care costs, and the need for a multidisciplinary approach make sexual violence and IPV important health care issues.
- Knowledge of state laws and collection of evidence requirements are essential for clinicians evaluating possible victims of sexual violence, including IPV.

► General Considerations

Rape, or sexual assault, is legally defined in different ways in various jurisdictions. Clinicians and emergency department personnel who deal with victims of sexual violence should be familiar with the laws pertaining to sexual assault in their own state. From a medical and psychological viewpoint, it is essential that persons treating victims of sexual violence recognize the nonconsensual and violent nature of the crime. About 95% of reported victims of sexual violence are women. Each year in the United States, 4.8 million incidents of physical or sexual assault are reported by women. Penetration may be vaginal, anal, or oral and may be by the penis, hand, or a foreign object. The assailant may be unknown to the victim or, more frequently, may be an acquaintance or even the spouse.

“Unlawful sexual intercourse,” or statutory rape, is intercourse with a female before the age of majority even with her consent.

Health care providers can have a significant impact in increasing the reporting of sexual violence and in identifying resources for the victims. The International Rescue Committee has developed a multimedia training tool to encourage competent, compassionate, and confidential clinical care for sexual violence survivors in low-resource settings. They have studied this intervention in over 100 health care providers and found that knowledge increased from 49% to 62% ($P < 0.001$) and confidence from 58% to 73% ($P < 0.001$) in clinical care for sexual violence survivors following training. There was also a documented increase in eligible survivors receiving emergency contraception from 50% to 82% ($P < 0.01$), HIV postexposure prophylaxis from 42% to 92% ($P < 0.001$), and sexually transmitted infection prophylaxis and treatment from 45% to 96% ($P < 0.01$). This training encourages providers to

offer care in the areas of pregnancy and sexually transmitted infection prevention as well as assistance for psychological trauma.

Because sexual violence is a personal crisis, each patient will react differently, but anxiety disorders and posttraumatic stress disorder (PTSD) are common sequelae. The **rape trauma syndrome** comprises two principal phases. (1) Immediate or acute: shaking, sobbing, and restless activity may last from a few days to a few weeks. The patient may experience anger, guilt, or shame or may repress these emotions. Reactions vary depending on the victim's personality and the circumstances of the attack. (2) Late or chronic: problems related to the attack may develop weeks or months later. Sexual violence survivors are at increased risk for developing several psychological and behavioral adverse effects, including PTSD, sleep disturbances, anxiety, depression, suicide attempt, and medication misuse.

Clinicians and emergency department personnel who deal with victims of sexual violence should work with community rape crisis centers or other sources of ongoing psychological support and counseling.

► Examination

The clinician who first sees the alleged victim of sexual violence should be empathetic and prepared with appropriate evidence collection and treatment materials. Standardized information and training, such as the program created by the International Rescue Committee, can be a helpful resource to the providers caring for these patients. Many emergency departments have a protocol for sexual violence victims and personnel who are trained in interviewing and examining victims of sexual violence.

► Treatment

- Give analgesics or sedatives if indicated. Administer tetanus toxoid if deep lacerations contain soil or dirt particles.
- Give ceftriaxone, 250 mg intramuscularly, plus azithromycin, 1 g orally, to prevent gonorrhea and chlamydia. In addition, give metronidazole, 2 g orally, as a single dose to treat trichomoniasis. Incubating syphilis will probably be prevented by these medications, but the VDRL test should be repeated 6 weeks after the assault.
- Prevent pregnancy by using one of the methods discussed under Emergency Contraception.
- Vaccinate against hepatitis B.
- Offer HIV prophylaxis (see Chapter 31).
- Because women who are sexually assaulted are at increased risk for long-term psychological sequelae, such as PTSD and anxiety disorders, it is critical that the patient and her family and friends have a source of ongoing counseling and psychological support.

► When to Refer

All women who seek care for sexual assault should be referred to a facility that has expertise in the management of victims of sexual violence and is qualified to perform expert forensic examination, if requested.

Adams JA et al. Interpretation of medical findings in suspected child sexual abuse: an update for 2018. *J Pediatr Adolesc Gynecol*. 2018;31:225. [PMID: 29294380]

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 777: Sexual assault. *Obstet Gynecol*. 2019;133:e296. [PMID: 30913202]

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BARTHOLIN DUCT CYSTS & ABSCESES

Trauma or infection may involve the Bartholin duct, causing obstruction of the gland. Drainage of secretions is obstructed, leading to pain, swelling, and abscess formation (Figure 18-1).

The principal symptoms are periodic painful swelling on either side of the introitus and dyspareunia. A fluctuant swelling, usually 1–4 cm in diameter lateral to either labium minus, is a sign of occlusion of a Bartholin duct. Tenderness is suggestive of active infection.

Purulent drainage or secretions from the gland should be tested for gonorrhea, *Chlamydia*, and other pathogens, and treated accordingly (see Chapter 33); frequent warm sitz baths may be helpful. Abscesses or cysts that are symptomatic should undergo incision and drainage with additional efforts to keep the drainage tract open (eg, Word catheter or marsupialization). Marsupialization should be considered for recurrence. Antibiotics are unnecessary unless cellulitis is present. In women under 40 years of age, asymptomatic cysts do not require therapy; in women over age 40, biopsy or removal should be considered to rule out vulvar carcinoma.

► When to Refer

When surgical therapy (marsupialization) is indicated.

Dole DM et al. Management of Bartholin duct cysts and gland abscesses. *J Midwifery Womens Health*. 2019;64:337. [PMID: 30734519]

Omole F et al. Bartholin duct cyst and gland abscess: office management. *Am Fam Physician*. 2019;99:760. [PMID: 31194482]



▲ Figure 18-1. Bartholin cyst (abscess). The Bartholin gland is located in the lower two-thirds of the introitus. (From Susan Lindsley, Public Health Image Library, CDC.)

VAGINITIS**ESSENTIALS OF DIAGNOSIS**

- ▶ Vaginal irritation.
- ▶ Pruritus.
- ▶ Abnormal or malodorous discharge.

► General Considerations

Inflammation and infection of the vagina are common gynecologic complaints, resulting from a variety of pathogens, allergic reactions to vaginal contraceptives or other products, vaginal atrophy, or friction during coitus. The normal vaginal pH is 4.5 or less, and *Lactobacillus* is the predominant organism. Normal secretions during the middle of the cycle, or during pregnancy, can be confused with vaginitis.

► Clinical Findings

When the patient complains of vaginal irritation, pain, pruritus or unusual or malodorous discharge, a history should be taken, noting the onset, location, duration, and characterization of symptoms including triggers and alleviating factors. Additional history should include the LMP; recent sexual activity; use of contraceptives, tampons, or douches; and recent changes in medications or use of antibiotics. The physical examination should include careful inspection of the vulva and speculum examination of the vagina and cervix. A vaginal, cervical, or urine sample can be obtained for detection of gonococcus and *Chlamydia*, if clinically indicated. Evaluation for yeast, bacterial vaginosis, and trichomonas should be performed. The vaginal pH should be tested; it is frequently greater than 4.5 in infections due to trichomonads and bacterial vaginosis. A bimanual examination to look for evidence of pelvic infection, namely cervical motion, uterine, or adnexal tenderness, should follow. Point-of-care testing is available for all three main organisms that cause vaginitis and can be used if microscopy is not available or for confirmatory testing of microscopy.

A. Vulvovaginal Candidiasis

Pregnancy, diabetes mellitus, and use of broad-spectrum antibiotics or corticosteroids predispose patients to *Candida* infections. Heat, moisture, and occlusive clothing also contribute to the risk. Pruritus, vulvovaginal erythema, and a white curd-like discharge that is not malodorous are found (Figure 18–2). Microscopic examination with 10% potassium hydroxide reveals hyphae and spores. A swab for cultures or for PCR testing may be performed if *Candida* is suspected but not demonstrated.

B. *Trichomonas vaginalis* Vaginitis

This sexually transmitted protozoal flagellate infects the vagina, Skene ducts, and lower urinary tract in women and the lower genitourinary tract in men. Pruritus and a malodorous frothy, yellow-green discharge occur, along with diffuse vaginal erythema and red macular lesions on the cervix in severe cases (“strawberry cervix,” Figure 18–3).



▲ Figure 18–2. Cervical candidiasis. (Public Health Image Library, CDC.)

Motile organisms with flagella seen by microscopic examination of a wet mount with saline solution is confirmatory but is identified in only 60–70% of cases. Nucleic acid amplification tests are highly sensitive and specific to identify *T vaginalis*. Other commercially available rapid diagnostic tests (eg, Affirm VP III and OSOM *Trichomonas* Rapid Test) have high sensitivity.

C. Bacterial Vaginosis

Bacterial vaginosis is a polymicrobial disease that is *not* considered a sexually transmitted infection, but sexual activity is a risk factor. An overgrowth of *Gardnerella* and



▲ Figure 18–3. Strawberry cervix in *Trichomonas vaginalis* infection, with inflammation and punctate hemorrhages. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)



▲ Figure 18–4. Clue cells seen in bacterial vaginosis due to *Gardnerella vaginalis*. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

other anaerobes is often associated with increased malodorous discharge without obvious vulvitis or vaginitis. The discharge is grayish and sometimes frothy, with a pH of 5.0–5.5. An amine-like (“fishy”) odor is present if a drop of discharge is alkalinized with 10% potassium hydroxide. On wet mount in saline, epithelial cells are covered with bacteria to such an extent that cell borders are obscured (**clue cells**, Figure 18–4). Vaginal cultures are generally not useful in diagnosis; however, molecular testing is available.

Treatment

A. Vulvovaginal Candidiasis

A variety of topical and oral regimens are available to treat vulvovaginal candidiasis. Women with uncomplicated vulvovaginal candidiasis will usually respond to a 1- to 3-day regimen of a topical azole or a one-time dose of oral fluconazole 150 mg. Women with complicated infection (including four or more episodes in 1 year [*recurrent vulvovaginal candidiasis*], severe signs and symptoms, non-albicans species, uncontrolled diabetes mellitus, HIV infection, corticosteroid treatment, or pregnancy) should receive 7–14 days of a topical regimen or two doses of oral fluconazole 3 days apart. In recurrent non-albicans infections, boric acid 600 mg in a gelatin capsule intravaginally once daily for 2 weeks is approximately 70% effective. If recurrence occurs, referral to a gynecologist or an infectious disease specialist is indicated.

1. Single-dose regimens—Effective single-dose regimens include miconazole (1200-mg vaginal suppository), tioconazole (6.5% cream, 5 g vaginally), sustained-release butoconazole (2% cream, 5 g vaginally), or fluconazole (150-mg oral tablet).

2. Three-day regimens—Effective 3-day regimens include butoconazole (2% cream, 5 g vaginally once daily), clotrimazole (2% cream, 5 g vaginally once daily), terconazole (0.8% cream, 5 g, or 80-mg vaginal suppository once daily), or miconazole (200-mg vaginal suppository once daily).

3. Seven-day regimens—The following regimens are given once daily: clotrimazole (1% cream), miconazole (2% cream, 5 g, or 100-mg vaginal suppository), or terconazole (0.4% cream, 5 g).

4. Recurrent vulvovaginal candidiasis (maintenance therapy)—Clotrimazole (500-mg vaginal suppository once weekly or 200 mg cream twice weekly) or fluconazole (100, 150, or 200 mg orally once weekly) is an effective regimen for maintenance therapy for up to 6 months.

B. *Trichomonas vaginalis* Vaginitis

Treatment of both partners simultaneously is recommended; metronidazole or tinidazole, 2 g orally as a single dose or 500 mg orally twice a day for 7 days, is usually used.

In the case of treatment failure with metronidazole in the absence of reexposure, the patient should be re-treated with metronidazole, 500 mg orally twice a day for 7 days, or tinidazole, 2 g orally as a single dose. If treatment failure occurs again, give metronidazole or tinidazole, 2 g orally once daily for 5 days. If this is not effective in eradicating the organisms, metronidazole and tinidazole susceptibility testing can be arranged with the Centers for Disease Control and Prevention (CDC) at 404-718-4141 or at <https://www.cdc.gov/std>. Women infected with *T vaginalis* are at increased risk for concurrent infection with other sexually transmitted diseases (STDs) and should be offered comprehensive STD testing.

C. Bacterial Vaginosis

The recommended regimens are metronidazole (500 mg orally, twice daily for 7 days), clindamycin vaginal cream (2%, 5 g, once daily for 7 days), or metronidazole gel (0.75%, 5 g, twice daily for 5 days). Alternative regimens include clindamycin (300 mg orally twice daily for 7 days), clindamycin ovules (100 g intravaginally at bedtime for 3 days), tinidazole (2 g orally once daily for 3 days), or tinidazole (1 g orally once daily for 7 days). The National STD Curriculum offers a helpful training module to clinicians to review current recommendations for treatment of vaginitis (<https://www.std.uw.edu/custom/self-study/vaginitis>).

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 215: Vaginitis in nonpregnant patient. Obstet Gynecol. 2020;135:e1. [PMID: 31856123]

Giovannini AF et al. Bacterial vaginosis and desquamative inflammatory vaginitis. N Engl J Med. 2019;380:1088. [PMID: 30865815]

Neal CM et al. Noncandidal vaginitis: a comprehensive approach to diagnosis and management. Am J Obstet Gynecol. 2020; 222:114. [PMID: 31513780]

PELVIC INFLAMMATORY DISEASE (Salpingitis, Endometritis)

ESSENTIALS OF DIAGNOSIS

- ▶ Lower abdominal or pelvic pain.
- ▶ Uterine, adnexal, or cervical motion tenderness.
- ▶ Absence of a competing diagnosis.

► General Considerations

Pelvic inflammatory disease (PID) is a polymicrobial infection of the upper genital tract associated with the sexually transmitted organisms *Neisseria gonorrhoeae* and *Chlamydia trachomatis* as well as endogenous organisms, including anaerobes, *Haemophilus influenzae*, enteric gram-negative rods, and streptococci. It is most common in young, nulliparous, sexually active women with multiple partners and is a leading cause of infertility and ectopic pregnancy. The use of barrier methods of contraception may provide significant protection.

► Clinical Findings

A. Symptoms and Signs

Patients with PID most commonly present with lower abdominal pain. Additional complaints may include AUB and abnormal vaginal discharge. Systemic features such as fever typically indicate more severe disease, including pelvic abscess. Right upper quadrant pain may indicate an associated perihepatitis (**Fitz-Hugh-Curtis syndrome**). Diagnosis of PID is complicated by the fact that many women may have subtle or mild symptoms that are not readily recognized as PID, such as postcoital bleeding, urinary frequency, or low back pain.

B. Minimum Diagnostic Criteria

PID is diagnosed clinically. Women with cervical motion, uterine, or adnexal tenderness meet diagnostic criteria for PID and should be treated with antibiotics unless there is a competing diagnosis, such as ectopic pregnancy or appendicitis.

C. Additional Criteria

No single historical, physical, or laboratory finding is definitive for acute PID. The following criteria may be used to enhance the specificity of the diagnosis: (1) oral temperature higher than 38.3°C, (2) abnormal cervical or vaginal discharge with white cells on saline microscopy (greater than 1 leukocyte per epithelial cell), (3) elevated erythrocyte sedimentation rate, (4) elevated C-reactive protein, and (5) laboratory documentation of cervical infection with *N gonorrhoeae* or *C trachomatis*. Testing for gonorrhea and chlamydia should be performed routinely, but treatment should not be delayed while awaiting results.

► Differential Diagnosis

Appendicitis, ectopic pregnancy, septic abortion, hemorrhagic or ruptured ovarian cysts or tumors, torsion of an ovarian cyst, degeneration of a myoma, and acute enteritis must be considered. PID is more likely to occur when there is a prior history of PID, recent sexual contact, recent onset of menses, recent insertion of an IUD, or recent intercourse with a partner who has a sexually transmitted infection. Acute PID is highly unlikely when recent (within 60 days) intercourse has not taken place. A sensitive serum pregnancy test should be obtained to rule out ectopic pregnancy. Pelvic ultrasonography is helpful to rule out tubo-ovarian abscess. Laparoscopy should be considered

when imaging is not informative and the patient has not responded to outpatient treatment for PID or has not improved after 72 hours of inpatient treatment; it should also be considered when an acutely ill patient has a high suspicion of a competing diagnosis requiring surgical intervention (eg, appendicitis). The appendix should be visualized at laparoscopy to rule out appendicitis. Cultures should be obtained at laparoscopy.

► Treatment

A. Antibiotics

Early treatment with appropriate antibiotics effective against *N gonorrhoeae*, *C trachomatis*, and the endogenous organisms listed above is essential to prevent long-term sequelae. The sexual partner should be treated appropriately. Most women with mild to moderate disease can be treated successfully as an outpatient. The recommended outpatient regimen is ceftriaxone (250 mg intramuscularly) plus doxycycline (100 mg orally twice a day for 14 days) or a single dose of cefoxitin (2 g intramuscularly) with probenecid (1 g orally) plus doxycycline (100 mg orally twice daily for 14 days). Metronidazole 500 mg orally twice daily for 14 days may also be added to either of these two regimens and will also treat bacterial vaginosis that is frequently associated with PID. For patients with severe disease or those who meet criteria for hospitalization, there are two recommended regimens. One regimen includes either cefotetan, 2 g intravenously every 12 hours, or cefoxitin, 2 g intravenously every 6 hours, plus doxycycline, 100 mg orally or intravenously every 12 hours. The other recommended regimen is clindamycin, 900 mg intravenously every 8 hours, plus gentamicin, a loading dose of 2 mg/kg intravenously or intramuscularly followed by a maintenance dose of 1.5 mg/kg every 8 hours (or as a single daily dose, 3–5 mg/kg). These regimens should be continued for a minimum of 24 hours after the patient shows significant clinical improvement. Then, an oral regimen should be given for a total course of antibiotics of 14 days with either doxycycline, 100 mg orally twice a day, or clindamycin, 450 mg orally four times a day. If a tubo-ovarian abscess is present, clindamycin or metronidazole should be used with doxycycline to complete the 14-day treatment for better anaerobic coverage.

B. Surgical Measures

Tubo-ovarian abscesses may require surgical excision or transcutaneous or transvaginal aspiration. Unless rupture is suspected, institute high-dose antibiotic therapy in the hospital, and monitor therapy with ultrasound. In 70% of cases, antibiotics are effective; in 30%, there is inadequate response in 48–72 hours, and surgical intervention is required. Unilateral adnexitomy is acceptable for unilateral abscess. Hysterectomy and bilateral salpingo-oophorectomy may be necessary for overwhelming infection or in cases of chronic disease with intractable pelvic pain.

► Prognosis

In spite of treatment, long-term sequelae, including repeated episodes of infection, chronic pelvic pain,

dyspareunia, ectopic pregnancy, or infertility, develop in one-fourth of women with acute disease. The risk of infertility increases with repeated episodes of salpingitis: it is estimated at 10% after the first episode, 25% after a second episode, and 50% after a third episode.

► When to Admit

The following patients with acute PID should be admitted for intravenous antibiotic therapy:

- The patient has a tubo-ovarian abscess (direct inpatient observation for at least 24 hours before switching to outpatient parenteral therapy).
- The patient is pregnant.
- The patient is unable to follow or tolerate an outpatient regimen.
- The patient has not responded clinically to outpatient therapy within 72 hours.
- The patient has severe illness, nausea and vomiting, or high fever.
- Another surgical emergency, such as appendicitis, cannot be ruled out.

Curry A et al. Pelvic inflammatory disease: diagnosis, management and prevention. *Am Fam Physician*. 2019;100:357. [PMID: 31524362]

Ross J et al. 2017 European guideline for the management of pelvic inflammatory disease. *Int J STD AIDS*. 2018;29:108. [PMID: 29198181]

US Preventive Services Task Force; Krist AH et al. Behavioral counseling interventions to prevent sexually transmitted infections: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;324:674. [PMID: 32809008]

CONDYLOMA ACUMINATA

Warty growths on the vulva, perianal area, vaginal walls, or cervix are caused by various types of the human papillomavirus (HPV). Pregnancy and immunosuppression favor growth. Ninety percent of genital warts are caused by HPV 6 and 11. With increasing use of the HPV vaccine in the United States, the prevalence of HPV types 6, 11, 16 and 18 decreased from 11.5% in 2003–2006 to 4.3% in 2009–2012 among girls aged 14–19 years, and from 18.5% to 12.1% in women aged 20–24 years. Vulvar lesions may be obviously wart-like or may be diagnosed only after application of 4% acetic acid (vinegar) and colposcopy, when they appear whitish, with prominent papillae. Vaginal lesions may show diffuse hypertrophy or a cobblestone appearance.

Recommended treatments for vulvar warts include podophyllium resin 10–25% in tincture of benzoin (do not use during pregnancy or on bleeding lesions) or 80–90% trichloroacetic or bichloroacetic acid, carefully applied to avoid the surrounding skin. The pain of bichloroacetic or trichloroacetic acid application can be lessened by a sodium bicarbonate paste applied immediately after treatment. Podophyllum resin must be washed off after 2–4 hours. Freezing with liquid nitrogen or a cryoprobe and electrocautery are also effective. Patient-applied regimens,

useful when the entire lesion is accessible to the patient, include podofilox 0.5% solution or gel, imiquimod 5% cream, or sinecatechins 15% ointment. Vaginal warts may be treated with cryotherapy with liquid nitrogen or trichloroacetic acid. Extensive warts may require treatment with CO₂ laser, electrocautery, or excision under local or general anesthesia.

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Meites E et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68:698. [PMID: 31415491]

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) (Dysplasia of the Cervix)



ESSENTIALS OF DIAGNOSIS

- The presumptive diagnosis is made by an abnormal Papanicolaou smear.
- Diagnose by colposcopically directed biopsy.

► General Considerations

The squamocolumnar junction of the cervix is an area of active squamous cell proliferation. In childhood, this junction is located on the exposed vaginal portion of the cervix. At puberty, because of hormonal influence and possibly because of changes in the vaginal pH, the squamous margin begins to encroach on the single-layered, mucus-secreting epithelium, creating an area of metaplasia (**transformation zone**). Infection with HPV (see Prevention, below) may lead to cellular abnormalities, which over time may develop into squamous cell dysplasia or cancer. There are varying degrees of dysplasia (Table 18–5), defined by the degree of cellular atypia; all atypia must be observed and treated if persistent or worsening.

Table 18–5. Classification systems for Papanicolaou smears.

Dysplasia	CIN	Bethesda System
Benign	Benign	Normal
Benign with inflammation	Benign with inflammation	Normal, ASC-US
Mild dysplasia	CIN I	Low-grade SIL
Moderate dysplasia	CIN II	High-grade SIL
Severe dysplasia	CIN III	High-grade SIL
Carcinoma in situ	—	—
Invasive cancer	Invasive cancer	Invasive cancer

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; SIL, squamous intraepithelial lesion.



▲ Figure 18–5. Erosion of the cervix due to cervical intraepithelial neoplasia (CIN), a precursor lesion to cervical cancer. (Public Health Image Library, CDC.)

► Clinical Findings

There are no specific symptoms or signs of CIN. The presumptive diagnosis is made by cytologic screening of an asymptomatic population with no grossly visible cervical changes. All visible abnormal cervical lesions should be biopsied (Figure 18–5).

► Screening & Diagnosis

A. Cytologic Examination (Papanicolaou Smear)

In immunocompetent women, cervical cancer screening should begin at age 21. The recommendation to start screening at age 21 years regardless of the age of onset of sexual intercourse is based on the very low incidence of cancer in younger women and the potential for adverse effects associated with treatment of young women with abnormal cytology screening results. In contrast to the high rate of infection with HPV in sexually active adolescents, invasive cervical cancer is very rare in women younger than age 21 years. The US Preventive Services Task Force (USPSTF) 2018 statement recommends screening for cervical cancer in women aged 21 to 65 years as follows: for women aged 21 to 29 years, screening with cytology (conventional [Papanicolaou smear] or liquid based) alone every 3 years; and for women aged 30 to 65 years, screening with cytology alone every 3 years, with high-risk HPV testing alone every 5 years, or with a combination of cytology and high-risk HPV testing (cotesting) every 5 years. These recommendations apply to women who have a cervix, regardless of their sexual history or HPV vaccination status. They do not apply to women who have previously been diagnosed with cervical cancer or a high-grade precancerous cervical lesion (ie, CIN grade II or III) or to women with immune compromise (eg, living with HIV) or with in utero exposure to diethylstilbestrol; such women may require more frequent screening.

The USPSTF recommends against screening for cervical cancer for women younger than age 21 years, for women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical

cancer, and for women who have had a hysterectomy with removal of the cervix and who have no history of cervical cancer or a high-grade precancerous lesion.

The goal of screening is to identify high-grade precancerous cervical lesions to prevent their progression to cervical cancer. These high-grade cervical lesions may be treated with excisional and ablative therapies. Screening and management guidelines are continually undergoing evaluation and change frequently. For the most current guidelines, please consult these sources: <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/cervical-cancer-screening> (August 2018) and <https://www.asccp.org/guidelines> (April 2019).

Cytologic reports from the laboratory may describe findings in one of several ways (see Table 18–5). The Bethesda System uses the terminology “atypical squamous cells of unknown significance” (ASC-US) and “squamous intraepithelial lesions,” either low-grade (LSIL) or high-grade (HSIL). HPV DNA testing can be used adjunctively as a triage test to stratify risk in women age 21 years and older with a cytologic diagnosis of ASC-US and in postmenopausal women with a cytologic diagnosis of ASC-US or LSIL.

B. Colposcopy

Women with ASC-US and a negative HPV screening may be followed up in 1 year for a repeat Papanicolaou smear and HPV co-testing. If the HPV screen is positive, colposcopy is indicated. If HPV screening is unavailable, repeat cytology may be done at 12 months. Women between ages 21–24 with LSIL should have repeat Papanicolaou smear in 1 year. Women age 25 and older with SIL or atypical glandular cells should undergo colposcopy. Viewing the cervix with 10–20 × magnification allows for assessment of the size and margins of an abnormal transformation zone and determination of extension into the endocervical canal. The application of 3–5% acetic acid (vinegar) dissolves mucus, and the acid's desiccating action sharpens the contrast between normal and actively proliferating squamous epithelium. Abnormal changes include white patches and vascular atypia, which indicate areas of greatest cellular activity.

C. Biopsy

Colposcopically directed biopsy and endocervical curettage are office procedures. Data from both cervical biopsy and endocervical curettage are important in deciding on treatment.

► Prevention

Cervical infection with the HPV is associated with virtually all cervical dysplasias and cancers. There are over 100 recognized HPV subtypes. Types 6 and 11 tend to cause genital warts and mild dysplasia and rarely progress to cervical cancer; types 16, 18, 31, and others cause higher-grade dysplasia. The HPV 9-valent (Gardasil-9) recombinant vaccine (9vHPV) is indicated for the prevention of cervical, vaginal, and vulvar cancers (in women) and anal cancers (in women and men) caused by HPV types 16, 18, 31, 33, 45, 52, and 58; genital warts (in women and men) caused by HPV types 6 and 11; and precancerous/dysplastic lesions of cervix, vagina, vulva (in women), and anus (in

women and men) caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Gardasil-9 is recommended for vaccination of females and males ages 9–45 years old. The earlier HPV 4-valent vaccine known as Gardasil that was indicated for prevention of diseases related to HPV types 6, 11, 16, and 18 has been discontinued in the United States. The use of HPV vaccination in the United States continues to increase; however, the HPV vaccination continues to lag far behind other vaccines recommended for adolescents. In 2018, 51% of adolescents were up to date with the three-dose HPV vaccine series compared with 48% in 2017.

Because complete coverage of all carcinogenic HPV types is not provided by either vaccine, all women need to have regular cervical cancer screening as outlined above. In addition to vaccination, preventive measures include limiting the number of sexual partners and thus exposure to HPV, using a condom for coitus, and smoking cessation and avoiding exposure to secondhand smoke.

Treatment

Treatment varies depending on the degree and extent of CIN. Biopsies should precede treatment, except in cases of HSIL where it may be appropriate to proceed directly to a LEEP.

A. Cryosurgery

The use of freezing (cryosurgery) is effective for noninvasive small lesions visible on the cervix without endocervical extension.

B. CO₂ Laser

This well-controlled method minimizes tissue destruction. It is colposcopically directed and requires special training. It may be used with large visible lesions and involves vaporization of the transformation zone on the cervix and the distal 5–7 mm of endocervical canal.

C. Loop Excision

When the CIN is clearly visible in its entirety, a wire loop can be used for excisional biopsy. This office procedure, called **LEEP (loop electrosurgical excision procedure)**, done with local anesthesia is quick and straightforward. Cutting and hemostasis are achieved with a low-voltage electrosurgical machine.

D. Conization of the Cervix

Conization is surgical removal of the entire transformation zone and endocervical canal. It is reserved for cases of severe dysplasia (CIN III) or carcinoma in situ, particularly those with endocervical extension. It can be performed with scalpel, CO₂ laser, needle electrode, or large-loop excision.

Follow-Up

Because recurrence is possible—especially in the first 2 years after treatment—and because the false-negative rate of a single cervical cytologic test is 20%, close follow-up after colposcopy and biopsy is imperative. Following excisional or ablative procedure, HPV-based testing should be performed at 6 months and then annually for 3 years

followed by HPV-based testing every 3 years for at least 25 years. Colposcopy and endocervical sampling should be performed for any abnormality.

The American Society for Colposcopy and Cervical Pathology Guidelines for cervical cancer screening and management of abnormal Papanicolaou smears are available online (<https://www.asccp.org/guidelines>).

When to Refer

- Patients with CIN II/III should be referred to an experienced colposcopist.
- Patients requiring conization biopsy should be referred to a gynecologist.

Arbyn M et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev*. 2018;5:CD009069. [PMID: 29740819]

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Smith RA et al. Cancer screening in the United States, 2019: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2019;69:184. [PMID: 30875085]

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CARCINOMA OF THE CERVIX



ESSENTIALS OF DIAGNOSIS

- Increased risk in women who smoke and those with HIV or high-risk HPV types.
- Gross lesions should be evaluated by colposcopically directed biopsies and not cytology alone.

General Considerations

Cervical cancer is the third most common cancer in the world and the leading cause of cancer death among women in developing countries. It is considered a sexually

transmitted disease as both squamous cell and adenocarcinoma of the cervix are secondary to infection with HPV, primarily types 16 and 18. Women infected with HIV and other forms of immunosuppression are at an increased risk for high-risk HPV infection and CIN. Smoking appears to be a cofactor for squamous cell carcinoma (SCC). SCC accounts for approximately 80% of cervical cancers, while adenocarcinoma accounts for 15%, and adenosquamous carcinoma for 3–5%; neuroendocrine or small cell carcinomas are rare.

SCC appears first in the intraepithelial layers (the preinvasive stage, or carcinoma in situ). Preinvasive cancer (CIN III) is most commonly diagnosed in women 25–35 years of age. Two to 10 years are required for carcinoma to penetrate the basement membrane and become invasive. While cervical cancer mortality has declined steadily in the United States due to high rates of screening and improved treatment, the rate of decline has slowed in recent years. In general, Black women experienced much higher incidence and mortality than White women. The 5-year survival rate ranges from 73% for stage II cervical cancer to less than 20% for stage IV.

► Clinical Findings

A. Symptoms and Signs

Early cervical cancer is often asymptomatic. The most common signs are irregular or heavy bleeding and postcoital spotting. Bladder and rectal dysfunction or fistulas and pain are late symptoms.

B. Cervical Biopsy and Endocervical Curettage or Conization

These procedures are necessary steps after a positive Pap–nicoletti smear to determine the extent and depth of invasion of the cancer. Even if the smear is positive, definitive diagnosis must be established through biopsy before additional treatment is given.

C. "Staging" or Estimate of Gross Spread of Cancer of the Cervix

Staging of invasive cervical cancer is achieved by clinical evaluation, usually conducted under anesthesia. Further examinations, such as ultrasonography, CT, MRI, lymphangiography, laparoscopy, and fine-needle aspiration, are valuable for treatment planning.

► Complications

Metastases to regional lymph nodes occur with increasing frequency from stage I to stage IV. Paracervical extension occurs in all directions from the cervix. The ureters may become obstructed lateral to the cervix, causing hydronephrosis and consequently impaired kidney function. Almost two-thirds of patients with untreated carcinoma of the cervix die of uremia when ureteral obstruction is bilateral. Pain in the back, in the distribution of the lumbosacral plexus, is often indicative of neurologic involvement. Gross edema of the legs may be indicative of vascular and lymphatic stasis due to tumor. Vaginal fistulas

to the rectum and urinary tract are severe late complications. Hemorrhage is the cause of death in 10–20% of patients with extensive invasive carcinoma.

► Prevention

Vaccination with the recombinant 9-valent HPV vaccine (Gardasil-9) can prevent cervical cancer by targeting the HPV types that pose the greatest risk as well as protect against low-grade and precancerous lesions caused by other HPV types (see Cervical Intraepithelial Neoplasia).

► Treatment

A. Emergency Measures

Vaginal hemorrhage originates from gross ulceration and cavitation in later stage cervical carcinoma. Ligation and suturing of the cervix are usually not feasible, but emergent vaginal packing, cauterization, tranexamic acid, and irradiation are helpful to stop bleeding temporarily. Ligation, resection, or embolization of the uterine or hypogastric arteries may be lifesaving when other measures fail.

B. Specific Measures

1. Carcinoma in situ (stage 0)—In women for whom childbearing is not a consideration, total hysterectomy is the definitive treatment. In women who wish to retain the uterus, acceptable alternatives include cryosurgery, laser surgery, LEEP, or cervical conization. HPV-based testing should be repeated at 6 months and then annually for 3 years followed by HPV-based testing every 3 years for at least 25 years.

2. Invasive carcinoma—Microinvasive carcinoma (stage IA1) is treated with simple, extrafascial hysterectomy. Stages IA2 and IB1 cancers are typically treated with modified radical hysterectomy and pelvic lymphadenectomy. Women with stage IB1 may be candidates for fertility-sparing surgery, which includes radical trachelectomy and lymph node dissection with preservation of the uterus and ovaries. Women with IB2 cancers typically undergo radical hysterectomy and pelvic lymphadenectomy. Adjuvant chemotherapy or radiation may be used for women with risk factors for recurrence. Women with locally advanced disease (stage IB3 to IVA) usually are treated with primary chemoradiation. Metastatic disease (stage IVB) typically is treated with chemotherapy.

► Prognosis

The overall 5-year relative survival rate for carcinoma of the cervix is 68% in White women and 55% in Black women in the United States. Survival rates are inversely proportionate to the stage of cancer: stage 0, 99–100%; stage IA, more than 94%; stage IB–IIA, 73–90%; stage IIB, 65%; stage III, 40%; and stage IV, less than 20%.

► When to Refer

All patients with invasive cervical carcinoma (stage IA or higher) should be referred to a gynecologic oncologist.

American Cancer Society. Survival rates for cervical cancer, by stage, January 3, 2020. <https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/survival.html>

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Johnson CA et al. Cervical cancer: an overview of pathophysiology and management. *Semin Oncol Nurs.* 2019;35:166. [PMID: 30878194]

Stolnicu S et al. Recent advances in invasive adenocarcinoma of the cervix. *Virchows Arch.* 2019;475:537. [PMID: 31209635]

US Preventive Services Task Force; Curry SJ et al. Screening for cervical cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2018;320:674. [PMID: 30140884]

CARCINOMA OF THE ENDOMETRIUM



ESSENTIALS OF DIAGNOSIS

- ▶ AUB is the presenting sign in 90% of cases.
- ▶ After a negative pregnancy test, endometrial tissue is required to confirm the diagnosis.

General Considerations

Adenocarcinoma of the endometrium is the most common cancer of the female genital tract in developed countries. It occurs most often in women 50–70 years of age. Obesity, nulliparity, diabetes mellitus, polycystic ovaries with prolonged anovulation, unopposed estrogen therapy, and the extended use of tamoxifen for the treatment of breast cancer are risk factors. Women with a family history of colon cancer (hereditary nonpolyposis colorectal cancer, Lynch syndrome) are at significantly increased risk, with a lifetime incidence as high as 30%.

Abnormal bleeding is the presenting sign in 90% of cases. Any postmenopausal bleeding requires investigation. Pain generally occurs late in the disease, with metastases or infection.

Papanicolaou smear of the cervix occasionally shows atypical endometrial cells but is an insensitive diagnostic tool. Endocervical and endometrial sampling is the only reliable means of diagnosis and is important to differentiate endometrial cancer from hyperplasia, which often can be treated hormonally. Simultaneous hysteroscopy can be a valuable addition in order to localize polyps or other lesions within the uterine cavity. Pelvic ultrasonography may be used to determine the thickness of the endometrium as an indication of hypertrophy and possible neoplastic change. The finding of a thin endometrial lining on ultrasound (4 mm or less) in a postmenopausal woman is clinically reassuring in cases where very little tissue is obtainable through endometrial biopsy.

Prevention

Prompt endometrial sampling for patients who report abnormal menstrual bleeding or postmenopausal uterine bleeding will reveal many incipient as well as clinical cases of endometrial cancer. Younger women with chronic

anovulation are at risk for endometrial hyperplasia and subsequent endometrial cancer; they can significantly reduce the risk of hyperplasia with the use of oral contraceptives, cyclic progestin therapy, or a levonorgestrel IUD.

Staging

Staging and prognosis are based on surgical and pathologic evaluation only. Examination under anesthesia, endometrial and endocervical sampling, chest radiography, intravenous urography, cystoscopy, sigmoidoscopy, transvaginal sonography, and MRI will help determine the extent of the disease and its appropriate treatment.

Treatment

Treatment consists of total hysterectomy and bilateral salpingo-oophorectomy. Peritoneal washings for cytologic examination are routinely taken and lymph node sampling may be done. Women with high-risk endometrial cancer (serous adenocarcinoma, clear cell carcinoma, grade 3 deeply invasive endometrioid carcinoma, and stages III/IV disease) are generally treated with surgery followed by chemotherapy and/or radiation therapy.

Prognosis

With early diagnosis and treatment, the overall 5-year survival for stage I disease is 80–90%. With stage I disease, the depth of myometrial invasion is the strongest predictor of survival, with a 90% 5-year survival with less than 50% depth of invasion and 80% survival with 50% or more invasion. Survival rates decrease with increasing stage of disease.

When to Refer

All patients with endometrial carcinoma should be referred to a gynecologic oncologist.

McDonald ME et al. Endometrial cancer: obesity, genetics and targeted agents. *Obstet Gynecol Clin North Am.* 2019;46:89. [PMID: 30683268]

Passarello K et al. Endometrial cancer: an overview of pathophysiology, management and care. *Semin Oncol Nurs.* 2019;35:157. [PMID: 30867105]

CARCINOMA OF THE VULVA



ESSENTIALS OF DIAGNOSIS

- ▶ Two independent pathways for development: HPV or chronic inflammation.
- ▶ History of prolonged vulvar irritation, with pruritus, local discomfort, or slight bloody discharge.
- ▶ Early lesions may suggest or include non-neoplastic epithelial disorders.
- ▶ Late lesions appear as a mass, an exophytic growth, or a firm, ulcerated area in the vulva.
- ▶ Biopsy is necessary for diagnosis.

► General Considerations

The majority of cancers of the vulva are squamous lesions that classically have occurred in women over 50 years of age. Vulvar low-grade squamous intraepithelial lesions (LSIL) are benign and do not require intervention. Vulvar high-grade squamous intraepithelial lesions (HSIL) and differentiated vulvar intraepithelial neoplasia (dVIN) are premalignant conditions. Vulvar HSIL (VIN usual type) is associated with HPV, while dVIN is associated with vulvar dermatoses, eg, lichen sclerosus. About 70–90% of premalignant lesions are vulvar HSIL, but HSIL is the precursor for only 20% of vulvar cancers, while dVIN is the precursor for approximately 80% of vulvar cancers. Given that high percentages of HSIL and vulvar cancers are HPV-related, immunization with the HPV vaccine is beneficial to reduce the risk of HPV-related vulvar disease.

► Differential Diagnosis

Other vulvar lesions must be considered. Vulvar intraepithelial neoplasia may resemble vulvar cancer and must be distinguished by histology. Benign vulvar disorders that must be excluded in the diagnosis of carcinoma of the vulva include inflammatory vulvar dermatoses (psoriasis, lichen sclerosus, lichen planus), chronic granulomatous lesions (eg, lymphogranuloma venereum, syphilis), condylomas, epidermal inclusion cysts, hidradenomas, or neurofibromas. Lichen sclerosus and other associated leukoplakic changes in the skin should be biopsied. The likelihood that a superimposed vulvar cancer will develop in a woman with a non-neoplastic epithelial disorder is very low (1–5%).

► Diagnosis

Biopsy is essential for the diagnosis of VIN and vulvar cancer and should be performed with any localized atypical vulvar lesion, including white patches and hyperpigmented lesions. Multiple skin-punch specimens can be taken in the office under local anesthesia, with care to include tissue from the edges of each lesion sampled. Colposcopy of vulva, vagina, and cervix can help in identifying areas for biopsy and in planning further treatment.

► Staging

Vulvar cancer generally spreads by direct extension into the vagina, urethra, perineum, and anus, with discontinuous spread into the inguinal and femoral lymph nodes. Staging is based on a combined clinical and surgical/pathologic system.

► Treatment

Invasive carcinoma confined to the vulva without evidence of spread to adjacent organs or to the regional lymph nodes is treated with wide local excision and inguinal lymphadenectomy or wide local excision alone if invasion is less than 1 mm. To avoid the morbidity of inguinal lymphadenectomy, some guidelines recommend sentinel lymph node sampling for women with early-stage vulvar cancer.

Patients with more advanced disease may receive preoperative radiation, chemotherapy, or both.

► Prognosis

Vulvar squamous cell carcinomas seldom metastasize. With adequate excision, the prognosis is excellent. Patients with invasive vulvar SCC 2 cm in diameter or less, without inguinal lymph node metastases, have an 85–90% 5-year survival rate. If the lesion is larger than 2 cm and lymph node involvement is present, the likelihood of 5-year survival is approximately 40%.

► When to Refer

All patients with invasive vulvar carcinoma should be referred to a gynecologic oncologist.

Gadducci A et al. Locally advanced squamous cell carcinoma of the vulva: a challenging question for gynecologic oncologists. *Gynecol Oncol*. 2020;158:208. [PMID: 32460996]

Morrison J et al. British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: recommendations for practice. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:502. [PMID: 32620514]

Singh N et al. Vulval squamous cell carcinoma and its precursors. *Histopathology*. 2020;76:128. [PMID: 31846523]

Tan A et al. Diagnosis and management of vulvar cancer: a review. *J Am Acad Dermatol*. 2019;81:1387. [PMID: 31349045]

OVARIAN CANCER & OVARIAN TUMORS



ESSENTIALS OF DIAGNOSIS

- ▶ Symptoms include vague gastrointestinal discomfort, pelvic pressure, or pain.
- ▶ Many cases of early-stage cancer are asymptomatic.
- ▶ Pelvic examination and ultrasound are mainstays of diagnosis.

► General Considerations

Ovarian tumors are common. Most are benign, but malignant ovarian tumors are the leading cause of death from gynecologic cancer. The wide range of types and patterns of ovarian tumors is due to the complexity of ovarian embryology and differences in tissues of origin.

In women with no family history of ovarian cancer, the lifetime risk is 1.6%, whereas a woman with one affected first-degree relative has a 5% lifetime risk. Ultrasound or tumor marker screening for women with one or no affected first-degree relatives has not been shown to reduce mortality from ovarian cancer, and the risks associated with unnecessary prophylactic surgical procedures outweigh the benefits in low-risk women. With two or more affected first-degree relatives, the risk is 7%. Approximately 3% of women with two or more affected first-degree relatives will have a **hereditary ovarian cancer syndrome** with a lifetime risk of 40%. Women with a *BRCA1* gene mutation

have a 45% lifetime risk of ovarian cancer and those with a *BRCA2* mutation, a 25% risk. Consideration should be given to screening with transvaginal sonography and serum CA 125 testing, starting at age 30–35 years for women with *BRCA1* or age 35–40 for women with *BRCA2* or 5–10 years earlier than the earliest age that ovarian cancer was first diagnosed in any family member. Of note, this screening regimen has not been shown to reduce mortality; thus, prophylactic oophorectomy should be considered at conclusion of childbearing.

► Clinical Findings

A. Symptoms and Signs

Most women with both benign and malignant ovarian neoplasms are either asymptomatic or experience only mild nonspecific gastrointestinal symptoms or pelvic pressure. Women with advanced malignant disease may experience abdominal pain and bloating, and a palpable abdominal mass with ascites is often present.

B. Laboratory Findings

Serum CA 125 is elevated in 80% of women with epithelial ovarian cancer overall but in only 50% of women with early disease. However, CA 125 may be elevated in premenopausal women with benign disease (such as endometriosis), minimizing its usefulness in ovarian cancer screening. In premenopausal women with ovarian masses, other tumor markers (such as human chorionic gonadotropin [hCG], lactate dehydrogenase, or alpha-fetoprotein) may be indicators of the tumor type.

C. Imaging

Transvaginal sonography is useful for screening high-risk women but has inadequate sensitivity for screening low-risk women. Ultrasound is helpful in differentiating ovarian masses that are benign and likely to resolve spontaneously from those with malignant potential. Color Doppler imaging may further enhance the specificity of ultrasound diagnosis.

► Differential Diagnosis

Once an ovarian mass has been detected, it must be categorized as functional, benign neoplastic, or potentially malignant. Predictive factors include age, size of the mass, ultrasound configuration, serum CA 125 level, the presence of symptoms, and whether the mass is unilateral or bilateral. Simple cysts up to 10 cm in diameter are almost universally benign in both premenopausal and

postmenopausal patients. Most will resolve spontaneously and may be monitored without intervention. If the mass is larger or unchanged on repeat transvaginal sonography, or if symptomatic, surgical evaluation is warranted.

► Treatment

If a malignant ovarian mass is suspected, surgical evaluation should be performed by a gynecologic oncologist. For benign neoplasms, tumor excision or unilateral oophorectomy is usually performed. For ovarian cancer in an early stage, the standard therapy is complete surgical staging including hysterectomy and bilateral salpingo-oophorectomy with omentectomy and selective lymphadenectomy. With more advanced disease, aggressive removal of all visible tumor improves survival. Except for women with low-grade ovarian cancer in an early stage, postoperative chemotherapy is indicated (see Table 39–3). Several chemotherapy regimens are effective, such as the combination of cisplatin or carboplatin with paclitaxel, with clinical response rates of up to 60–70%.

► Prognosis

Advanced disease is diagnosed in approximately 75% of women with ovarian cancer. The overall 5-year survival is approximately 17% with distant metastases but is 89% with early stage disease.

► When to Refer

If a malignant mass is suspected, surgical evaluation should be performed by a gynecologic oncologist.

Centers for Disease Control and Prevention (CDC). Ovarian cancer screening. 2021. https://www.cdc.gov/cancer/ovarian/basic_info/screening.htm

Fujiwara K et al. Landscape of systemic therapy for ovarian cancer in 2019: primary therapy. *Cancer*. 2019;125:4582. [PMID: 31967679]

González-Martín A et al. Immunotherapy with checkpoint inhibitors in patients with ovarian cancer: still promising? *Cancer*. 2019;125:4616. [PMID: 31967676]

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Obstetrics & Obstetric Disorders

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19

DIAGNOSIS OF PREGNANCY

It is advantageous to diagnose pregnancy as promptly as possible when a sexually active woman misses a menstrual period or has symptoms suggestive of pregnancy. Prenatal care can begin early for a desired pregnancy, and potentially harmful medications and activities such as drug and alcohol use, smoking, and occupational chemical exposure can be eliminated. In the event of an unwanted pregnancy, counseling about options can be provided at an early stage.

► Pregnancy Tests

All urine or blood pregnancy tests rely on the detection of human chorionic gonadotropin (hCG) produced by the placenta. Levels increase shortly after implantation, approximately double every 48 hours (this rise can range from 30% to 100% in normal pregnancies), reach a peak at 50–75 days, and fall to lower levels in the second and third trimesters. Pregnancy tests are performed on serum or urine and are accurate at the time of the missed period or shortly after it.

Compared with intrauterine pregnancies, **ectopic pregnancies** may show lower levels of hCG that plateau or fall in serial determinations. Quantitative assays of hCG repeated at 48-hour intervals are used in the diagnosis of ectopic pregnancy as well as in cases of molar pregnancy and early pregnancy loss. Comparison of hCG levels between laboratories may be misleading in a given patient because different international standards may produce results that vary by as much as twofold. Consistent follow up is necessary to make the correct diagnosis and management plan. **Pregnancy of unknown location** is a term used to describe a situation where a woman has a positive pregnancy test, but the location and viability of the pregnancy are not known because it is not seen on transvaginal ultrasound.

► Manifestations of Pregnancy

The following symptoms and signs are usually due to pregnancy, but none are diagnostic. A record of the time and frequency of coitus is helpful for diagnosing and dating a pregnancy.

A. Symptoms

Amenorrhea, nausea and vomiting, breast tenderness and tingling, urinary frequency and urgency, “quickenings” (perception of first movement noted at about the 18th week), weight gain.

B. Signs (in Weeks From Last Menstrual Period)

Breast changes (enlargement, vascular engorgement, colostrum) begin very early in pregnancy and continue until the postpartum period. Cyanosis of the vagina and cervical portio and softening of the cervix occur in about the 7th week. Softening of the cervicouterine junction takes place in the 8th week, and generalized enlargement and diffuse softening of the corpus occurs after the 8th week. When a woman’s abdomen will start to enlarge depends on her body habitus but typically starts in the 16th week.

The uterine fundus is palpable above the pubic symphysis by 12–15 weeks from the last menstrual period and reaches the umbilicus by 20–22 weeks. Fetal heart tones can be heard by Doppler at 10–12 weeks of gestation.

► Differential Diagnosis

The nonpregnant uterus enlarged by myomas can be confused with the gravid uterus, but it is usually very firm and irregular. An ovarian tumor may be found midline, displacing the nonpregnant uterus to the side or posteriorly. Ultrasonography and a pregnancy test will provide accurate diagnosis in these circumstances.

ESSENTIALS OF PREGNATAL CARE

Prenatal visits should begin as early as possible after the diagnosis of pregnancy. The initial visit should include a history, physical examination, advice to the patient, and appropriate tests and procedures (see *CMDT Online* at AccessMedicine.com for a discussion of routine prenatal care).

A. Medications

Only medications prescribed or authorized by the obstetric provider should be taken since certain medications are contraindicated during pregnancy (Table 19–1).

Table 19–1. Common drugs that are teratogenic or fetotoxic.¹

ACE inhibitors	Lithium
Alcohol	Methotrexate
Androgens	Misoprostol
Angiotensin-II receptor blockers	NSAIDs (third trimester)
Antiepileptics (phenytoin, valproic acid, carbamazepine)	Opioids (prolonged use)
Benzodiazepines	Radioiodine (antithyroid)
Cyclophosphamide	Reserpine
Diazoxide	Ribavirin
Diethylstilbestrol	Sulfonamides (second and third trimesters)
Disulfiram	Tetracycline (third trimester)
Ergotamine	Thalidomide
Estrogens	Tobacco smoking
Griseofulvin	Warfarin and other coumarin anticoagulants
Isotretinoin	

¹Many other drugs are also contraindicated during pregnancy. Evaluate any drug for its need versus its potential adverse effects. Further information can be obtained from the manufacturer or from any of several teratogenic registries around the country. Go to <https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm> for more information. ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

B. Alcohol and Other Drugs

Patients should be encouraged to abstain from alcohol, tobacco, and all recreational (“street”) drugs. No safe level of alcohol intake has been established for pregnancy. Fetal effects are manifest in the **fetal alcohol syndrome**, which includes growth restriction; facial, skeletal, and cardiac abnormalities; and serious central nervous system dysfunction.

Cigarette smoking results in fetal exposure to carbon monoxide and nicotine, which may eventuate to adverse pregnancy outcomes. An increased risk of placental abruption (abruptio placentae), placenta previa, and premature rupture of the membranes is documented among women who smoke. Preterm delivery, low birth weight, and ectopic pregnancy are also more likely among smokers. Women who smoke should quit smoking or at least reduce the number of cigarettes smoked per day to as few as possible. Clinicians should ask all pregnant women about their smoking history and offer smoking cessation counseling during pregnancy, since women are more motivated to change at this time. Pregnant women should also avoid exposure to environmental smoke (“passive smoking”), smokeless tobacco, and e-cigarettes. Pharmacotherapy for smoking cessation has been used with mixed results. Studies of bupropion and nicotine replacement systems are inadequate to properly weigh risks and benefits, and prolonged cessation from smoking has not been proven.

Sometimes compounding the above effects on pregnancy outcome are the independent adverse effects of illicit drugs. Cocaine use in pregnancy is associated with an increased risk of premature rupture of membranes, preterm delivery, placental abruption, intrauterine growth restriction, neurobehavioral deficits, and sudden infant death syndrome. Similar adverse effects on pregnancy are associated with amphetamine use, perhaps reflecting the

vasoconstrictive properties of both amphetamines and cocaine. Adverse effects associated with opioid use include intrauterine growth restriction, prematurity, and fetal death. For pregnant women with opioid use disorder, opioid agonist therapy is the standard of care (see Chapter 5).

C. Radiographs and Noxious Exposures

Radiographs should be avoided unless essential and approved by a clinician. Abdominal shielding should be used whenever possible. The patient should be told to inform her other health care providers that she is pregnant. Chemical or radiation hazards should be avoided as should excessive heat in hot tubs or saunas. Patients should be told to avoid handling cat feces or cat litter and to wear gloves when gardening to avoid infection with toxoplasmosis.

LACTATION

Drugs taken by a nursing mother may accumulate in milk and be transmitted to the infant (Table 19–2). The amount of drug entering the milk depends on the drug’s lipid solubility, mechanism of transport, and degree of ionization.

Sattari M et al. Maternal implications of breastfeeding: a review for the internist. Am J Med. 2019;132:912. [PMID: 30853481]

TRAVEL & IMMUNIZATIONS DURING PREGNANCY

During an otherwise normal low-risk pregnancy, travel can be planned most safely up to the 32nd week. Commercial flying in pressurized cabins does not pose a threat to the fetus. An aisle seat will allow frequent walks. Adequate fluids should be taken during the flight. Travelling to endemic areas of yellow fever (Africa or Latin America) or of Zika virus (Latin America) is not advisable; since Zika virus can be sexually transmitted, partner travel should also be discussed (see Chapter 32). Similarly, it is inadvisable to travel to areas of Africa or Asia where chloroquine-resistant falciparum malaria is a hazard, since complications of malaria are more common in pregnancy. Travel can also increase women’s chances of exposure to SARS-CoV-2, the virus that causes COVID-19; pregnant women infected with SARS-CoV-2 are believed to be at increased risk for serious illness and preterm birth. Pregnant women should limit their exposure to people outside their household, wear a mask while outside the home, practice frequent hand washing, and social distance whenever possible.

Ideally, all immunizations should precede pregnancy. *Live virus products are contraindicated during pregnancy (measles, rubella, yellow fever, and smallpox).* Inactivated polio vaccine should be given subcutaneously instead of the oral live-attenuated vaccine. The varicella vaccine should be given 1–3 months before becoming pregnant. It is not recommended in pregnancy. Vaccines against pneumococcal pneumonia, meningococcal meningitis, and hepatitis A can be used as indicated. Pregnant women who are considered to be at high risk for hepatitis B and who have not been previously vaccinated should be vaccinated during pregnancy. The HPV vaccine is not recommended for pregnant women. However, adverse outcomes have not

Table 19–2. Drugs and substances that require a careful assessment of risk before they are prescribed for breastfeeding women.¹

Drugs	Concern
Atenolol	Hypotension and bradycardia in the infant. Metoprolol and propranolol are preferred.
Ciprofloxacin	Adverse effects on fetal cartilage and bone. Must weigh risks versus benefits.
Codeine, oxycodone	CNS depression. Unpredictable metabolism.
Cyclophosphamide	Neonatal neutropenia. No breastfeeding.
Diphenhydramine	Present in very small quantities in milk; sources are conflicting with regard to its safety.
Fluoxetine	Present in breast milk in higher levels than other SSRIs. Watch for adverse effects like an infant's fussiness and crying.
Lisinopril	Unknown effects. Captopril or enalapril is preferred if an ACE inhibitor is needed.
Lithium	Circulating levels in the neonate are variable. Follow infant's serum creatinine and blood urea nitrogen levels and thyroid function tests.
Tetracyclines	Adverse effects on fetal bone growth and dental staining.
Valproic acid	Long-term effects are unknown. Although levels in milk are low, it is teratogenic, so it should be avoided if possible.

¹The above list is not all-inclusive. For additional information, see the reference from which this information is adapted: Rowe H et al. Maternal medication, drug use, and breastfeeding. *Pediatr Clin North Am.* 2013;60:275, or the online drug and lactation database, Lactmed, at <https://www.ncbi.nlm.nih.gov/books/NBK501922/>.

ACE, angiotensin-converting enzyme; CNS, central nervous system; SSRIs, selective serotonin reuptake inhibitors.

been described when used during pregnancy. If a woman who has started the vaccine series is found to be pregnant, the remaining doses should be administered when she is no longer pregnant.

The CDC lists pregnant women as a high-risk group for influenza. Annual influenza vaccination is indicated in all women who are pregnant or will be pregnant during the “flu season.” It can be given in the first trimester. There is increased urgency for pregnant women to get vaccinated against influenza because it is not known how the influenza virus will interact with SARS-CoV-2. The CDC also recommends that every pregnant woman receive a dose of Tdap during each pregnancy irrespective of her prior vaccination history. The optimal timing for such Tdap administration is between 27 and 36 weeks of gestation, in order to maximize the antibody response of the pregnant woman against pertussis and the passive antibody transfer to the infant. For any woman who was not previously vaccinated with Tdap and for whom the vaccine was not given during her pregnancy, Tdap should be administered immediately postpartum. Further, any teenagers or adults not previously vaccinated who will have close contact with the infant should also receive it, ideally 2 weeks before exposure to the child. This vaccination strategy is referred to as “cocooning,” and its purpose is to protect the infant aged younger than 12 months who is at particularly high risk for lethal pertussis.

Hepatitis A vaccine contains formalin-inactivated virus and can be given in pregnancy when needed. Pooled immune globulin to prevent hepatitis A is safe and does not carry risk of HIV transmission. Chloroquine can be used for malaria prophylaxis in pregnancy, and proguanil is also safe.

Water should be purified by boiling, since iodine purification may provide more iodine than is safe during pregnancy.

Prophylactic antibiotics or bismuth subsalicylate should not be used during pregnancy to prevent diarrhea. Oral rehydration and treatment of bacterial diarrhea with erythromycin or ampicillin if necessary is preferred.

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 741: Maternal immunization. *Obstet Gynecol.* 2018;131:e214. [PMID: 29794683]

Centers for Disease Control and Prevention. COVID-19: Pregnancy, breastfeeding, and caring for newborns. 2020 Dec 28. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnancy-breastfeeding.html>.

OBSTETRIC COMPLICATIONS OF THE FIRST & SECOND TRIMESTERS

VOMITING OF PREGNANCY & HYPEREMESIS GRAVIDARUM

ESSENTIALS OF DIAGNOSIS

- Hyperemesis gravidarum.
- Persistent, severe vomiting.
- Weight loss, dehydration, hypochloremic alkalosis, hypokalemia.
- May have transient elevation of liver enzymes.
- Appears related to high or rising serum hCG.
- More common with multi-fetal pregnancies or hydatidiform mole.

General Considerations

Nausea and vomiting begin soon after the first missed period and cease by the fifth month of gestation. Up to three-fourths of women complain of nausea and vomiting during early pregnancy, with the vast majority noting nausea throughout the day. This problem exerts no adverse effects on the pregnancy and does not presage other complications.

Persistent, severe vomiting during pregnancy—hyperemesis gravidarum—can be disabling and require hospitalization. Hyperthyroidism can be associated with hyperemesis gravidarum, so it is advisable to determine thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) values in these patients. Of note, these patients will not have a goiter.

► Treatment

A. Mild Nausea and Vomiting of Pregnancy

In most instances, only reassurance and dietary advice are required. Because of possible teratogenicity, drugs used during the first half of pregnancy should be restricted to those of major importance to life and health. Vitamin B₆ (pyridoxine), 50–100 mg/day orally, is nontoxic and may be helpful in some patients. Pyridoxine alone or in combination with doxylamine (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, two tablets at bedtime) is first-line pharmacotherapy. Antiemetics, antihistamines, and antispasmodics are generally unnecessary to treat nausea of pregnancy.

B. Hyperemesis Gravidarum

With more severe nausea and vomiting, it may become necessary to hospitalize the patient. In this case, a private room with limited activity is preferred. It is recommended to give nothing by mouth until the patient is improving, and maintain hydration and electrolyte balance by giving appropriate parenteral fluids and vitamin supplements as indicated. Antiemetics such as promethazine (12.5–25 mg orally, rectally, or intravenously every 4–6 hours), metoclopramide (5–10 mg orally or intravenously every 6 hours), or ondansetron (4–8 mg orally or intravenously every 8 hours) should be started. Ondansetron has been associated in some studies with congenital anomalies. Data are limited, but the risks and benefits of treatment should be addressed with the patient. If there is an increased risk, it is probably low. Antiemetics will likely need to be given intravenously initially. Rarely, total parenteral nutrition may become necessary but only if enteral feedings cannot be done. As soon as possible, the patient should be placed on a dry diet consisting of six small feedings daily. Antiemetics may be continued orally as needed. After in-patient stabilization, the patient can be maintained at home even if she requires intravenous fluids in addition to her oral intake. There are conflicting studies regarding the use of corticosteroids for the control of hyperemesis gravidarum, and it has also been associated with fetal anomalies, specifically oral clefts. The increase in risk is likely small. However, this treatment should be withheld before 10 weeks' gestation and until more accepted treatments have been exhausted.

► When to Refer

- Patient does not respond to first-line outpatient management.
- There is concern for other pathology (ie, hydatidiform mole).

► When to Admit

- Patient is unable to tolerate any food or water.
- Patient cannot ingest necessary medications.
- Weight loss.
- Presence of a hydatidiform mole.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 189: Nausea and vomiting of pregnancy. Obstet Gynecol. 2018;131:e15. [Reaffirmed 2019] [PMID: 29266076]

SPONTANEOUS ABORTION



ESSENTIALS OF DIAGNOSIS

- Intrauterine pregnancy at < 20 weeks.
- Low or falling levels of hCG.
- Bleeding, midline cramping pain.
- Open cervical os.
- Complete or partial expulsion of products of conception.

► General Considerations

About three-fourths of spontaneous abortions occur before the 16th week; of these, three-fourths occur before the 8th week. Almost 20% of all clinically recognized pregnancies terminate in spontaneous abortion.

More than 60% of spontaneous abortions result from chromosomal defects due to maternal or paternal factors; about 15% appear to be associated with maternal trauma, infections, dietary deficiencies, diabetes mellitus, hypothyroidism, antiphospholipid antibody syndrome, or anatomic malformations. There is no reliable evidence that abortion may be induced by psychic stimuli such as severe fright, grief, anger, or anxiety. In about one-fourth of cases, the cause of abortion cannot be determined. There is no evidence that video display terminals or associated electromagnetic fields are related to an increased risk of spontaneous abortion.

It is important to distinguish women with a history of incompetent cervix from those with more typical early abortion. Factors that predispose to incompetent cervix are a history of incompetent cervix with a previous pregnancy, cervical conization or surgery, cervical injury, diethylstilbestrol (DES) exposure, and anatomic abnormalities of the cervix. Prior to pregnancy or during the first trimester, there are no methods for determining whether the cervix will eventually be incompetent. After 14–16 weeks, ultrasound may be used to evaluate the internal anatomy of the lower uterine segment and cervix for the funneling and shortening abnormalities consistent with cervical incompetence.

► Clinical Findings

A. Symptoms and Signs

1. **Incompetent cervix**—Characteristically, incompetent cervix presents as “silent” cervical dilation (ie, with

minimal uterine contractions) in the second trimester. When the cervix reaches 4 cm or more, active uterine contractions or rupture of the membranes may occur secondary to the degree of cervical dilation. This does not change the primary diagnosis.

2. Threatened abortion—Bleeding or cramping occurs, but the pregnancy continues. The cervix is not dilated.

3. Inevitable abortion—The cervix is dilated and the membranes may be ruptured, but passage of the products of conception has not yet occurred. Bleeding and cramping persist, and passage of the products of conception is considered inevitable.

4. Complete abortion—Products of conception are completely expelled. Pain ceases, but spotting may persist. Cervical os is closed.

5. Incomplete abortion—The cervix is dilated. Some portion of the products of conception remains in the uterus. Only mild cramps are reported, but bleeding is persistent and often excessive.

6. Missed abortion—The pregnancy has ceased to develop, but the conceptus has not been expelled. Symptoms of pregnancy disappear. There may be a brownish vaginal discharge but no active bleeding. Pain does not develop. The cervix is semifirm and slightly patulous; the uterus becomes smaller and irregularly softened; the adnexa are normal.

B. Laboratory Findings

Pregnancy tests show low or falling levels of hCG. A CBC should be obtained if bleeding is heavy. Determine Rh type, and give Rh_O(D) immune globulin if Rh-negative. All tissue recovered should be assessed by a pathologist and may be sent for genetic analysis in selected cases.

C. Ultrasonographic Findings

Transvaginal ultrasound can detect the gestational sac at 5–6 weeks from the last menstruation, a fetal pole at 6 weeks, and fetal cardiac activity at 6–7 weeks. Serial observations are often required to evaluate changes in size of the embryo. Diagnostic criteria of early pregnancy loss are a crown-rump length of 7 mm or more and no heartbeat or a mean sac diameter of 25 mm or more and no embryo.

► Differential Diagnosis

The bleeding that occurs in abortion of a uterine pregnancy must be differentiated from the abnormal bleeding of an ectopic pregnancy and anovulatory bleeding in a nonpregnant woman. The passage of hydropic villi in the bloody discharge is diagnostic of hydatidiform mole.

► Treatment

A. General Measures

1. Threatened abortion—Studies have failed to demonstrate benefit of bedrest for 1–2 days followed by gradual resumption of usual activities. Abstinence from sexual

activity has also been suggested without proven benefit. Data are lacking to support the administration of progestins to all women with a threatened abortion. If during the patient's evaluation, an infection is diagnosed (ie, urinary tract infection), it should be treated.

2. Missed abortion—This calls for counseling regarding the fate of the pregnancy and planning for its elective termination at a time chosen by the patient and clinician. Management can be medical or surgical. Each has risks and benefits. Medically induced first-trimester termination with prostaglandins (ie, misoprostol given vaginally or orally in a dose of 200–800 mcg) is safe, effective, less invasive, and more private than surgical intervention; however, if it is unsuccessful or if there is excessive bleeding, a surgical procedure (dilation and curettage) may still be needed. Patients must be counseled about the different therapeutic options.

B. Surgical Measures

1. Inevitable or incomplete abortion—Prompt removal of any products of conception remaining within the uterus is required to stop bleeding and prevent infection. Analgesia and a paracervical block are useful, followed by uterine exploration with ovum forceps or uterine aspiration. Regional anesthesia may be required.

2. Cerclage and restriction of activities—A cerclage is the treatment of choice for incompetent cervix, but a viable intrauterine pregnancy should be confirmed prior to placement of the cerclage.

A variety of suture materials including a 5-mm Mersilene tape or No. 2 nonabsorbable monofilament suture can be used to create a purse-string type of stitch around the cervix, using either the McDonald or Shirodkar method. Cerclage should be undertaken with caution when there is advanced cervical dilation or when the membranes are prolapsed into the vagina. *Rupture of the membranes and infection are specific contraindications to cerclage.* Testing for *N gonorrhoeae*, *C trachomatis*, and group B streptococci should be obtained before elective placement of a cerclage. *N gonorrhoeae* and *C trachomatis* should be treated before placement.

► When to Refer

- Patient with history of two second-trimester losses.
- Vaginal bleeding in a pregnant patient that resembles menstruation.
- Patient with an open cervical os.
- No signs of uterine growth in serial examinations of a pregnant patient.
- Leakage of amniotic fluid.

► When to Admit

- Open cervical os.
- Heavy vaginal bleeding.
- Leakage of amniotic fluid.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 142: Cerclage for the management of cervical insufficiency. *Obstet Gynecol.* 2014;123:372. [Reaffirmed 2019] [PMID: 24451674]

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 200: Early pregnancy loss. *Obstet Gynecol.* 2018;132:e197. [PMID: 30157093]

RECURRENT ABORTION

According to the American Society of Reproductive Medicine, recurrent abortion is defined as the loss of two or more previable (less than 24 weeks' gestation or 500 g) pregnancies in succession. Recurrent abortion affects about 1–5% of couples. Abnormalities related to recurrent abortion can be identified in approximately 50% of these couples. If a woman has lost three previous pregnancies without identifiable cause, she still has at least a 55% chance of carrying a fetus to viability.

Recurrent abortion is a clinical rather than pathologic diagnosis. The clinical findings are similar to those observed in other types of abortion. It is appropriate to begin a medical evaluation in a woman who has had two first-trimester losses.

Treatment

A. Preconception Therapy

Preconception therapy is aimed at detection of maternal or paternal defects that may contribute to abortion. A thorough history and examination is essential. A random blood glucose test and thyroid function studies (including thyroid antibodies) can be done if history indicates a possible predisposition to diabetes mellitus or thyroid disease. Detection of lupus anticoagulant and other hemostatic abnormalities (proteins S and C and antithrombin deficiency, hyperhomocysteinemia, anticardiolipin antibody, factor V Leiden mutations) and an antinuclear antibody test may be indicated. Hysteroscopy, saline infusion sonogram, or hysteroscopy can be used to exclude submucosal myomas and congenital anomalies of the uterus. In women with recurrent losses, resection of a uterine septum, if present, has been recommended. Chromosomal (karyotype) analysis of both partners can be done to rule out balanced translocations (found in 3–4% of infertile couples), but karyotyping is expensive and may not be helpful.

Many therapies have been tried to prevent recurrent abortion from immunologic causes. Low-molecular-weight heparin (LMWH), aspirin, intravenous immunoglobulin, and corticosteroids have all been used but the definitive treatment has not yet been determined (see Antiphospholipid Syndrome, below). Prophylactic low-dose heparin and low-dose aspirin have been recommended for women with antiphospholipid antibodies and recurrent pregnancy loss.

B. Postconception Therapy

The patient should be provided early prenatal care and scheduled frequent office visits. Empiric sex steroid hormone therapy is complicated and should be done by an expert if undertaken.

► Prognosis

The prognosis is excellent if the cause of abortion can be corrected or treated.

Homer HA. Modern management of recurrent miscarriage. *Aust N Z J Obstet Gynaecol.* 2019;59:36. [PMID: 30393965]

ECTOPIC PREGNANCY

ESSENTIALS OF DIAGNOSIS

- ▶ Amenorrhea or irregular bleeding and spotting.
- ▶ Pelvic pain, usually adnexal.
- ▶ Adnexal mass by clinical examination or ultrasound.
- ▶ Failure of serum beta-hCG to double every 48 hours.
- ▶ No intrauterine pregnancy on transvaginal ultrasound with serum beta-hCG > 2000 milli-units/mL.

► General Considerations

Ectopic implantation occurs in approximately 2% of first trimester pregnancies. About 98% of ectopic pregnancies are tubal. Other sites of ectopic implantation are the peritoneum or abdominal viscera, the ovary, and the cervix. Any condition that prevents or inhibits migration of the fertilized ovum to the uterus can predispose to an ectopic pregnancy, including a history of infertility, pelvic inflammatory disease, ruptured appendix, and prior tubal surgery. Combined intrauterine and extrauterine pregnancy (heterotopic) may occur rarely. In the United States, undiagnosed or undetected ectopic pregnancy is one of the most common causes of maternal death during the first trimester.

► Clinical Findings

A. Symptoms and Signs

Severe lower quadrant pain occurs in almost every case. It is sudden in onset, stabbing, intermittent, and does not radiate. Backache may be present during attacks. Shock occurs in about 10%, often after pelvic examination. At least two-thirds of patients give a history of abnormal menstruation; many have been infertile.

Blood may leak from the tubal ampulla over a period of days, and considerable blood may accumulate in the peritoneum. Slight but persistent vaginal spotting is usually reported, and a pelvic mass may be palpated. Abdominal distention and mild paralytic ileus are often present.

B. Laboratory Findings

The CBC may show anemia and slight leukocytosis. Quantitative serum pregnancy tests will show levels generally lower than expected for normal pregnancies of the same duration. If beta-hCG levels are followed over a few days, there may be a slow rise or a plateau rather than the near

doubling every 2 days associated with normal early intrauterine pregnancy or the falling levels that occur with spontaneous abortion.

C. Imaging

Ultrasonography can reliably demonstrate a gestational sac 5–6 weeks from the last menstruation and a fetal pole at 6 weeks if located in the uterus. An empty uterine cavity raises a strong suspicion of extrauterine pregnancy, which can occasionally be revealed by transvaginal ultrasound. Specified levels of serum beta-hCG have been reliably correlated with ultrasound findings of an intrauterine pregnancy. For example, a beta-hCG level of 6500 milli-units/mL with an empty uterine cavity by transabdominal ultrasound is highly suspicious for an ectopic pregnancy. Similarly, a beta-hCG value of 2000 milli-units/mL or more can be indicative of an ectopic pregnancy if no products of conception are detected within the uterine cavity by transvaginal ultrasound. Serum beta-hCG values can vary by laboratory, so clinical decisions should not be made based solely on beta-hCG levels.

D. Special Examinations

Laparoscopy is the surgical procedure of choice both to confirm an ectopic pregnancy and in most cases to permit removal of the ectopic pregnancy without the need for exploratory laparotomy.

Ectopic pregnancy should be suspected when postabortal tissue examination fails to reveal chorionic villi. Steps must be taken for immediate diagnosis, including prompt microscopic tissue examination, ultrasonography, and serial beta-hCG titers every 48 hours.

► Differential Diagnosis

Clinical and laboratory findings suggestive or diagnostic of pregnancy will distinguish ectopic pregnancy from many acute abdominal illnesses such as acute appendicitis, acute pelvic inflammatory disease, ruptured corpus luteum cyst or ovarian follicle, and urinary calculi. Uterine enlargement with clinical findings similar to those found in ectopic pregnancy is also characteristic of an aborting uterine pregnancy or hydatidiform mole.

► Treatment

Patients must be warned about the complications of an ectopic pregnancy and monitored closely. In a stable patient with normal liver and renal function tests, methotrexate (50 mg/m^2) intramuscularly—given as single or multiple doses—is acceptable medical therapy for early ectopic pregnancy. Favorable criteria are that the pregnancy should be less than 3.5 cm in largest dimension and unruptured, with no active bleeding and no fetal heart tones. Several small studies have not found an increased risk of fetal malformations or pregnancy losses in women who conceive within 6 months of methotrexate therapy.

When a patient with an ectopic pregnancy is unstable or when surgical therapy is planned, the patient is hospitalized. Blood is typed and cross-matched. The goal is to diagnose and operate before there is frank rupture of the

tube and intra-abdominal hemorrhage. *The use of methotrexate in an unstable patient is absolutely contraindicated.*

Surgical treatment is definitive. In most patients, diagnostic laparoscopy is the initial surgical procedure performed. Depending on the size of the ectopic pregnancy and whether or not it has ruptured, salpingostomy with removal of the ectopic pregnancy or a partial or complete salpingectomy can usually be performed. Clinical conditions permitting, patency of the contralateral tube can be established by injection of indigo carmine into the uterine cavity and flow through the contralateral tube confirmed visually by the surgeon; iron therapy for anemia may be necessary during convalescence. Rh_O(D) immune globulin (300 mcg) should be given to Rh-negative patients.

► Prognosis

Repeat tubal pregnancy occurs in about 10% of cases. This should not be regarded as a contraindication to future pregnancy, but the patient requires careful observation and early ultrasound confirmation of an intrauterine pregnancy.

► When to Refer

- Severe abdominal pain.
- Palpation of an adnexal mass on pelvic examination.
- Abdominal pain and vaginal bleeding in a pregnant patient.

► When to Admit

Presence of symptoms or signs of a ruptured ectopic pregnancy.

Carusi D. Pregnancy of unknown location: evaluation and management. Semin Perinatol. 2019;43:95. [PMID: 30606496]

GESTATIONAL TROPHOBLASTIC DISEASE (Hydatidiform Mole & Choriocarcinoma)

ESSENTIALS OF DIAGNOSIS

Hydatidiform mole

- Amenorrhea.
- Irregular uterine bleeding.
- Serum beta-hCG $> 40,000 \text{ milli-units/mL}$.
- Passage of grapelike clusters of enlarged edematous villi per vagina.
- Uterine ultrasound shows characteristic heterogeneous echogenic image and no fetus or placenta.
- Cytogenetic composition is 46,XX (85%), of paternal origin.

Choriocarcinoma

- Persistence of detectable beta-hCG after mole evacuation.

► General Considerations

Gestational trophoblastic disease is a spectrum of disorders that includes hydatidiform mole (partial and complete), invasive mole (local extension into the uterus or vagina), choriocarcinoma (malignancy often complicated by distant metastases), and placental site trophoblastic tumor. Complete moles show no evidence of a fetus on ultrasonography. The majority are 46,XX, with all chromosomes of paternal origin. Partial moles generally show evidence of an embryo or gestational sac; are triploid, slower-growing, and less symptomatic; and often present clinically as a missed abortion. Partial moles tend to follow a benign course, while complete moles have a greater tendency to become choriocarcinoma.

In North America, the frequency of gestational trophoblastic disease is 1:1500 pregnancies. The highest rates occur in Asians. Risk factors include prior spontaneous abortion, a history of mole, and age younger than 21 or older than 35. Approximately 10% of women require further treatment after evacuation of the mole; choriocarcinoma develops in 2–3% of women.

► Clinical Findings

A. Symptoms and Signs

Uterine bleeding, beginning at 6–16 weeks, is observed in most instances. In some cases, the uterus is larger than would be expected in a normal pregnancy of the same duration. Excessive nausea and vomiting may occur. Bilaterally enlarged cystic ovaries are sometimes palpable. They are the result of ovarian hyperstimulation due to excess beta-hCG.

Preeclampsia-eclampsia may develop during the second trimester of an untreated molar pregnancy, but this is unusual because most are diagnosed early.

Choriocarcinoma may be manifested by continued or recurrent uterine bleeding after evacuation of a mole or following delivery, abortion, or ectopic pregnancy. The presence of an ulcerative vaginal tumor, pelvic mass, or distant metastases may be the presenting manifestation.

B. Laboratory Findings

Hydatidiform moles are generally characterized by high serum beta-hCG values, which can range from high normal to the millions. Levels are higher with complete moles than with partial moles. Serum beta-hCG values, if extremely high, can assist in making the diagnosis, but they are more helpful in managing response to treatment. Hemoglobin/hematocrit, creatinine, blood type, liver biochemical tests, and thyroid function tests should also be measured. High beta-hCG levels can cause the release of thyroid hormone, and rarely, symptoms of hyperthyroidism. Patients with hyperthyroidism may require beta-blocker therapy until the mole has been evacuated.

C. Imaging

The preoperative diagnosis of hydatidiform mole is confirmed by ultrasound. Placental vesicles can be easily seen on transvaginal ultrasound. A preoperative chest film is indicated to rule out pulmonary metastases of the trophoblast.

► Treatment

A. Specific (Surgical) Measures

The uterus should be emptied as soon as the diagnosis of hydatidiform mole is established, preferably by suction curettage. The products of conception removed from the uterus should be sent to a pathologist for review. Ovarian cysts should not be resected nor ovaries removed; spontaneous regression of theca lutein cysts will occur with elimination of the mole. In patients who have completed their childbearing, hysterectomy is an acceptable alternative. Hysterectomy does not preclude the need for follow-up of beta-hCG levels.

B. Follow-Up Measures

Weekly quantitative beta-hCG level measurements are initially required. Following successful surgical evacuation, moles show a progressive decline in beta-hCG. After three negative weekly tests (less than 5 milli-units/mL), the interval may be increased to every 1 month for an additional 6 months. The purpose of this follow-up is to identify persistent nonmetastatic and metastatic disease, including choriocarcinoma, which is more likely to occur if the initial beta-hCG is high and the uterus is large. If levels plateau or begin to rise, the patient should be evaluated by repeat laboratory tests, chest film, and dilatation and curettage (D&C) before the initiation of chemotherapy. Effective contraception (preferably birth control pills) should be prescribed to avoid the hazard and confusion of elevated beta-hCG from a new pregnancy. The beta-hCG levels should be negative for 6 months before pregnancy is attempted again. Because the risk of recurrence of a molar pregnancy is 1–2%, an ultrasound should be performed in the first trimester of the pregnancy following a mole to ensure that the pregnancy is normal. In addition, a beta-hCG level should then be checked 6 weeks postpartum (after the subsequent normal pregnancy) to ensure there is no persistent trophoblastic tissue, and the placenta should be examined by a pathologist.

C. Antitumor Chemotherapy

If malignant tissue is discovered at surgery or during the follow-up examination, chemotherapy is indicated. For low-risk patients with a good prognosis, methotrexate is considered first-line therapy followed by dactinomycin (see Table 39–3). Patients with high-risk disease should be referred to a cancer center, where multiple-agent chemotherapy probably will be given.

► Prognosis

Five-year survival after courses of chemotherapy, even when metastases have been demonstrated, can be expected in at least 85% of cases of choriocarcinoma.

► When to Refer

- Uterine size exceeds that anticipated for gestational age.
- Vaginal bleeding similar to menstruation.
- Pregnant patient with a history of a molar pregnancy.

► When to Admit

- Confirmed molar pregnancy by ultrasound and laboratory studies.
- Heavy vaginal bleeding in a pregnant patient under evaluation.

Elias KM et al. State-of-the-art workup and initial management of newly diagnosed molar pregnancy and postmolar gestational trophoblastic neoplasia. *J Natl Compr Canc Netw*. 2019;17:1396. [PMID: 31693988]

OBSTETRIC COMPLICATIONS OF THE SECOND & THIRD TRIMESTERS

PREECLAMPSIA-ECLAMPSIA



ESSENTIALS OF DIAGNOSIS

Gestational Hypertension

- Blood pressure of $\geq 140/90$ mm Hg systolic or > 90 mm Hg diastolic after 20 weeks' gestation.

Preeclampsia

- Blood pressure of ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic after 20 weeks of gestation.
- Proteinuria of ≥ 0.3 g in 24 hours.

Preeclampsia with severe features

- Blood pressure of ≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic.
- Progressive kidney injury.
- Thrombocytopenia.
- Hemolysis, elevated liver enzymes, low platelets (HELLP).
- Pulmonary edema.
- Vision changes or headache.
- When hypertension is present with severe features of preeclampsia, seizure prophylaxis could be beneficial.

Eclampsia

- Seizures in a patient with evidence of preeclampsia.

► General Considerations

Preeclampsia is defined as the presence of newly elevated blood pressure and proteinuria during pregnancy. Eclampsia is diagnosed when seizures develop in a patient with evidence of preeclampsia. Historically, the presence of three elements was required for the diagnosis of preeclampsia: hypertension, proteinuria, and edema. Edema was difficult to objectively quantify and is no longer a required element. In addition, proteinuria may not always be present in preeclampsia with severe features.

Preeclampsia-eclampsia can occur any time after 20 weeks of gestation and up to 6 weeks postpartum. It is a disease unique to pregnancy, with the only cure being delivery of the fetus and placenta. Preeclampsia develops in approximately 7% of pregnant women in the United States; of those, eclampsia will develop in 5% (0.04% of pregnant women). Primiparas are most frequently affected; however, the incidence of preeclampsia-eclampsia is increased with multifetal gestations, preeclampsia in a previous pregnancy, chronic hypertension, pregestational diabetes, gestational diabetes, thrombophilia, kidney disease, systemic lupus erythematosus, prepregnancy BMI above 30, antiphospholipid antibody syndrome, maternal age 35 years or older, assisted reproductive technology, and obstructive sleep apnea. Eclampsia is a significant cause of maternal death.

► Clinical Findings

Clinically, the severity of preeclampsia-eclampsia can be measured with reference to the six major sites in which it exerts its effects: the central nervous system, the kidneys, the liver, the hematologic system, the vascular system, and the fetal-placental unit. By evaluating each of these areas for the presence of mild to severe preeclampsia, the degree of involvement can be assessed, and an appropriate management plan can be formulated that balances the severity of disease and gestational age (Table 19–3).

A. Preeclampsia

1. Without severe features—Patients usually have few complaints, and the diastolic blood pressure is less than 110 mm Hg. Edema may be present. The platelet count is over 100,000/mcL ($100 \times 10^9/L$), antepartum fetal testing is reassuring (see Tests & Procedures, above), central nervous system irritability is minimal, epigastric pain is not present, and liver enzymes are not elevated. Proteinuria is present with urine protein greater than or equal to 0.3/24 hours. Gestational hypertension may be present in the absence of proteinuria.

2. With severe features—Symptoms are more dramatic and persistent. Patients may complain of headache and changes in vision. The blood pressure is often above 160/110 mm Hg. Thrombocytopenia (platelet count less than 100,000/mcL [$100 \times 10^9/L$]) may be present and progress to disseminated intravascular coagulation. Severe epigastric pain may be present from hepatic subcapsular hemorrhage with significant stretch or rupture of the liver capsule. HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) is an advanced form of severe preeclampsia.

B. Eclampsia

The occurrence of seizures defines eclampsia. It is a manifestation of severe central nervous system involvement. Other findings of preeclampsia are observed.

► Differential Diagnosis

Preeclampsia-eclampsia can mimic and be confused with many other diseases, including chronic hypertension,

Table 19–3. Indicators of mild and severe preeclampsia-eclampsia, and gestational hypertension with severe features.

Site	Indicator	Mild	Severe
Central nervous system	Symptoms and signs	Hyperreflexia	Seizures, blurred vision, scotomas, headache, clonus, irritability
Kidney	Proteinuria Urinary output	> 0.3 g/24 h > 30 mL/h	> 0.3 g/24 h < 30 mL/h
Liver	AST, ALT, LD	Normal liver enzymes	Elevated liver enzymes, epigastric pain, ruptured liver
Hematologic	Platelets Hemoglobin	Normal Normal	< 100,000/mcL ($100 \times 10^9/L$) Low, normal, or elevated
Vascular	Blood pressure Retina	< 160/110 mm Hg Arteriolar spasm	> 160/110 mm Hg Retinal hemorrhages
Fetal-placental unit	Growth restriction Oligohydramnios Fetal distress	Absent Absent Absent	Present Present Present

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LD, lactate dehydrogenase.

chronic kidney disease, primary seizure disorders, gallbladder and pancreatic disease, immune thrombocytopenia, thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome. It must always be considered in any pregnant woman beyond 20 weeks of gestation with consistent signs and symptoms. Although it is most common in the third trimester, it can occur earlier, especially in women with comorbid conditions like hypertension, kidney disease, and systemic lupus erythematosus. It is particularly difficult to diagnose when a preexisting disease such as hypertension is present.

Treatment

Based on evidence and expert consensus, the American College of Obstetricians and Gynecologists (ACOG) supports considering the use of low-dose aspirin (81 mg orally daily) initiated between 12 weeks' and 28 weeks' gestation for women at increased risk for preeclampsia; risk factors include a history of preeclampsia, multifetal gestation, chronic hypertension, diabetes mellitus, kidney disease, or autoimmune diseases (such as systemic lupus erythematosus or antiphospholipid syndrome). Clinicians may also consider low-dose aspirin (81 mg orally daily) if more than one of the following moderate risk factors are present: nulliparity, obesity, family history of preeclampsia, Black race, age greater than 35 years, low socioeconomic status, and personal history factors (eg, mother having a previous baby with low birth weight). In clinical studies, diuretics, dietary restriction or enhancement, sodium restriction, and vitamin-mineral supplements (eg, calcium or vitamin C and E) have not been confirmed to be useful. The only cure is delivery of the fetus at a time as favorable as possible for its survival.

A. Preeclampsia

Early recognition is the key to treatment. This requires careful attention to the details of prenatal care—especially subtle changes in blood pressure and weight. The objectives are to prolong pregnancy, if possible, to allow fetal lung maturity while preventing progression to severe

disease and eclampsia. The critical factors are the gestational age of the fetus, fetal pulmonary maturity, and the severity of maternal disease. Preeclampsia-eclampsia without severe features and gestational hypertension at term is managed by delivery. Prior to term, severe preeclampsia-eclampsia requires delivery with very few exceptions. Epigastric pain, seizures, severe range blood pressures, thrombocytopenia, and visual disturbances are strong indications for delivery of the fetus. Marked proteinuria alone can be managed more conservatively.

1. Home management—Home management may be attempted for patients with gestational hypertension and preeclampsia without severe features and a stable home situation. This requires assistance at home, rapid access to the hospital, a reliable patient, and the ability to obtain frequent blood pressure readings. A home health nurse can often provide frequent home visits and assessments.

2. Hospital care—Hospitalization is required for women with preeclampsia with severe features or those with unreliable home situations. Regular assessments of blood pressure, urine protein, and fetal heart tones and activity are required. A CBC with platelet count, electrolyte panel, and liver enzymes should be checked regularly, with frequency dependent on severity. A 24-hour urine collection for total protein and creatinine clearance should be obtained on admission and repeated as indicated. Magnesium sulfate is not used until the diagnosis of severe preeclampsia is made and delivery planned (see Eclampsia, below).

Fetal evaluation should be obtained as part of the workup. If the patient is being admitted to the hospital, fetal testing should be performed on the same day to assess fetal well-being. This may be done by fetal heart rate testing with nonstress testing or by biophysical profile. A regular schedule of fetal surveillance must then be followed. Daily fetal kick counts can be recorded by the patient herself. If the fetus is less than 34 weeks' gestation, corticosteroids (betamethasone 12 mg intramuscularly every 24 h for two doses, or dexamethasone 6 mg intramuscularly every 12 h for four doses) can be administered

to the mother. However, when a woman clearly has unstable severe preeclampsia, delivery should not be delayed for fetal lung maturation or administration of corticosteroids. In women with gestational hypertension or preeclampsia without severe features at or beyond 37 weeks' gestation, delivery rather than expectant management upon diagnosis is recommended.

The method of delivery is determined by the maternal and fetal status. A vaginal delivery is preferred because it has less blood loss than a cesarean section and requires less coagulation factors. Cesarean section is reserved for the usual fetal indications. For mild preeclampsia, delivery should take place at term.

B. Eclampsia

1. Emergency care—If the patient is convulsing, she is turned on her side to prevent aspiration and to improve blood flow to the placenta. The seizure may be stopped by giving an intravenous bolus of magnesium sulfate (the preferred agent), 4–6 g over 4 minutes or until the seizure stops. A continuous intravenous infusion of magnesium sulfate is then started at a rate of 2–3 g/h unless the patient is known to have reduced kidney function (serum creatinine 1.0–1.5 mg/dL). Reducing maintenance dosing to 1 g/h or temporarily stopping infusion may be necessary to address instances of kidney dysfunction and magnesium toxicity. Magnesium blood levels may be checked every 4–6 hours and ideally the infusion rate adjusted to maintain a therapeutic blood level (4–7 mEq/L). Urinary output is checked hourly and the patient assessed for signs of possible magnesium toxicity such as loss of deep tendon reflexes or decrease in respiratory rate and depth, which can be reversed with calcium gluconate, 1 g intravenously over 2 minutes. If seizures continue, an additional dose of magnesium sulfate, 2 g intravenously, may be infused. Alternative agents should be used only if magnesium sulfate is unavailable: phenobarbital, 15–20 mg/kg intravenous loading dose infused at 25–100 mg/min (may repeat once after 10 minutes with additional 5–10 mg/kg); clonazepam, 1 mg intravenously; or diazepam, 5–10 mg intravenously. Respiratory support with intubation and airway control may be necessary, especially when the maximum dosage of these medications is administered. Midazolam, 10 mg intramuscularly, can be used in rare cases for the extremely agitated patient.

2. General care—In patients who have preeclampsia with severe features, magnesium sulfate should be given intravenously, 4- to 6-g load over 15–20 minutes followed by 2–3 g/h maintenance, for seizure prophylaxis. The occurrence of eclampsia necessitates delivery once the patient is stabilized. It is important, however, that assessment of the status of the patient and fetus take place first. Continuous fetal monitoring must be performed and maternal blood typed and cross-matched quickly. A urinary catheter is inserted to monitor urinary output, and a CBC with platelets, electrolytes, creatinine, and liver enzymes are obtained. If hypertension is present with systolic values of 160 mm Hg or higher or diastolic values 110 mm Hg or higher, antihypertensive medications should be administered to reduce the blood pressure to 140–150/90–100 mm Hg.

Lower blood pressures than this may induce placental insufficiency through reduced perfusion. Hydralazine, given in 5- to 10-mg increments intravenously every 20 minutes, is frequently used to lower blood pressure. Labetalol, 10–20 mg intravenously, every 20 minutes as needed, can also be used. Immediate-release oral nifedipine 10–20 mg may be administered and then repeated in 20 minutes, followed by 10–20 mg every 4–6 hours for a maximum daily dosage of 180 mg. This medication is particularly helpful if the patient does not have intravenous access.

3. Delivery—Delivery is mandated once eclampsia has occurred. Vaginal delivery is preferred. Subsequent prolonged fetal heart rate decelerations are frequent after an eclamptic seizure. However, delivery should proceed only after there is maternal hemodynamic stabilization. Furthermore, maternal resuscitation is usually followed by normalization of the fetal tracing. The rapidity with which delivery must be achieved depends on the fetal and maternal status following the seizure and the availability of laboratory data on the patient. Oxytocin, given intravenously and titrated to a dose that results in adequate contractions, may be used to induce or augment labor. Oxytocin should only be administered by a clinician specifically trained in its use. Regional analgesia or general anesthesia is acceptable. Cesarean section is used for the usual obstetric indications.

4. Postpartum—Magnesium sulfate infusion (2–3 g/h with noted exceptions, see above) should be continued for 24 hours postpartum. Late-onset preeclampsia-eclampsia can occur during the postpartum period. It is usually manifested by either hypertension or seizures. Treatment is the same as prior to delivery—ie, with hydralazine and magnesium sulfate.

► When to Refer

- New onset of hypertension and proteinuria in a pregnant patient more than 20 weeks' gestation.
- New onset of seizure activity in a pregnant patient.

► When to Admit

- Symptoms of preeclampsia with severe features in a pregnant patient with elevated blood pressure above baseline.
- Evaluation for preeclampsia when severe features of the disease are suspected.
- Evaluation for preeclampsia in a patient with an unstable home environment.
- Evidence of eclampsia.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 202: Gestational hypertension and preeclampsia. *Obstet Gynecol*. 2020;135:e237. [PMID: 32443079]

American College of Obstetrics and Gynecologists. Committee Opinion No. 692: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol*. 2017;129:e90. [PMID: 28333820]

American College of Obstetricians and Gynecologists. Committee Opinion No. 743. Low-dose aspirin use during pregnancy. *Obstet Gynecol*. 2018;132:e44. [PMID: 29939940]

PRETERM LABOR



ESSENTIALS OF DIAGNOSIS

- ▶ Preterm regular uterine contractions approximately 5 minutes apart.
- ▶ Cervical dilatation, effacement, or both.

General Considerations

Preterm birth is defined as birth between 20 0/7 and 36 6/7 weeks' gestation, and spontaneous preterm labor with or without premature rupture of the fetal membranes is responsible for at least two-thirds of all preterm births. Prematurity is the largest single contributor to infant mortality, and survivors are at risk for a myriad of short- and long-term complications. It is also the most common reason for antepartum hospitalization. Rates of infant death and long-term neurologic impairment are inversely related to gestational age at birth. The cusp of viability in contemporary practice is 23–25 weeks' gestation, and infants born prior to 23 weeks rarely survive. About two-thirds of the preterm births occur between 34 weeks and 36 weeks and 6 days (termed “late preterm birth”), and good outcomes are expected at these gestational ages. Importantly, however, even these late preterm infants are at significantly increased risk for both morbidity and mortality when compared to those infants born at term.

Major risk factors for spontaneous preterm labor include a past history of preterm birth and a short cervical length as measured by transvaginal ultrasound. Patients with one or both of these risk factors have largely been the focus of recent intervention trials aiming to prevent preterm birth. Other known risk factors are many but include Black race, multifetal pregnancies, intrauterine infection, substance abuse, smoking, periodontal disease, and socio-economic deprivation. Numerous preterm births are preceded by ruptured membranes.

Clinical Findings

In women with regular uterine contractions and cervical change, the diagnosis of preterm labor is straightforward. However, symptoms such as pelvic pressure, cramping, or vaginal discharge may be the first complaints in high-risk patients who later develop preterm labor. Because these complaints may be vague and irregular uterine contractions are common, distinguishing which patients merit further evaluation can be problematic. In some cases, this distinction can be facilitated by the use of fetal fibronectin measurement in cervicovaginal specimens. This test is most useful when it is negative (less than 50 ng/mL), since the negative predictive value for delivery within 7–14 days is 93–97%. A negative test, therefore, usually means the patient can be reassured and discharged home. Because of its low sensitivity, however, fetal fibronectin is not recommended as a screening test in asymptomatic women.

Treatment

A. General Measures

Patients must be educated to identify symptoms associated with preterm labor to avoid unnecessary delay in their evaluation. In patients who are believed to be at increased risk for preterm delivery, randomized trials have failed to demonstrate improved outcomes in women placed on activity restriction. Paradoxically, such recommendations may place a woman at an *increased* risk to deliver preterm. Women with preterm labor at the threshold of viability present unique ethical and obstetric challenges and are best managed in consultation with maternal-fetal medicine and neonatology specialists. The families in such situations should be actively and continually engaged about decisions regarding the aggressiveness of resuscitative efforts.

B. Corticosteroids

In pregnancies between 23 weeks' and 34 weeks' gestation where preterm birth is anticipated, a single short course of corticosteroids should be administered to promote fetal lung maturity. Such therapy has been demonstrated to reduce the frequency of respiratory distress syndrome, intracranial hemorrhage, and even death in preterm infants. Betamethasone, 12 mg intramuscularly repeated once 24 hours later, and dexamethasone, 6 mg intramuscularly repeated every 12 hours for four doses, both cross the placenta and are the preferred treatments in this setting. A single repeat course of antenatal corticosteroids should be considered in women who are at risk for preterm delivery within the next 7 days, and whose prior dose of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. Administration of betamethasone may be considered in pregnant women between 34 0/7 and 36 6/7 weeks of gestation at imminent risk for preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.

C. Antibiotics

Despite the finding that preterm labor is associated with intrauterine infection in certain cases, there is no evidence that antibiotics forestall delivery in women with preterm labor and intact membranes. However, women in preterm labor should receive antimicrobial prophylaxis against group B *Streptococcus* unless a single standard culture of the distal vagina and anorectum has been negative for the organism in the preceding 5 weeks.

D. Tocolytic Agents

Evidence supports the use of first-line tocolytic treatment with beta-adrenergic receptor agonists, calcium channel blockers, or indomethacin for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids, and (if appropriate), transport the patient to a facility better equipped to care for premature infants. Maintenance therapy (continuation of

treatment beyond 48 hours) is not effective at preventing preterm birth and is not recommended.

Beta-adrenergic drugs, such as terbutaline, can be given every 30 minutes as an intravenous infusion starting at 2.5 mcg/min or as a subcutaneous injection starting at 250 mcg. Oral terbutaline is not recommended because of the lack of proven efficacy and concerns about maternal safety. Serious maternal side effects have been reported with the use of terbutaline and include tachycardia, pulmonary edema, arrhythmias, metabolic derangements (such as hyperglycemia and hypokalemia), and even death. Pulmonary edema occurs with increased frequency with concomitant administration of corticosteroids, large-volume intravenous fluid infusion, maternal sepsis, or prolonged tocolysis. Because of these safety concerns, the US Food and Drug Administration (FDA) warns that terbutaline be administered exclusively in a hospital setting and discontinued after 48–72 hours of treatment.

Nifedipine, 20 mg orally every 6 hours, and **indomethacin**, 50 mg orally once then 25 mg orally every 6 hours up to 48 hours, have also been used with limited success.

Magnesium sulfate is commonly used (but no longer recommended as a first-line agent) for tocolysis, and there is evidence that it may also be protective against cerebral palsy in infants from 24 weeks' to 32 weeks' gestation when given at time of birth. Magnesium sulfate is given intravenously as a 4- to 6-g bolus followed by a continuous infusion of 2 g/h. Magnesium levels are not typically checked but should be monitored if there is any concern for toxicity. Magnesium sulfate is entirely cleared by the kidney and must, therefore, be used with caution in women with any degree of kidney disease.

Before attempts are made to prevent preterm delivery with tocolytic agents, the patient should be assessed for conditions in which delivery would be indicated. Severe pre-eclampsia, lethal fetal anomalies, placental abruption, and intrauterine infection are all examples of indications for preterm delivery. In such cases, attempts to forestall delivery would be inappropriate.

► Preterm Birth Prevention

Strategies aimed at preventing preterm birth in high-risk women—principally those with a history of preterm birth or a shortened cervix (or both)—have focused on the administration of progesterone or progesterone compounds and the use of cervical cerclage. Prospective randomized controlled trials have demonstrated reductions in rates of preterm birth in high-risk women with singleton pregnancies who received progesterone supplementation, although the optimal preparation, dose, and route of administration (intramuscular injection versus vaginal suppository) are unclear. Although the issue has not been settled, there is also some evidence that progesterone therapy may decrease rates of preterm birth in nulliparous women who have a shortened cervix as measured by transvaginal ultrasound. ACOG does not recommend universal transvaginal cervical length screening but acknowledges that this strategy may be considered.

There is also evidence that women with a previous spontaneous preterm birth and a shortened cervix (less than 25 mm before 24 weeks' gestation) may benefit from placement of a cervical cerclage. Incidentally detected short cervical length in the second trimester in the absence of a prior singleton preterm birth is not diagnostic of cervical insufficiency, and cerclage is not indicated in this setting. In twin and triplet gestations, however, neither progesterone administration nor cervical cerclage placement has been effective at prolonging pregnancy, and these therapies are not recommended in women with multifetal pregnancies.

► When to Refer

- Symptoms of increased pelvic pressure or cramping in high-risk patients.
- Regular uterine contractions.
- Rupture of membranes.
- Vaginal bleeding.

► When to Admit

- Cervical dilation of 2 cm or more before 34 weeks' gestation.
- Contractions that cause cervical change.
- Rupture of membranes.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 130: Prediction and prevention of preterm birth. *Obstet Gynecol.* 2012;120:964. [Reaffirmed 2018] [PMID: 22996126]

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 142: Cerclage for the management of cervical insufficiency. *Obstet Gynecol.* 2014;123:372. [Reaffirmed 2019] [PMID: 24451674]

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 171: Management of preterm labor. *Obstet Gynecol.* 2016;128:e155. [Reaffirmed 2020] [PMID: 27661654]

American College of Obstetricians and Gynecologists. Committee Opinion No. 713: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol.* 2017;130:e102. [PMID: 28742678]

American College of Obstetricians and Gynecologists. Practice Bulletin No. 188: Prelabor rupture of membranes. *Obstet Gynecol.* 2018;131:e1. [PMID: 29266075]

THIRD-TRIMESTER BLEEDING

Five to 10 percent of women have vaginal bleeding in late pregnancy. The clinician must distinguish between placental causes (placenta previa, placental abruption, vasa previa) and nonplacental causes (labor, infection, disorders of the lower genital tract, systemic disease). The approach to bleeding in late pregnancy depends on the underlying cause, the gestational age at presentation, the degree of blood loss, and the overall status of the mother and her fetus. The cause of antepartum bleeding after midpregnancy is unknown in one-third of cases.

Treatment

A. General Measures

The patient should initially be observed closely with continuous fetal monitoring to assess for fetal distress. A complete blood count with platelets and a prothrombin time (INR) should be obtained and repeated serially if the bleeding continues. If hemorrhage is significant or if there is evidence of acute hypovolemia, the need for transfusion should be anticipated and an appropriate volume of red cells prepared with cross-matching. Ultrasound examination should be performed to determine placental location. Digital pelvic examinations are done only after ultrasound examination has ruled out placenta previa. Administration of anti-D immune globulin may be required for women who are Rh negative.

B. Placenta Previa

Placenta previa occurs when the placenta implants over the internal cervical os. Risk factors for this condition include previous cesarean delivery, increasing maternal age, multiparity, and smoking. If the diagnosis is initially made in the first or second trimester, the ultrasound should be repeated in the third trimester. Persistence of placenta previa at this point is an indication for cesarean as the route of delivery. Painless vaginal bleeding is the characteristic symptom in placenta previa and can range from light spotting to profuse hemorrhage. Hospitalization for extended evaluation is the appropriate initial management approach. For pregnancies that have reached 37 weeks' gestation or beyond with continued bleeding, cesarean delivery is generally indicated. Pregnancies at 36 weeks or earlier are candidates for expectant management provided the bleeding is not prodigious, and a subset of these women can be discharged if the bleeding and contractions completely subside.

C. Morbidly Adherent Placenta

Morbidly adherent placenta is a general term describing an abnormally adherent placenta that has invaded into the uterus. The condition can be further classified depending on whether the depth of invasion is limited to the endometrium (*accreta*), extends into the myometrium (*increta*), or invades beyond the uterine serosa (*percreta*). The most important risk factor for a morbidly adherent placenta is a prior uterine scar—typically from one or more prior cesarean deliveries. The focus of invasion usually involves the scar itself, and *placenta previa* is commonly associated with morbid adherence. Of serious concern for the field of obstetrics, the incidence of these syndromes has increased dramatically over the last 50 years commensurate with the increasing cesarean delivery rate.

After delivery of the infant, almost always in a repeat cesarean section, the morbidly adherent placenta does not separate normally, and the bleeding that results can be torrential. Emergency hysterectomy is usually required to stop the hemorrhage, and transfusion requirements are often massive. Because of the considerable increase in both maternal morbidity and mortality associated with this condition, careful preoperative planning is imperative when

the diagnosis is suspected antenatally. Ultrasound findings such as intraplacental lacunae, bridging vessels into the bladder, and loss of the retroplacental clear space suggest placental invasion in women who have placenta previa. *Importantly, however, even if ultrasound findings are subtle, an abnormally adherent placenta should be suspected in any patient with one or more prior cesarean deliveries and an anterior placenta previa.* Ideally, delivery planning should involve a multidisciplinary team, and the surgery should take place at an institution with appropriate personnel and a blood bank equipped to handle patients requiring massive transfusion. It has been demonstrated that a systematic approach to management with a multidisciplinary team improves patient outcomes. Evidence-based recommendations regarding delivery timing are lacking, but the goal is to have a planned, late-preterm cesarean delivery. As such, delivery at 34–36 weeks in a stable patient seems a reasonable approach.

D. Placental Abruptio

Placental abruption is the premature separation of the placenta from its implantation site before delivery. Hypertension is a known risk factor for abruption. Other risk factors include multiparity, cocaine use, smoking, previous abruption, and thrombophilias. Classic symptoms are vaginal bleeding, uterine tenderness, and frequent contractions, but the clinical presentation is highly variable. There is often concealed hemorrhage when the placenta abrupts, which causes increased pressure in the intervillous space. Excess amounts of thromboplastin escape into the maternal circulation and defibrillation occurs. Profound coagulopathy and acute hypovolemia from blood loss can occur and are more likely with an abruption severe enough to kill the fetus. Ultrasound may be helpful to exclude placenta previa, but failure to identify a retroplacental clot does not exclude abruption. In most cases, abruption is an indication for immediate cesarean delivery because of the high risk of fetal death.

American College of Obstetricians and Gynecologists. Obstetric Care Consensus No. 7: Placenta accreta spectrum. *Obstet Gynecol.* 2018;132:e259. [PMID: 30461695]

American College of Obstetricians and Gynecologists. Practice Bulletin No. 183: Postpartum hemorrhage. *Obstet Gynecol.* 2017;130:e168. [Reaffirmed 2019] [PMID: 28937571]

Bartels HC et al. Association of implementing a multidisciplinary team approach in the management of morbidly adherent placenta with maternal morbidity and mortality. *Obstet Gynecol.* 2018;132:1167. [PMID: 30234729]

Shamshirsaz AA et al. Outcomes of planned compared with urgent deliveries using a multidisciplinary team approach for morbidly adherent placenta. *Obstet Gynecol.* 2018;131:234. [PMID: 29324609]

OBSTETRIC COMPLICATIONS OF THE PERIPARTUM PERIOD

PUERPERAL MASTITIS

Postpartum mastitis occurs sporadically in nursing mothers, usually with symptom onset after discharge from the hospital. *Staphylococcus aureus* is usually the causative agent. Women nursing for the first time and those with

difficulty breastfeeding appear to be at greatest risk. Rarely, inflammatory carcinoma of the breast can be mistaken for puerperal mastitis (see also Chapter 17). Unfortunately, strategies aimed at preventing mastitis in breastfeeding women have been unsuccessful.

Mastitis frequently begins within 3 months after delivery and may start with an engorged breast and a sore or fissured nipple. Cellulitis is typically unilateral with the affected area of breast being red, tender, and warm. Fever and chills are common complaints as well. Treatment consists of antibiotics effective against penicillin-resistant staphylococci (dicloxacillin 500 mg orally every 6 hours or a cephalosporin for 10–14 days) and regular emptying of the breast by nursing or by using a mechanical suction device. Although nursing from the infected breast is safe for the infant, local inflammation of the nipple may complicate latching. Failure to respond to usual antibiotics within 3 days may represent an organizing abscess or infection with a resistant organism. When the causative organism is methicillin-resistant *S aureus* (MRSA), the risk for abscess formation is increased when compared with infection caused by nonresistant staphylococcal species. If an abscess is suspected, ultrasound of the breast can help confirm the diagnosis. In these cases, aspiration or surgical evacuation is usually required. Changing antibiotics based on culture sensitivity (to vancomycin or trimethoprim-sulfamethoxazole, for example) is useful, especially if the clinical course is not improving appropriately.

Yu Z et al. High-risk factors for suppurative mastitis in lactating women. *Med Sci Monit.* 2018;24:e192. [PMID: 29916453]

CHORIOAMNIONITIS & METRITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Fever not attributable to another source.
- ▶ Uterine tenderness.
- ▶ Tachycardia in the mother, fetus, or both.

General Considerations

Pelvic infections are relatively common problems encountered during the peripartum period. Chorioamnionitis is an infection of the amnion and chorion (fetal parts), usually occurring during labor. Uterine infection after delivery is often called endometritis or endomyometritis, but the term “metritis” is probably most accurate to emphasize that the infection extends throughout the uterine tissue. These infections are polymicrobial and are most commonly attributed to urogenital pathogens. The single most important risk factor for puerperal infection is cesarean delivery, which increases the risk from 5- to 20-fold. Other recognized risk factors include prolonged labor, use of internal monitors, nulliparity, multiple pelvic examinations, prolonged rupture of membranes, and lower genital tract infections. Although maternal complications such as dysfunctional labor and

postpartum hemorrhage are increased with clinical chorioamnionitis, the principal reason to initiate treatment is to prevent morbidity in the offspring. Neonatal complications such as sepsis, pneumonia, intraventricular hemorrhage, and cerebral palsy are increased in the setting of chorioamnionitis. Intrapartum initiation of antibiotics, however, significantly reduces neonatal morbidity.

Clinical Findings

Puerperal infections are diagnosed principally by the presence of fever (38°C or higher) in the absence of any other source and one or more of the following signs: maternal or fetal tachycardia (or both), and uterine tenderness. Foul-smelling lochia may be present, but is an insensitive marker of infection as many women without infection also experience an unpleasant odor. Likewise, some life-threatening infections such as necrotizing fasciitis are typically odorless. Cultures are typically not done because of the polymicrobial nature of the infection.

Treatment

Treatment is empiric with broad-spectrum antibiotics that will cover gram-positive and gram-negative organisms if still pregnant and gram-negative organisms and anaerobes if postpartum. A common regimen for chorioamnionitis is ampicillin, 2 g intravenously every 6 hours, and gentamicin, 2 mg/kg intravenous load then 1.5 mg/kg intravenously every 8 hours. A common regimen for metritis is gentamicin, 2 mg/kg intravenous load then 1.5 mg/kg intravenously every 8 hours, and clindamycin, 900 mg intravenously every 8 hours. Antibiotics are stopped in the mother when she has been afebrile (and asymptomatic) for 24 hours. No oral antibiotics are subsequently needed. Patients with metritis who do not respond in the first 24–48 hours may have an enterococcal component of metritis and require additional gram-positive coverage (such as ampicillin) to the regimen.

American College of Obstetricians and Gynecologists. Committee Opinion No. 712: Intrapartum management of intraamniotic infection. *Obstet Gynecol.* 2017;130:e95. [PMID: 28742677]

MEDICAL CONDITIONS COMPLICATING PREGNANCY

ANEMIA

Normal pregnancy is characterized by an increase in maternal plasma volume of about 50% and an increase in red cell volume of about 25%. Because of these changes, the mean hemoglobin and hematocrit values are lower than in the nonpregnant state. Anemia in pregnancy is considered when the hemoglobin measurement is below 11 g/dL. By far, the most common causes are iron deficiency and acute blood loss anemia, the latter usually occurring in the peripartum period. Symptoms such as fatigue and dyspnea that would otherwise suggest the presence of anemia in nonpregnant women are common in

pregnant women; therefore, periodic measurement of hematocrits in pregnancy is essential so that anemia can be identified and treated. In addition to its impact on maternal health, untoward pregnancy outcomes such as low birthweight and preterm delivery have been associated with second- and third-trimester anemia.

A. Iron Deficiency Anemia

The increased requirement for iron over the course of pregnancy is appreciable in order to support fetal growth and expansion of maternal blood volume. Dietary intake of iron is generally insufficient to meet this demand, and it is recommended that all pregnant women receive about 30 mg of elemental iron per day in the second and third trimesters. Oral iron therapy is commonly associated with gastrointestinal side effects, such as nausea and constipation, and these symptoms often contribute to noncompliance. If supplementation is inadequate, however, anemia often becomes evident by the third trimester of pregnancy. Because iron deficiency is by far the most common cause of anemia in pregnancy, treatment is usually empiric and consists of 60–100 mg of elemental iron per day and a diet containing iron-rich foods. Iron studies can confirm the diagnosis if necessary (see Chapter 13), and further evaluation should be considered in patients who do not respond to oral iron. Intermittent iron supplementation (eg, every other day) has been associated with fewer side effects and may be reasonable for women who cannot tolerate daily therapy.

B. Folic Acid Deficiency Anemia

Megaloblastic anemia in pregnancy is almost always caused by folic acid deficiency, since vitamin B₁₂ deficiency is extremely uncommon in the childbearing years. Folate deficiency is usually caused by inadequate dietary intake of fresh leafy vegetables, legumes, and animal proteins.

The diagnosis is made by finding macrocytic red cells and hypersegmented neutrophils on a blood smear (see Chapter 13). However, blood smears in pregnancy may be difficult to interpret, since they frequently show iron deficiency changes as well. With established folate deficiency, a supplemental dose of 1 mg/day and a diet with increased folic acid is generally sufficient to correct the anemia.

C. Sickle Cell Anemia

Women with sickle cell anemia are subject to serious complications in pregnancy. The anemia becomes more severe, and acute pain crises often occur more frequently. When compared with women who do not have hemoglobinopathies, women with hemoglobin SS are at increased risk for infections (especially pulmonary and urinary tract), thromboembolic events, pregnancy-related hypertension, transfusion, cesarean delivery, preterm birth, and fetal growth restriction. There also continues to be an increased rate of maternal mortality, despite an increased recognition of the high-risk nature of these pregnancies. Intensive medical treatment may improve the outcomes for both mother and fetus. Prophylactically transfusing packed red

cells to lower the level of hemoglobin S and elevate the level of hemoglobin A is a controversial practice without clear benefit. Most women with sickle cell disease will not require iron supplementation, but folate requirements can be appreciable due to red cell turnover from hemolysis.

D. Other Anemias

Although many of the inherited or acquired causes of anemia are relatively rare in women of childbearing age, they can be encountered in pregnancy. The implications for the mother and her offspring vary widely depending on the etiology of anemia. For example, mild microcytic anemia may be caused by iron deficiency, but it could also represent anemia of chronic disease as a result of previously undiagnosed malignancy. As such, women who have anemia caused by a disorder besides a nutritional deficiency are best managed in conjunction with a maternal fetal medicine specialist and a hematologist. Additionally, women who have an inherited form of anemia (hemoglobinopathies and thalassemia syndromes, for example) should be offered genetic counseling; prenatal diagnosis, if available, should be discussed if the parents wish to know whether the fetus is affected.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 95: Anemia in pregnancy. *Obstet Gynecol*. 2008;112:201. [Reaffirmed 2019] [PMID: 18591330]

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 78: Hemoglobinopathies in pregnancy. *Obstet Gynecol* 2007;109:229. [Reaffirmed 2019] [PMID: 17197616]

ANTIPHOSPHOLIPID SYNDROME

The antiphospholipid syndrome (APS) is characterized by autoantibodies, notably in association with arterial and venous thrombosis and adverse pregnancy outcomes (see Chapter 20).

THYROID DISEASE

Thyroid disease is relatively common in pregnancy, and in their overt states, both hypothyroidism and hyperthyroidism have been consistently associated with adverse pregnancy outcomes. There are gestational age-specific effects that pregnancy has on thyroid function tests; failure to recognize these physiologic alterations can result in misclassification or misdiagnosis. Women who have a history of a thyroid disorder or symptoms that suggest thyroid dysfunction should be screened with thyroid function tests. Screening asymptomatic pregnant women, however, is of unproven benefit and is not currently recommended.

Overt hypothyroidism is defined by an elevated serum TSH level with a depressed FT₄ level. During pregnancy, several factors occur that affect maternal thyroid hormones: (1) Rising estrogen levels increase thyroxine binding globulin (TBG) serum concentrations, reducing FT₄ levels. (2) Placental deiodinase promotes the turnover of T₄. (3) Supplemental iron and prenatal multivitamins containing iron can bind to oral T₄ and reduce its intestinal absorption.

The most common etiology of hypothyroidism during pregnancy is Hashimoto (autoimmune) thyroiditis. Many of the symptoms of hypothyroidism mimic those of normal pregnancy, making its clinical identification difficult. Maternal hypothyroidism has consistently been associated with an increase in complications such as spontaneous abortion, preterm birth, preeclampsia, placental abruption, and impaired neuropsychological development in the offspring; the fetus is at least partially dependent on maternal T₄ for its CNS development—particularly in the second trimester. Therefore, for women who need levothyroxine, it is prudent to increase the dosages by approximately 20–30% as soon as pregnancy is confirmed. Pregnant women with overt hypothyroidism or myxedema should be treated immediately with levothyroxine at full replacement doses of 1.6 mcg/kg/day (about 100–150 mcg daily). For titration, the levothyroxine dosage may be increased according to clinical response and serum TSH, measuring serum TSH every 4–6 weeks and trying to keep the serum TSH level in a trimester-specific gestational reference range. An increase in the dose of levothyroxine may be required in the second and third trimesters. By mid-pregnancy, women require an average of 47% increase in their levothyroxine dosage.

Subclinical hypothyroidism is defined as an increased serum TSH with a normal FT₄ level. Although some studies have found associations with untoward pregnancy outcomes such as miscarriage, preterm birth, and preeclampsia, others have failed to confirm these findings. There is currently no evidence, however, that identification and treatment of subclinical hypothyroidism will prevent any of these outcomes. Data from an NIH-sponsored Maternal-Fetal Medicine Units Network randomized, controlled trial demonstrated no improvement in cognitive function of 5-year-olds born to women screened and treated for subclinical hypothyroidism. For these reasons, the American College of Obstetricians and Gynecologists and the American Association of Clinical Endocrinologists recommend against universal screening for thyroid disease in pregnancy.

Overt hyperthyroidism, defined as excessive production of thyroxine with a depressed (usually undetectable) serum TSH level, is also associated with increased risks in pregnancy. Spontaneous abortion, preterm birth, preeclampsia, and maternal heart failure occur with increased frequency with untreated thyrotoxicosis. Thyroid storm, although rare, can be a life-threatening complication. Medical treatment of thyrotoxicosis is usually accomplished with the antithyroid drugs propylthiouracil or methimazole. Although teratogenicity has not been clearly established, in utero exposure to methimazole has been associated with aplasia cutis and choanal and esophageal atresia in the offspring of pregnancies so treated. Propylthiouracil is not believed to be teratogenic, but it has been associated with the rare complications of hepatotoxicity and agranulocytosis. Recommendations by the American Thyroid Association are to treat with propylthiouracil in the first trimester and convert to methimazole for the remainder of the pregnancy. The therapeutic target for the FT₄ level is the upper limit of the normal reference range.

The TSH levels generally stay suppressed even with adequate treatment. A beta-blocker can be used for such symptoms as palpitations or tremors. Fetal hypothyroidism or hyperthyroidism is uncommon but can occur with maternal Graves disease, which is the most common cause of hyperthyroidism in pregnancy. *Radioiodine ablation is absolutely contraindicated in pregnancy because it may destroy the fetal thyroid as well.*

Postpartum thyroiditis is discussed in Chapter 26; see Thyroiditis.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 148: Thyroid disease in pregnancy. *Obstet Gynecol*. 2015;125:996. [Reaffirmed 2019] [PMID: 25798985]

Casey BM et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. *N Engl J Med*. 2017; 376:815. [PMID: 28249134]

DIABETES MELLITUS

Normal pregnancy can be characterized as a state of increased insulin resistance that helps ensure a steady stream of glucose delivery to the developing fetus. Thus, both mild fasting hypoglycemia and postprandial hyperglycemia are physiologic. These metabolic changes are felt to be hormonally mediated with likely contributions from human placental lactogen, estrogen, and progesterone.

A. Gestational Diabetes Mellitus

Gestational diabetes mellitus is abnormal glucose tolerance in pregnancy and is generally believed to be an exaggeration of the pregnancy-induced physiologic changes in carbohydrate metabolism. Alternatively, pregnancy may unmask an underlying propensity for glucose intolerance, which will be evident in the nonpregnant state at some future time if not in the immediate postpartum period. Indeed, at least 50% of women with gestational diabetes are diagnosed with overt diabetes at some point in their lifetime. During the pregnancy, the principal concern in women identified to have gestational diabetes is excessive fetal growth, which can result in increased maternal and perinatal morbidity. Shoulder dystocia occurs more frequently in infants of diabetic mothers because of fetal overgrowth and increased fat deposition on the shoulders. Cesarean delivery and preeclampsia are also significantly increased in women with diabetes, both gestational and overt.

All asymptomatic pregnant women should undergo laboratory screening for gestational diabetes after 24 weeks' gestation. The diagnostic thresholds for glucose tolerance tests in pregnancy are not universally agreed upon, and importantly, adverse pregnancy outcomes appear to occur along a continuum of glucose intolerance even if the diagnosis of gestational diabetes is not formally assigned. A two-stage testing strategy is recommended by the American College of Obstetricians and Gynecologists, starting with a 50-g screening test offered to all pregnant women at 24–28 weeks' gestation. If this test is abnormal, the diagnostic test is a 100-g oral glucose tolerance test (Table 19-4).

Table 19–4. Screening and diagnostic criteria for gestational diabetes mellitus.

Screening for gestational diabetes mellitus

1. 50-g oral glucose load, administered between 24 and 28 weeks, without regard to time of day or time of last meal.
2. Venous plasma glucose measured 1 hour later.
3. Value of 140 mg/dL (7.8 mmol/L) or above in venous plasma indicates the need for a diagnostic glucose tolerance test.

Diagnosis of gestational diabetes mellitus

1. 100-g oral glucose load, administered in the morning after overnight fast lasting at least 8 hours but not more than 14 hours, and following at least 3 days of unrestricted diet (> 150 g carbohydrate) and physical activity.
2. Venous plasma glucose is measured fasting and at 1, 2, and 3 hours. Patient should remain seated and should not smoke throughout the test.
3. The diagnosis of gestational diabetes is made when two or more of the following venous plasma concentrations are met or exceeded: fasting, 95 mg/dL (5.3 mmol/L); 1 hour, 180 mg/dL (10 mmol/L); 2 hours, 155 mg/dL (8.6 mmol/L); 3 hours, 140 mg/dL (7.8 mmol/L).

Women in whom gestational diabetes is diagnosed should undergo nutrition counseling, and medications are typically initiated for those with persistent fasting hyperglycemia. Insulin has historically been considered the standard medication used to achieve glycemic control. Oral hypoglycemic agents, principally glyburide and metformin, have been evaluated in short-term clinical trials and appear to achieve similar degrees of glycemic control to insulin without increasing maternal or neonatal morbidity. These medications, however, have not been approved by the FDA for this indication; the long-term safety of oral agents has not been adequately studied in the women or in their offspring, and study quality of these agents has been poor. The current standard of care is insulin, unless circumstances preclude its use. In those cases, metformin is a reasonable choice. Insulin regimens commonly include multiple daily injections of a split-dose mix of intermediate-acting and short-acting agents. Regular and NPH insulins, as well as insulin lispro and aspart, do not cross the placenta. Once therapy is initiated, blood glucose surveillance is important to assess for adequacy of glycemic control. Capillary blood glucose levels should be checked four times per day, once fasting and three times after meals. Euglycemia is considered to be 60–90 mg/dL (3.3–5.0 mmol/L) while fasting and less than 120 mg/dL (6.7 mmol/L) 2 hours postprandially. Intensive therapy with dietary modifications or insulin therapy, or both, has been demonstrated to decrease rates of macrosomia, shoulder dystocia, and preeclampsia. Because of the increased prevalence of overt diabetes in women identified to have gestational diabetes, they should be screened at 6–12 weeks' postpartum with a fasting plasma glucose test or a 2-hour oral glucose tolerance test (75-g glucose load).

B. Overt Diabetes Mellitus

Overt diabetes is diabetes mellitus that antedates the pregnancy. There is an inverse relationship between glycemic control and the occurrence of fetal malformations, and

women whose periconceptional glycosylated hemoglobin levels are at or near normal levels have rates of malformations that approach baseline. In gestational diabetes, fetal overgrowth from inadequately controlled hyperglycemia remains a significant concern because of the increased maternal and perinatal morbidity that accompany macrosomia. Women with overt diabetes are subject to a number of other complications as well. Spontaneous abortions and third-trimester stillbirths occur with increased frequency in these women. There is also at least a twofold to threefold increased risk for fetal malformations, as hyperglycemia during organogenesis is teratogenic. The most common malformations in offspring of diabetic women are cardiac, skeletal, and neural tube defects. For the mother, the likelihood of infections and pregnancy-related hypertension is increased.

Preconception counseling and evaluation in a diabetic woman is ideal to maximize the pregnancy outcomes. This provides an opportunity to optimize glycemic control and evaluate for evidence of end-organ damage. The initial evaluation of diabetic women should include a complete chemistry panel, HbA_{1c} determination, 24-hour urine collection for total protein and creatinine clearance, funduscopic examination, and an ECG. Hypertension is common and may require treatment. Optimally, euglycemia should be established before conception and maintained during pregnancy with daily home glucose monitoring by the patient. A well-planned dietary program is a key component, with an intake of 1800–2200 kcal/day divided into three meals and three snacks. Insulin is given subcutaneously in a split-dose regimen as described above for women with gestational diabetes. The use of continuous insulin pump therapy may be helpful for some patients (see Chapter 27).

Throughout the pregnancy, diabetic women should be seen every 2–3 weeks and more frequently depending on the clinical condition. Adjustments in the insulin regimen may be necessary as the pregnancy progresses to maintain optimal glycemic control. A specialized ultrasound is often performed around 20 weeks to screen for fetal malformations. Symptoms and signs of infections should be evaluated and promptly treated. In the third trimester, fetal surveillance is indicated, and women with diabetes should receive serial antenatal testing (usually in the form of a nonstress test or biophysical profile). The timing of delivery is dictated by the quality of diabetic control, the presence or absence of medical complications, and fetal status. The goal is to reach 39 weeks (38 completed weeks) and then proceed with delivery. Confirmation of lung maturity may be appropriate if preterm delivery is contemplated.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 201: Pregestational diabetes mellitus. *Obstet Gynecol*. 2018;132:e228. [PMID: 30461693]

American College of Obstetricians and Gynecologists. Practice Bulletin No. 190: Gestational diabetes mellitus. *Obstet Gynecol*. 2018;131:e49. [PMID: 29370047]

Bryant SN et al. Diabetic ketoacidosis complicating pregnancy. *J Neonatal Perinatal Med*. 2017;10:17. [PMID: 28304323]

Melamed N et al. Induction of labor before 40 weeks is associated with lower rate of cesarean delivery in women with gestational diabetes mellitus. *Am J Obstet Gynecol*. 2016;214:364-e1. [PMID: 26928149]

CHRONIC HYPERTENSION

Chronic hypertension is estimated to complicate up to 5% of pregnancies. To establish this diagnosis, hypertension should antedate the pregnancy or be evident before 20 weeks' gestation to differentiate it from pregnancy-related hypertension. This distinction can be problematic when the initial presentation is after 20 weeks, but chronic hypertension is confirmed if the blood pressure remains elevated beyond 12 weeks postpartum. Risk factors for chronic hypertension include older maternal age, Black race, and obesity. While essential hypertension is by far the most common cause, secondary causes should be sought when clinically indicated.

Women with chronic hypertension are at increased risk for adverse maternal and perinatal outcomes. Superimposed preeclampsia develops in up to 20% of women with mild hypertension, but the risk increases up to 50% when there is severe baseline hypertension (160/110 mm Hg or higher) and may be even higher when there is evidence of end-organ damage. When preeclampsia is superimposed on chronic hypertension, there is a tendency for it to occur at an earlier gestational age, be more severe, and impair fetal growth. Women with chronic hypertension are also at increased risk for placental abruption, cesarean delivery, preterm birth, and perinatal mortality.

Ideally, women with chronic hypertension should undergo a preconceptional evaluation to detect end-organ damage, assess the need for antihypertensive therapy, and discontinue teratogenic medications. The specific tests ordered may vary depending on the severity of the hypertensive disorder, but an evaluation of liver, kidney, and cardiac function (eg, 24-hour urine protein and maternal echocardiogram if mother takes medications) is appropriate.

If the woman is not known to have chronic hypertension, then initiation of antihypertensive therapy in pregnant women is indicated only if the blood pressure is sustained at or above 160/110 mm Hg or if there is evidence of end-organ damage. Treatment of hypertension has not been demonstrated to improve pregnancy outcomes, but it is indicated in women with significant hypertension for long-term maternal cardiovascular health. Although methyldopa (Table 11–10) has the longest record of safety in pregnancy, nifedipine (Table 11–7) and labetalol (Table 11–9) are also acceptable, and these three agents are recommended above all others when initiating therapy in pregnancy. Care must be taken not to excessively reduce the blood pressure, as this may decrease uteroplacental perfusion. The goal is a modest reduction in blood pressure and avoidance of severe hypertension.

If a woman with mild chronic hypertension is stable on a medical regimen when she becomes pregnant, it is usually appropriate to continue this therapy, although the benefits of doing so are not well established. *Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, however, are contraindicated in all trimesters of pregnancy.* These medications are teratogenic in the first trimester and cause fetal hypocalvaria and acute kidney injury in the second and third trimesters.

When there is sustained severe hypertension despite multiple medications or significant end-organ damage

from hypertensive disease, pregnancy is not likely to be tolerated well. In these situations, therapeutic abortion may be appropriate. If the pregnancy is continued, the woman must be counseled that the maternal and perinatal risks are appreciable, and complications such as superimposed preeclampsia and fetal growth restriction should be anticipated.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 203: Chronic hypertension in pregnancy. *Obstet Gynecol.* 2019;133:e26. [PMID: 3057567]

Moussa HN et al. Pregnancy outcomes in women with preeclampsia superimposed on chronic hypertension with and without severe features. *Am J Perinatol.* 2017;34:403. [PMID: 27606778]

HEART DISEASE

Normal pregnancy physiology is characterized by cardiovascular adaptations in the mother. Cardiac output increases markedly as a result of both augmented stroke volume and an increase in the resting heart rate, and the maternal blood volume expands by up to 50%. These changes may not be tolerated well in women with functional or structural abnormalities of the heart. Thus, although only a small number of pregnancies are complicated by cardiac disease, these contribute disproportionately to overall rates of maternal morbidity and mortality. Most cardiac disease in women of childbearing age in the United States is caused by congenital heart disease. Ischemic heart disease, however, is being seen more commonly in pregnant women due to increasing rates of comorbid conditions, such as diabetes mellitus, hypertension, and obesity.

For practical purposes, the best single measurement of cardiopulmonary status is defined by the New York Heart Association Functional Classification. Most pregnant women with cardiac disease have class I or II functional disability, and although good outcomes are generally anticipated in this group, complications such as preeclampsia, preterm birth, and low birth weight appear to occur with increased frequency. Women with more severe disability (class III or IV) are rare in contemporary obstetrics; however, the maternal mortality is markedly increased in this setting and is usually the result of heart failure. Because of these risks, therapeutic abortion for maternal health should be considered in women who are severely disabled from cardiac disease. Specific conditions that have been associated with a particularly high risk for maternal death include Eisenmenger syndrome, primary pulmonary hypertension, Marfan syndrome with aortic root dilatation, and severe aortic or mitral stenosis. In general, these conditions should be considered contraindications to pregnancy.

The importance of preconceptional counseling for women with heart disease cannot be overstated. A thorough evaluation prior to pregnancy provides an opportunity for comprehensive risk assessment and detailed planning. Once pregnant, women with cardiac disease are best treated by a team of practitioners with experience in caring for such patients. Heart failure and arrhythmias are the most common cardiovascular complications associated

with heart disease in pregnancy, and adverse maternal and fetal outcomes are increased when they occur. Symptoms of volume overload should therefore be evaluated and treated promptly. Labor management depends on the underlying cardiac lesion and the degree of disability. Women with a history of arrhythmia should have continuous cardiac monitoring throughout labor, delivery, and the immediate postpartum period. Cesarean delivery is generally reserved for obstetric indications but may be appropriate for women in whom Valsalva maneuvers are contraindicated. The early postpartum period is a critical time for fluid management. Patients who are predisposed to heart failure should be monitored closely during the puerperium.

Infective endocarditis prophylaxis is not recommended for a vaginal or cesarean delivery in the absence of infection, except in the very small subset of patients at highest risk for adverse outcomes from endocarditis. The women at highest risk include those with cyanotic heart disease, prosthetic valves, or both. Prophylactic antibiotics for endocarditis, if required, should be given intravenously (see Table 33–5). If infection is present, such as chorioamnionitis, the underlying infection should be treated with the usual regimen and additional agents are not needed specifically for endocarditis prophylaxis.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 199: Use of prophylactic antibiotics in labor and delivery. *Obstet Gynecol.* 2018;132:e103. [PMID: 30134425]
Canobbio MM et al. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation.* 2017;135:e50. [PMID: 28082385]

ASTHMA

(See also Chapter 9.)

Asthma is one of the most common medical conditions encountered in pregnancy. Women with mild to moderate asthma can generally expect excellent pregnancy outcomes, but severe or poorly controlled asthma has been associated with a number of pregnancy complications, including preterm birth, small-for-gestational-age infants, and preeclampsia. The effects of pregnancy on asthma are likely minimal as asthma severity in the pregnancy has been reported to be similar to its severity during the year preceding the pregnancy. Strategies for treatment are similar to those in nonpregnant women. Patients should be educated about symptom management and avoidance of asthma triggers. Baseline pulmonary function tests can provide an objective assessment of lung function and may help the patient with self-monitoring of her asthma severity using a peak flow meter. As in nonpregnant women, treatment algorithms generally follow a stepwise approach, and commonly used medications, particularly those for mild to moderate asthma symptoms, are generally considered safe in pregnancy. Concerns about teratogenicity and medication effects on the fetus should be thoroughly discussed with the patient to decrease noncompliance rates. Inhaled beta-2-agonists are indicated for all asthma patients, and low to moderate dose inhaled corticosteroids are added for persistent symptoms when a rescue inhaler

alone is inadequate. Systemic corticosteroid administration is reserved for severe exacerbations but should not be withheld, if indicated, irrespective of gestational age. Cromolyn, leukotriene receptor antagonists, and theophylline are appropriate alternative therapies if first-line management is ineffective. The primary goals of management in pregnancy include minimizing symptoms and avoiding hypoxic episodes to the fetus. Prostaglandin F2a and ergonovine—medications frequently used to treat postpartum uterine atony—should be avoided because they can precipitate bronchospasm in women with asthma.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 90: Asthma in pregnancy. *Obstet Gynecol.* 2008;111:457. [Reaffirmed 2019] [PMID: 18238988]
Bonham CA et al. Asthma outcomes and management during pregnancy. *Chest.* 2018;153:515. [PMID: 28867295]

SEIZURE DISORDERS

Epilepsy is one of the most common serious neurologic disorders in pregnant women. Many of the commonly used antiepileptic drugs are known human teratogens. Therefore, the principal objectives in managing pregnancy in epileptic women are achieving adequate control of seizures while minimizing exposure to medications that can cause congenital malformations. Certain women who are contemplating pregnancy and have been seizure-free for 2–5 years may be considered candidates for discontinuation of antiseizure medication prior to pregnancy. For those who continue to require treatment, however, therapy with one medication is preferred. Selecting a regimen should be based on the type of seizure disorder and the risks associated with each medication. Valproic acid should not be considered first-line therapy because it has consistently been associated with higher rates of fetal malformations than most other commonly used antiepileptic drugs, and it may be associated with impaired neurocognitive development in the offspring. Phenytoin and carbamazepine both have established patterns of associated fetal malformations. Concerns about teratogenicity have prompted increasing use of the newer antiepileptic drugs such as lamotrigine, topiramate, oxcarbazepine, and levetiracetam. Although the safety of these medications in pregnancy continues to be evaluated, experiences from ongoing registries and large, population-based studies suggest that in utero exposure to the newer antiepileptic drugs in the first trimester of pregnancy carries a lower risk of major malformations than older medications. Lamotrigine and levetiracetam are considered the least teratogenic. One birth registry, however, found an increase in oral clefts among women taking lamotrigine. Several small studies have found an association between levetiracetam and low birth weight. Some studies suggest that topiramate is associated with a slightly increased risk of oral clefts. Although it is recommended that pregnant women with epilepsy be given supplemental folic acid, it is unclear if supplemental folate decreases rates of fetal malformations in women taking anticonvulsant therapy. Antiepileptic medications may be affected by volume of distribution changes in pregnancy, and serum levels should be followed when appropriate.

Harden C et al. Epilepsy in pregnancy. *Neurol Clin.* 2019;37:53. [PMID: 30470275]

INFECTIOUS CONDITIONS COMPLICATING PREGNANCY

URINARY TRACT INFECTION

The urinary tract is especially vulnerable to infections during pregnancy because the altered secretions of steroid sex hormones and the pressure exerted by the gravid uterus on the ureters and bladder cause hypotonia and congestion and predispose to urinary stasis. Labor and delivery and urinary retention postpartum also may initiate or aggravate infection. *Escherichia coli* is the offending organism in over two-thirds of cases.

From 2% to 15% of pregnant women have asymptomatic bacteriuria, which some believe to be associated with an increased risk of preterm birth. It is estimated that pyelonephritis will develop in 20–40% of these women if untreated.

An evaluation for asymptomatic bacteriuria at the first prenatal visit is recommended for all pregnant women. If a urine culture is positive, treatment should be initiated. Nitrofurantoin (100 mg orally twice daily), ampicillin (250 mg orally four times daily), and cephalaxin (250 mg orally four times daily) are acceptable medications for 4–7 days. Sulfonamides should be avoided in the third trimester because they may interfere with bilirubin binding and thus impose a risk of neonatal hyperbilirubinemia and kernicterus. Fluoroquinolones are also contraindicated because of their potential teratogenic effects on fetal cartilage and bone. Patients with recurrent bacteriuria should receive suppressive medication (once daily dosing of an appropriate antibiotic) for the remainder of the pregnancy. Acute pyelonephritis requires hospitalization for intravenous administration of antibiotics and crystalloids until the patient is afebrile; this is followed by a full course of oral antibiotics.

Kalinderi K et al. Urinary tract infection during pregnancy: current concepts on a common multifaceted problem. *J Obstet Gynaecol.* 2018;38:448. [PMID: 29402148]

GROUP B STREPTOCOCCAL INFECTION

Group B streptococci frequently colonize the lower female genital tract, with an asymptomatic carriage rate in pregnancy of 10–30%. This rate depends on maternal age, gravidity, and geographic variation. Vaginal carriage is asymptomatic and intermittent, with spontaneous clearing in approximately 30% and recolonization in about 10% of women. Adverse perinatal outcomes associated with group B streptococcal colonization include urinary tract infection, intrauterine infection, premature rupture of membranes, preterm delivery, and postpartum metritis.

Women with postpartum metritis due to infection with group B streptococci, especially after cesarean section, develop fever, tachycardia, and abdominal pain, usually

within 24 hours after delivery. Approximately 35% of these women are bacteremic.

Group B streptococcal infection is a common cause of neonatal sepsis. Transmission rates are high, yet the rate of neonatal sepsis is surprisingly low at less than 1:1000 live births. Unfortunately, the mortality rate associated with early-onset disease can be as high as 20–30% in premature infants. In contrast, it is approximately 2–3% in those at term. Moreover, these infections can contribute markedly to chronic morbidity, including mental retardation and neurologic disabilities. Late-onset disease develops through contact with hospital nursery personnel. Up to 45% of these health care workers can carry the bacteria on their skin and transmit the infection to newborns.

The 2019 American College of Obstetricians and Gynecologists recommendations for screening and prophylaxis for group B streptococcal colonization are available at <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/02/prevention-of-group-b-streptococcal-early-onset-disease-in-newborns>.

VARICELLA

Commonly known as chickenpox, varicella-zoster virus (VZV) infection has a fairly benign course when incurred during childhood but may result in serious illness in adults, particularly during pregnancy. Infection results in lifelong immunity. Approximately 95% of women born in the United States have VZV antibodies by the time they reach reproductive age. The incidence of VZV infection during pregnancy has been reported as up to 7:10,000. *The vaccine is contraindicated in pregnancy because the effects of the vaccine on the fetus are unknown.* Nonpregnant women who are vaccinated should avoid pregnancy for 1 month after injection. Inadvertent vaccination in early pregnancy or within a month of pregnancy is not an indication for termination, although women should be counseled about theoretical risks.

Clinical Findings

A. Symptoms and Signs

The incubation period for this infection is 10–20 days. A primary infection follows and is characterized by a flu-like syndrome with malaise, fever, and development of a pruritic maculopapular rash on the trunk, which becomes vesicular and then crusts. Pregnant women are prone to the development of VZV pneumonia, often a fulminant infection sometimes requiring respiratory support. After primary infection, the virus becomes latent, ascending to dorsal root ganglia. Subsequent reactivation can occur as zoster, often under circumstances of immunocompromise, although this is rare during pregnancy.

Two types of fetal infection have been documented. The first is congenital VZV syndrome, which typically occurs in 0.4–2% of fetuses exposed to primary VZV infection during the first trimester. Anomalies include limb and digit abnormalities, microphthalmos, and microcephaly.

Infection during the second and third trimesters is less threatening. Maternal IgG crosses the placenta, protecting

the fetus. The only infants at risk for severe infection are those born after maternal viremia but before development of maternal protective antibody. Maternal infection manifesting 5 days before or up to 2 days after delivery is the time period believed to be most hazardous for transmission to the fetus.

B. Laboratory Findings

Diagnosis is commonly made on clinical grounds. Laboratory verification is made by enzyme-linked immunosorbent assay (ELISA), fluorescent antibody, and hemagglutination inhibition antibody techniques. Vesicular fluid can be sent for qualitative varicella polymerase chain reaction assay.

Treatment

Varicella-zoster immune globulin (VZIG) has been shown to prevent or modify the symptoms of infection in exposed persons. Treatment success depends on identification of susceptible women at or just following exposure. Exposed women with a questionable or negative history of chickenpox should be checked for antibody, since the overwhelming majority will have been previously exposed. If the antibody is negative, VZIG (625 units intramuscularly) should ideally be given within 96 hours of exposure for greatest efficacy, but the CDC reports it can be given for up to 10 days. There are no known adverse effects of VZIG administration during pregnancy, although the incubation period for disease can be lengthened. Infants born to women in whom symptoms develop in the period from 5 days before delivery to 2 days after delivery should also receive VZIG (125 units).

Pregnant women with varicella may benefit from treatment with oral acyclovir, 800 mg orally four times daily for 5 days, if started within 24 hours of rash onset. Treatment has been shown to improve maternal symptoms but does not prevent congenital varicella. Infected pregnant women should be closely observed and hospitalized at the earliest signs of pulmonary involvement. Intravenous acyclovir (10 mg/kg intravenously every 8 hours) is recommended in the treatment of VZV pneumonia.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 151: Cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. *Obstet Gynecol.* 2015;125:1510. [Reaffirmed 2019] [PMID: 26000539]

and interferon gamma release assays are acceptable tests in pregnancy.

Decisions on treatment depend on whether the patient has active disease or is at high risk for progression to active disease. Pregnant women with latent disease not at high risk for disease progression can receive treatment postpartum, which does not preclude breastfeeding. The concentration of medication in breast milk is neither toxic nor adequate for treatment of the newborn. Isoniazid, ethambutol, and rifampin are used to treat tuberculosis (see Chapters 9 and 33). Because isoniazid therapy may result in vitamin B₆ deficiency, a supplement of 50 mg/day of vitamin B₆ should be given simultaneously. There is concern that isoniazid, particularly in pregnant women, can cause hepatitis. Liver biochemical tests should be performed regularly in pregnant women who receive treatment. Streptomycin, ethionamide, and most other antituberculous drugs should be avoided in pregnancy. If adequately treated, tuberculosis in pregnancy has an excellent prognosis.

Nahid P et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis.* 2016;63:e147. [PMID: 27516382]

HIV/AIDS DURING PREGNANCY

Asymptomatic HIV infection is associated with a normal pregnancy rate and no increased risk of adverse pregnancy outcomes. There is no evidence that pregnancy causes AIDS progression.

Previously, two-thirds of HIV-positive neonates acquired their infection close to, or during, the time of delivery. Routine HIV screening in pregnancy, including the use of rapid HIV tests in Labor and Delivery units, and the use of antiretroviral drugs has markedly reduced this transmission risk to approximately 1%. In an HIV-positive pregnant woman, a CD4 count, plasma RNA level, and resistance testing (if virus is detectable, and the patient has not already had this) should be obtained at the first prenatal visit. Treatment should not be delayed while waiting for the results of resistance testing. Prior or current antiretroviral use should be reviewed. The patient should be tested for HLA-B*5701 if abacavir may be prescribed; HLA-B*5701 positivity puts the patient at risk for a serious hypersensitivity reaction and its use is contraindicated.

A woman already taking and tolerating an acceptable antiretroviral regimen does not have to discontinue it in the first trimester. Patients should also be tested for hepatitis A, hepatitis C, tuberculosis, toxoplasmosis, and cytomegalovirus.

Women not taking medication should be offered combination antiretroviral therapy (commonly a dual nucleoside reverse transcriptase inhibitor combination and a ritonavir-boosted protease inhibitor or an integrase strand transfer inhibitor) after counseling regarding the potential impact of therapy on both mother and fetus (see Chapter 31). Antiretroviral therapy should be offered regardless of viral load and CD4 count. Whether to start in the first or second trimester should be determined on a case-by-case basis, but it should be started as early as

TUBERCULOSIS

The diagnosis of tuberculosis in pregnancy is made by history taking, physical examination, and testing, with special attention to women in high-risk groups. Women at high risk include those who are from endemic areas, those infected with HIV, drug users, health care workers, and close contacts of people with tuberculosis. Chest radiographs should not be obtained as a routine screening measure in pregnancy but should be used only in patients with a positive test or with suggestive findings in the history and physical examination. Abdominal shielding must be used if a chest radiograph is obtained. Both tuberculin skin testing

reasonably possible. It can be started in the first trimester after explanation of risks and benefits, provided the mother is not experiencing nausea and vomiting. The majority of medications used to treat HIV/AIDS have thus far proven to be safe in pregnancy with an acceptable risk/benefit ratio. The physiologic changes that occur during pregnancy may alter the effect of some medications. Before starting any regimen, the safety and efficacy of the medications selected should be reviewed. Standard of care also includes administration of intravenous zidovudine (2 mg/kg intravenously over 1 hour followed by 1 mg/kg/h intravenously) begun 3 hours before cesarean delivery and continued through the surgery until cord clamping in women whose viral load near delivery is greater than or equal to 1000 copies/mL or unknown. Antiretroviral therapy on the patient's usual schedule should be continued in labor. Intravenous zidovudine is not required for antiretroviral therapy-compliant women whose viral load is less than or equal to 50 copies/mL near delivery; data are limited in cases where the viral load is between 50 copies/mL and 999 copies/mL.

The use of prophylactic elective cesarean section at 38 weeks (before the onset of labor or rupture of the membranes) to prevent vertical transmission of HIV infection from mother to fetus has been shown to further reduce the transmission rate. In patients with a viral load of less than 1000 copies/mL, there may be no additional benefit of cesarean delivery, and those women can be offered a vaginal delivery. Amniotomy should not be performed in the setting of viremia unless there is a clear obstetric indication. Amniotomy, however, has not been associated with an increased risk of perinatal transmission when the mother is receiving antiretroviral therapy and virologically suppressed. Internal monitors, particularly the fetal scalp electrode, should be avoided as should operative deliveries (forceps-assisted and vacuum-assisted vaginal deliveries). Methergine (used for postpartum hemorrhage) should be avoided, if possible, in patients receiving regimens that include cytochrome P450 (CYP) 3A4 inhibitors and CYP3A4 enzyme inducers. HIV-infected women should be advised not to breastfeed their infants.

The Public Health Task Force provides guidelines for the management of HIV/AIDS in pregnancy that are regularly updated and available at <http://www.aidsinfo.nih.gov>. In addition, there is the National Perinatal HIV Hotline, which provides free consultation regarding perinatal HIV care (1-888-448-8765).

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. 2020 Jun 29. <https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf>.

MATERNAL HEPATITIS B & C CARRIER STATE

A. Hepatitis B Virus

There are an estimated 350 million chronic carriers of hepatitis B virus worldwide (see also Chapter 1). In the United States, 1.4 million people are infected, with the

highest rate among Asian Americans. All pregnant women should be screened for HBsAg. Transmission of the virus to the baby after delivery is likely if both surface antigen and e antigen are positive. Vertical transmission can be blocked by the immediate postdelivery administration to the newborn of hepatitis B immunoglobulin and hepatitis B vaccine intramuscularly. The vaccine dose is repeated at 1 and 6 months of age. Third trimester administration of tenofovir disoproxil fumarate, 300 mg orally once per day starting at 28–32 weeks and continuing through delivery (first line), lamivudine, or telbivudine to women with a viral load of greater than 10^6 – 10^8 copies/mL has been shown to reduce vertical transmission particularly if the viral load is less than 10^6 copies/mL at delivery. This therapy appears safe in pregnancy although long-term follow-up data are lacking. Pregnant women with chronic hepatitis B should have liver biochemical tests and viral load testing during the pregnancy. Hepatitis B infection is not a contraindication to breastfeeding, and antiviral therapy if given does not need to be continued postpartum.

B. Hepatitis C Virus

This infection is the most common chronic blood-borne infection in the United States. The average rate of hepatitis C virus (HCV) infection among infants born to HCV-positive, HIV-negative women is 5–6%. However, the average infection rate increases to 10–11% when mothers are coinfected with HCV and HIV. The principal factor associated with transmission is the presence of HCV RNA in the mother at the time of birth. Treatment is not recommended in pregnancy. Interferon and ribavirin have been considered contraindicated. Ledipasvir/sofosbuvir (Harvoni) has been shown to be safe in animal studies. There is one open-label, phase 1 study of pregnant women with hepatitis C treated with ledipasvir-sofosbuvir for 12 weeks starting in the second trimester. The study only had nine participants, but ledipasvir-sofosbuvir was safe and effective at the standard dose.

Chappell CA et al; Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study. Lancet Microbe. 2020;1:e200. [PMID: 32939459]

Jin J. JAMA patient page. Screening for hepatitis B in pregnant women. JAMA. 2019;322:376. [PMID: 31334796]

Society for Maternal-Fetal Medicine (SMFM). Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol. 2017;217:B2. [PMID: 28782502]

HERPES GENITALIS

Infection of the lower genital tract by herpes simplex virus type 2 (HSV-2) (see also Chapter 6) is a common STD with potentially serious consequences to pregnant women and their newborn infants. Although up to 25% of women in an obstetric practice may have antibodies to HSV-2, a history of the infection is unreliable and the incidence of neonatal infection is low (10–60/100,000 live births). Most infected neonates are born to women with no history, symptoms, or signs of infection.

Women who have had *primary* herpes infection late in pregnancy are at high risk for shedding virus at delivery.

Some experts suggest use of prophylactic acyclovir, 400 mg orally three times daily, to decrease the likelihood of active lesions at the time of labor and delivery.

Women with a history of *recurrent* genital herpes have a lower neonatal attack rate than women infected during the pregnancy, but they should still be monitored with clinical observation and culture of any suspicious lesions. Since asymptomatic viral shedding is not predictable by antepartum cultures, current recommendations do not include routine cultures in individuals with a history of herpes without active disease. However, when labor begins, vulvar and cervical inspection should be performed. Cesarean delivery is indicated at the time of labor if there are prodromal symptoms or active genital lesions.

For treatment, see Chapter 32. The use of acyclovir in pregnancy is acceptable, and prophylaxis starting at 36 weeks' gestation has been shown to decrease the number of cesarean sections performed for active disease.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 82: Management of herpes in pregnancy. *Obstet Gynecol*. 2007;109:1489. [Reaffirmed 2018] [PMID: 17569194]

SYPHILIS, GONORRHEA, & CHLAMYDIA TRACHOMATIS INFECTION

These STDs have significant consequences for mother and child (see also Chapters 33 and 34). Untreated syphilis in pregnancy can cause late abortion, stillbirth, transplacental infection, and congenital syphilis. Gonorrhea can produce large-joint arthritis by hematogenous spread as well as ophthalmia neonatorum. Maternal chlamydial infections are largely asymptomatic but are manifested in the newborn by inclusion conjunctivitis and, at age 2–4 months, by pneumonia. The diagnosis of each can be reliably made by appropriate laboratory tests. All women should be tested for syphilis and *C trachomatis* as part of their routine prenatal care. Repeat testing is dependent on risk factors, prevalence, and state laws. A pregnant patient treated for *C trachomatis* should have a test of cure 3–4 weeks later and then 3 months after that because of high reinfection rates. Women at risk should be tested for gonorrhea. The sexual partners of women with STDs should be identified and treated also if possible; the local health department can assist with this process.

Workowski KA et al; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64:1. [PMID: 26042815]

GASTROINTESTINAL, HEPATIC, & BILIARY DISORDERS OF PREGNANCY

Complications involving the gastrointestinal tract, liver, and gallbladder are common in pregnancy. Nausea and vomiting in the first trimester affect the majority of pregnant women to some degree (see *Obstetric Complications*

of the First & Second Trimesters). *Nausea and vomiting in the last half of pregnancy, however, are never normal*; a thorough evaluation of such complaints is mandatory. Some of these conditions are incidental to pregnancy (eg, appendicitis), while others are related to the gravid state and tend to resolve with delivery (eg, acute fatty liver of pregnancy). Importantly, the myriad anatomic and physiologic changes associated with normal pregnancy must be considered when assessing for a disease state. Likewise, interpretation of laboratory studies must take into account the pregnancy-associated changes in hepatic protein production.

For conditions in which surgery is clinically indicated, operative intervention should never be withheld based solely on the fact that a woman is pregnant. While purely elective surgery is avoided during pregnancy, women who undergo surgical procedures for an urgent or emergent indication during pregnancy do not appear to be at increased risk for adverse outcomes. Obstetric complications, when they occur, are more likely to be associated with the underlying maternal illness. Recommendations have held that the optimal time for semi-elective surgery is the second trimester to avoid exposure to anesthesia in the first trimester and the enlarged uterus in the third. Importantly, however, there is no convincing evidence that general anesthesia induces malformations or increases the risk for abortion.

CHOLELITHIASIS & CHOLECYSTITIS

Cholelithiasis is common in pregnancy as physiologic changes such as increased cholesterol production and incomplete gallbladder emptying predispose to gallstone formation. The diagnosis is usually suspected based on classic symptoms of nausea, vomiting, and right upper quadrant pain, usually after meals, and is confirmed with right upper quadrant ultrasound. Symptomatic cholelithiasis without cholecystitis is usually managed conservatively, but recurrent symptoms are common. Cholecystitis results from obstruction of the cystic duct and often is accompanied by bacterial infection. Medical management with antibiotics is reasonable in selected cases, but definitive treatment with cholecystectomy will help prevent complications such as gallbladder perforation and pancreatitis. Cholecystectomy has successfully been performed in all trimesters of pregnancy and should not be withheld based on the stage of pregnancy if clinically indicated. Laparoscopy is preferred in the first half of pregnancy, but becomes more technically challenging in the last trimester due to the enlarged uterus and cephalad displacement of abdominal contents.

Obstruction of the common bile duct, which can lead to cholangitis, is an indication for surgical removal of gallstones and establishment of biliary drainage. Endoscopic retrograde cholangiopancreatography (ERCP) with or without sphincterotomy is a nonsurgical alternative. Pregnant women can safely undergo ERCP provided that precautions are taken to minimize fetal exposure to radiation. There does, however, appear to be a slightly higher rate of post-procedure pancreatitis in pregnant women who undergo ERCP. Magnetic resonance cholangiopancreatography (MRCP) can also be of use in patients with suspected

common bile duct obstruction. This study is particularly useful for those women in whom the etiology of common duct dilatation is unclear on ultrasound. MRCP can provide detailed evaluation of the entire biliary system and the pancreas while avoiding ionizing radiation.

Cappell MS et al. Systematic review of safety and efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography during pregnancy including studies of radiation-free therapeutic endoscopic-retrograde-cholangiopancreatography. *World J Gastrointest Endosc.* 2018;10:308. [PMID: 30364767]

Van der Woude CJ. Preface: Pregnancy in GI disorders. *Best Pract Res Clin Gastroenterol.* 2020;44:101672. [PMID: 32359681]

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy, a disorder limited to the gravid state, occurs in the third trimester of pregnancy and causes acute hepatic failure. With improved recognition and immediate delivery, the maternal mortality rate in contemporary reports is about 4%. The disorder is usually seen after the 35th week of gestation and is more common in primigravidae and those with twins. The incidence is about 1:10,000 deliveries.

The etiology of acute fatty liver of pregnancy is likely poor placental mitochondrial function. Many cases may be due to a homozygous fetal deficiency of long-chain acyl coenzyme A dehydrogenase (LCHAD).

► Clinical Findings

Pathologic findings are unique to the disorder, with fatty engorgement of hepatocytes. Clinical onset is gradual, with nausea and vomiting being the most common presenting symptoms. Varying degrees of flu-like symptoms are also typical. Eventually, symptoms progress to those of fulminant hepatic failure: jaundice, encephalopathy, disseminated intravascular coagulation, and death. On examination, the patient shows signs of hepatic failure.

Laboratory findings include marked elevation of alkaline phosphatase but only moderate elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Hypocholesterolemia and hypofibrinogenemia are typical, and hypoglycemia can be extreme. Coagulopathy is also frequently seen with depressed procoagulant protein production. Kidney function should be assessed for hepatorenal syndrome. The white blood cell count is elevated, and the platelet count is depressed.

► Differential Diagnosis

The differential diagnosis is that of fulminant hepatitis. Liver aminotransferases for fulminant hepatitis are higher (greater than 1000 units/mL) than those for acute fatty liver of pregnancy (usually 500–1000 units/mL). Preeclampsia may involve the liver but typically does not cause jaundice; the elevations in liver biochemical tests in patients with preeclampsia usually do not reach the levels seen in patients with acute fatty liver of pregnancy.

► Treatment

Diagnosis of acute fatty liver of pregnancy mandates immediate delivery. Intensive supportive care with ICU-level observation is essential and typically includes administration of blood products and glucose as well as correction of acidemia. Vaginal delivery is preferred. Resolution of encephalopathy and laboratory derangements occurs over days with supportive care, and recovery is usually complete. Rare cases of liver transplantation have been reported.

Naoum EE et al. Acute fatty liver in pregnancy; pathophysiology, anesthetic implications, and obstetrical management. *Anesthesiology.* 2019;130:446. [PMID: 30707120]

Nelson DB et al. Acute fatty liver of pregnancy. *Clin Obstet Gynecol.* 2020;63:152. [PMID: 31725416]

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy is characterized by incomplete clearance of bile acids in genetically susceptible women. The principal symptom is pruritus, which can be generalized but tends to have a predilection for the palms and soles. Presentation is typically in the third trimester, and women with multi-fetal pregnancies are at increased risk. The finding of an elevated serum bile acid level, ideally performed in the fasting state, confirms the diagnosis. Associated laboratory derangements include modest elevations in hepatic transaminase levels and mild hyperbilirubinemia. Although rare, the bilirubin level may be sufficiently elevated to result in clinical jaundice. The symptoms and laboratory abnormalities resolve quickly after delivery but can recur in subsequent pregnancies or with exposure to combination oral contraceptives.

Adverse fetal outcomes, particularly preterm birth, nonreassuring fetal status, meconium-stained amniotic fluid, and stillbirth, have consistently been reported in women with cholestasis of pregnancy. The risk for adverse perinatal outcomes appears to correlate with disease severity as measured by the degree of bile acid elevation, and women with fasting bile acids greater than 40 μmol/L have been reported to be at greatest risk. Because of the risks associated with cholestasis of pregnancy, many clinicians recommend antenatal testing in the third trimester and elective early delivery in attempt to avoid stillbirth. Evidence-based recommendations regarding such management practices, however, are not currently available. The use of ursodeoxycholic acid is not recommended for the treatment of intrahepatic cholestasis of pregnancy; a 2019 randomized controlled trial did not find that ursodeoxycholic acid reduced symptoms and morbidity for intrahepatic cholestasis of pregnancy.

Chappell LC et al; PITCHES study group. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. *Lancet.* 2019;394:849. [PMID: 31378395]

APPENDICITIS

Appendicitis occurs in about 1 of 1500 pregnancies. The diagnosis is more difficult to make clinically in pregnant women where the appendix is displaced cephalad from McBurney point. Furthermore, nausea, vomiting, and mild leukocytosis occur in normal pregnancy, so with or without these findings, any complaint of right-sided pain should raise suspicion. Imaging can help confirm the diagnosis if clinical findings are equivocal. Abdominal sonography is a reasonable initial imaging choice, but nonvisualization of the appendix is common in pregnancy. CT scanning is more sensitive than ultrasound, and with

proper shielding, the radiation exposure to the fetus is minimized. MRI is also used to evaluate for appendicitis in pregnant women and is a reasonable alternative to CT scanning. Unfortunately, the diagnosis of appendicitis is not made until the appendix has ruptured in at least 20% of obstetric patients. Peritonitis in these cases can lead to preterm labor or abortion. With early diagnosis and appendectomy, the prognosis is good for mother and baby.

Prodromidou A et al. Outcomes after open and laparoscopic appendectomy during pregnancy: a meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2018;225:40. [PMID: 29656140]

Rheumatologic, Immunologic, & Allergic Disorders

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20

RHEUMATOLOGIC DISORDERS

► Diagnosis & Evaluation

A. Examination of the Patient

Two helpful clinical clues for diagnosing arthritis are the joint pattern and the presence or absence of extra-articular manifestations. The joint pattern is defined by the answers to three questions: (1) Is inflammation present? (2) How many joints are involved? and (3) What joints are affected? Joint inflammation manifests as warmth, swelling, and morning stiffness of at least 30 minutes' duration. Overlying erythema occurs with the intense inflammation of crystal-induced and septic arthritis. Both the number of affected joints and the specific sites of involvement affect the differential diagnosis (Table 20-1). Some diseases—gout, for example—are characteristically monoarticular, whereas other diseases, such as rheumatoid arthritis, are usually polyarticular. The location of joint involvement can also be distinctive. Only two diseases frequently cause prominent involvement of the distal interphalangeal (DIP) joint: osteoarthritis and psoriatic arthritis. Extra-articular manifestations such as fever (eg, gout, Still disease, endocarditis, vasculitis, systemic lupus erythematosus [SLE]), rash (eg, SLE, psoriatic arthritis, inflammatory myositis), nodules (eg, rheumatoid arthritis, gout), or neuropathy (eg, vasculitis) narrow the differential diagnosis further.

B. Arthrocentesis and Examination of Joint Fluid

If the diagnosis is uncertain, synovial fluid should be examined whenever possible (Table 20-2). Most large joints are easily aspirated, and contraindications to arthrocentesis are few. The aspirating needle should never be passed through an overlying cellulitis or psoriatic plaque because of the risk of introducing infection. For patients who are receiving direct-acting oral anticoagulants or long-term anticoagulation therapy with warfarin, joints can be aspirated with a small-gauge needle (eg, 22F); the international normalized ratio (INR) should be less than 3.0 for patients taking warfarin.

1. Types of studies—

A. GROSS EXAMINATION—Clarity is an approximate guide to the degree of inflammation. Noninflammatory fluid is transparent, mild inflammation produces translucent fluid,

and purulent effusions are opaque. Traumatic taps, trauma, and bleeding disorders are the most common causes of bloody effusions.

b. CELL COUNT—Normal synovial fluid contains less than 200 white cells/mcL ($0.2 \times 10^9/L$). Higher synovial fluid white cell counts can discriminate between noninflammatory (less than 2000 white cells/mcL [$2.0 \times 10^9/L$]), inflammatory (2000–75,000 white cells/mcL [$2.0\text{--}75 \times 10^9/L$]), and purulent (greater than 100,000 white cells/mcL [$100 \times 10^9/L$]) joint effusions. Synovial fluid glucose and protein levels add little information and should not be ordered.

c. MICROSCOPIC EXAMINATION—Compensated polarized light microscopy identifies and distinguishes monosodium urate (gout, negatively birefringent) and calcium pyrophosphate (pseudogout, positive birefringent) crystals. Gram stain has specificity but limited sensitivity (50%) for septic arthritis.

d. CULTURE—Bacterial cultures as well as special studies for gonococci, tubercle bacilli, or fungi are ordered as appropriate.

2. Interpretation—Synovial fluid analysis is diagnostic in infectious or microcrystalline arthritis. Although the severity of inflammation in synovial fluid can overlap among various conditions, the synovial fluid white cell count is a helpful guide to diagnosis (Table 20-3).

DEGENERATIVE & CRYSTAL-INDUCED ARTHRITIS

DEGENERATIVE JOINT DISEASE (Osteoarthritis)



- A degenerative disorder with minimal articular inflammation.
- No systemic symptoms.
- Pain relieved by rest; morning stiffness brief.
- Radiographic findings: narrowed joint space, osteophytes, increased subchondral bone density, bony cysts.

Table 20–1. Diagnostic value of the joint pattern.

Characteristic	Status	Representative Disease
Inflammation	Present	Rheumatoid arthritis, SLE, gout
	Absent	Osteoarthritis
Number of involved joints	Monoarticular	Gout, trauma, septic arthritis, Lyme disease, osteoarthritis
	Oligoarticular (2–4 joints)	Reactive arthritis, psoriatic arthritis, inflammatory bowel disease
	Polyarticular (≥ 5 joints)	Rheumatoid arthritis, SLE
Site of joint involvement	Distal interphalangeal	Osteoarthritis, psoriatic arthritis (not rheumatoid arthritis)
	Metacarpophalangeal, wrists	Rheumatoid arthritis, SLE, calcium pyrophosphate deposition disease (not osteoarthritis)
	First metatarsal phalangeal	Gout, osteoarthritis

SLE, systemic lupus erythematosus.

► General Considerations

Osteoarthritis, the most common form of joint disease, is chiefly a disease of aging. Ninety percent of all people have radiographic features of osteoarthritis in weight-bearing joints by age 40. Symptomatic disease increases with age. Sex is also a risk factor; osteoarthritis develops in women more frequently than in men.

This arthropathy is characterized by degeneration of cartilage and by hypertrophy of bone at the articular margins. Inflammation is usually minimal. Hereditary and mechanical factors may be involved in the pathogenesis.

Table 20–2. Examination of joint fluid.

Measure	(Normal)	Group I (Noninflammatory)	Group II (Inflammatory)	Group III (Purulent)
Volume (mL) (knee)	< 3.5	Often > 3.5	Often > 3.5	Often > 3.5
Clarity	Transparent	Transparent	Translucent to opaque	Opaque
Color	Clear	Yellow	Yellow to opalescent	Yellow to green
WBC per mL	< 200 ($0.2 \times 10^9/L$)	< 2000 ($2.0 \times 10^9/L$)	2000–75,000 ¹ ($2.0\text{--}75.0 \times 10^9/L$)	> 100,000 ² ($100 \times 10^9/L$)
Polymorphonuclear leukocytes	< 25%	< 25%	50% or more	75% or more
Culture	Negative	Negative	Negative	Usually positive ²

¹Gout, rheumatoid arthritis, and other inflammatory conditions occasionally have synovial fluid WBC counts > 75,000/mL ($75.0 \times 10^9/L$) but rarely > 100,000/mL ($100 \times 10^9/L$).

²Most purulent effusions are due to septic arthritis. Septic arthritis, however, can present with group II synovial fluid, particularly if infection is caused by organisms of low virulence (eg, *Neisseria gonorrhoeae*) or if antibiotic therapy has been started. WBC, white blood cell count.

Obesity is a risk factor for osteoarthritis of the knee, hand, and probably of the hip. Recreational running does not increase the incidence of osteoarthritis, but participation in competitive contact sports does. Jobs requiring frequent bending and carrying increase the risk of knee osteoarthritis (see Chapter 41).

► Clinical Findings

A. Symptoms and Signs

Degenerative joint disease is divided into two types: (1) primary, which most commonly affects some or all of the following: the DIP and the proximal interphalangeal (PIP) joints of the fingers, the carpometacarpal joint of the thumb, the hip, the knee, the metatarsophalangeal (MTP) joint of the big toe, and the cervical and lumbar spine; and (2) secondary, which may occur in any joint as a sequela to articular injury. The injury may be acute, as in a fracture; or chronic, as from occupational overuse of a joint or metabolic disease (eg, hyperparathyroidism, hemochromatosis, ochronosis) or joint inflammation (eg, rheumatoid arthritis).

The onset is insidious. Initially, there is articular stiffness, seldom lasting more than 15 minutes; this develops later into pain on motion of the affected joint and is made worse by activity or weight bearing and relieved by rest. Flexion contracture or varus deformity of the knee is not unusual, and bony enlargements of the DIP (Heberden nodes) and PIP (Bouchard nodes) are occasionally prominent (Figure 20–1). There is no ankylosis, but limitation of motion of the affected joint or joints is common. Crepitus may often be felt over the knee. Joint effusion and other articular signs of inflammation are mild. However, in some cases a one-way valve effect between the knee joint and gastrocnemius-semimembranosus bursa can lead to accumulation of synovial fluid, referred to as a popliteal (Baker) cyst. There are no systemic manifestations.

B. Laboratory Findings

Osteoarthritis does not cause elevation of the erythrocyte sedimentation rate (ESR) or other laboratory signs of inflammation. Synovial fluid is noninflammatory.

Table 20–3. Differential diagnosis by joint fluid groups.

Noninflammatory (< 2000 white cells/mcL [$2 \times 10^9/L$])	Inflammatory (2000–75,000 white cells/mcL [$2.0\text{--}75.0 \times 10^9/L$])	Purulent (> 100,000 white cells/mcL [$100 \times 10^9/L$])	Hemorrhagic
Osteoarthritis Traumatic arthritis Osteonecrosis Charcot arthropathy	Rheumatoid arthritis Systemic lupus erythematosus Polymyositis or dermatomyositis Systemic sclerosis Systemic necrotizing vasculitides Polychondritis Gout Calcium pyrophosphate deposition disease Hydroxyapatite deposition disease Juvenile rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Reactive arthritis Inflammatory bowel disease arthritis Hypogammaglobulinemia Sarcoidosis Rheumatic fever Indolent/low virulence infections (viral, mycobacterial, fungal, Whipple disease, Lyme disease)	Septic arthritis (bacterial)	Trauma Pigmented villonodular synovitis Tuberculosis Neoplasia Coagulopathy Charcot arthropathy

Reproduced, with permission, from Klippen JH et al (eds). *Primer on the Rheumatic Diseases*, 13th ed. Springer, 2008.

C. Imaging

Radiographs may reveal narrowing of the joint space; osteophyte formation and lipping of marginal bone; and thickened, dense subchondral bone. Bone cysts may also be present.

Differential Diagnosis

Because articular inflammation is minimal and systemic manifestations are absent, degenerative joint disease should



Figure 20–1. Osteoarthritis in an older woman with Heberden nodes at the distal interphalangeal joints. There is some swelling beginning at the proximal interphalangeal joints creating Bouchard nodes. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw Hill, 2019.)

seldom be confused with other arthritides. The distribution of joint involvement in the hands also helps distinguish osteoarthritis from rheumatoid arthritis. Osteoarthritis chiefly affects the DIP and PIP joints and spares the wrist and metacarpophalangeal (MCP) joints; rheumatoid arthritis involves the wrists and MCP joints and spares the DIP joints. Furthermore, the joint enlargement is bony-hard and cool in osteoarthritis but spongy and warm in rheumatoid arthritis. Skeletal symptoms due to degenerative changes in joints—especially in the spine—may cause coexistent metastatic neoplasia, osteoporosis, plasma cell myeloma, or other bone disease to be overlooked.

Prevention

Weight reduction reduces the risk of developing symptomatic knee and hand osteoarthritis. Correcting leg length discrepancy of greater than 1 cm with shoe modification may prevent knee osteoarthritis from developing in the shorter leg.

Treatment

A. General Measures

Patients with osteoarthritis of the hand may benefit from assistive devices and instruction on techniques for joint protection; splinting is beneficial for those with symptomatic osteoarthritis of the first carpometacarpal joint. Patients with mild to moderate osteoarthritis of the knee or hip should participate in a regular exercise program (eg, a supervised walking program, hydrotherapy classes) and, if overweight, should lose weight. A randomized, controlled trial of 156 individuals with knee osteoarthritis found that physical therapy was more effective at reducing pain and disability at 1 year than intra-articular glucocorticoid

injections. The use of assistive devices (eg, a cane on the contralateral side) can improve functional status.

B. Medical Management

1. Oral nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs (see Table 5–5) are more effective than acetaminophen for osteoarthritis but have greater toxicity. NSAIDs inhibit cyclooxygenase (COX), the enzyme that converts arachidonic acid to prostaglandins. COX exists in two isomers—COX-1, which is expressed continuously in many cells and is responsible for the homeostatic effects of prostaglandins, and COX-2, which is induced by cytokines and expressed in inflammatory tissues. Most NSAIDs inhibit both isomers. Celecoxib is the only selective COX-2 inhibitor currently available in the United States.

Gastrointestinal toxicity, such as gastric ulceration, perforation, and gastrointestinal hemorrhage, are the most common serious side effects of NSAIDs. The overall rate of bleeding with NSAID use in the general population is low (1:6000 users or less) but is increased by the risk factors of long-term use, higher NSAID dose, concomitant corticosteroids or anticoagulants, selective serotonin reuptake inhibitors, the presence of rheumatoid arthritis, history of peptic ulcer disease or alcoholism, and age over 70. *Proton pump inhibitors and histamine type-2 receptor antagonists reduce the incidence of serious gastrointestinal toxicity and should be used for patients with risk factors for NSAID-induced gastrointestinal toxicity.* Patients who have recently recovered from an NSAID-induced bleeding gastric ulcer appear to be at high risk for rebleeding (about 5% in 6 months) when an NSAID is reintroduced, even if prophylactic measures (such as proton pump inhibitors) are used. Compared with nonselective NSAIDs, celecoxib is less likely to cause upper gastrointestinal tract adverse events, including bleeding.

All of the NSAIDs, including aspirin and celecoxib, can produce renal toxicity, including interstitial nephritis, nephrotic syndrome, prerenal azotemia, and aggravation of hypertension. Hyperkalemia due to hyporeninemic hypoaldosteronism is seen rarely. Renal toxicity is uncommon but is increased by the following risk factors: age older than 60 years, history of kidney disease, heart failure, cirrhosis, and diuretic use.

All NSAIDs, except the nonacetylated salicylates and celecoxib, interfere with platelet function and prolong bleeding time. Aspirin irreversibly inhibits platelet function, so the bleeding time effect resolves only as new platelets are made. In contrast, the effect of nonselective NSAIDs on platelet function is reversible and resolves as the drug is cleared. Concomitant administration of a non-selective NSAID can interfere with the ability of aspirin to acetylate platelets and thus may interfere with the cardio-protective effects of low-dose aspirin. *All NSAIDs are associated with a small increase in the absolute risk of myocardial infarction and stroke in patients with or without risk factors for heart disease or known heart disease.* While the cardiovascular risk is related to the dose and duration of treatment, stroke and myocardial infarction can occur within the first week of treatment. Cardiovascular risks associated with naproxen, ibuprofen, and moderate dose celecoxib (200 mg orally daily) are comparable.

Chondroitin sulfate and glucosamine, alone or in combination, are no better than placebo in reducing pain in patients with knee or hip osteoarthritis.

2. Topical therapies—Topical NSAIDs (eg, 4 g of diclofenac gel 1% applied to the affected joint four times daily) appear more effective than placebo for knee and hand osteoarthritis and have lower rates of systemic side effects than with oral NSAIDs. Topical NSAIDs are preferred for patients 75 years of age and older. Topical capsaicin may be of benefit for osteoarthritis of the hand or the knee.

3. Acetaminophen and opioids—Acetaminophen is not recommended given that its impact on pain is frequently negligible and hepatotoxicity can occur from high doses. Opioids are generally not appropriate for the long-term management of pain due to osteoarthritis.

4. Intra-articular injections—Many patients with moderately severe osteoarthritis of the knee who do not respond to NSAIDs receive intra-articular injections of corticosteroids, hyaluronate, or platelet-rich plasma. Although each of these can temporarily reduce pain, none has convincingly produced long-term benefits in reducing pain or preserving function. A 2-year controlled trial demonstrated that injecting the knee with triamcinolone every 6 months was no more effective than injecting saline in reducing knee pain. The American College of Rheumatology does not recommend corticosteroid injections for osteoarthritis of the hand.

5. Duloxetine—For patients with osteoarthritis in multiple joints who either have not responded to or cannot use NSAIDs, the selective serotonin and norepinephrine reuptake inhibitor duloxetine, 30–60 mg orally daily, can reduce pain. Nausea occurs in 6–15% of patients.

C. Surgical Measures

Total hip and knee replacements provide excellent symptomatic and functional improvement when involvement of that joint severely restricts walking or causes pain at rest, particularly at night. Arthroscopic surgery for knee osteoarthritis is ineffective. Severe first carpometacarpal osteoarthritis can be treated surgically when other treatments are inadequate.

► Prognosis

Symptoms may be quite severe and limit activity considerably (especially with involvement of the hips, knees, and cervical spine).

► When to Refer

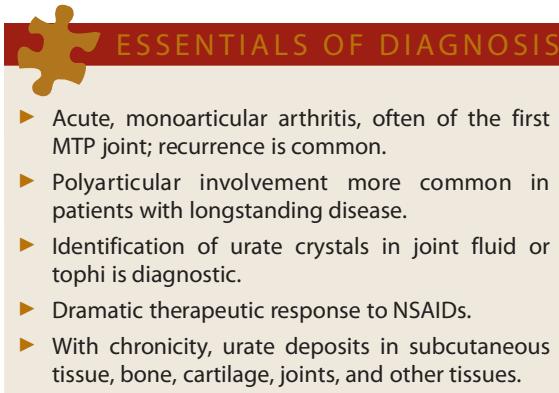
Refer patients to an orthopedic surgeon when recalcitrant symptoms or functional impairment, or both, warrant consideration of joint replacement surgery of the hip, knee, or thumb.

Bannuru RR et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage.* 2019;27:1578. [PMID: 31278997]

- Deyle GD et al. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. *N Engl J Med.* 2020;382:1420. [PMID: 32268027]
- Khan M et al. Cochrane in CORR®: intra-articular corticosteroid for knee osteoarthritis. *Clin Orthop Relat Res.* 2018;476:1391. [PMID: 29846205]

CRYSTAL DEPOSITION ARTHRITIS

1. Gouty Arthritis



► General Considerations

Gout is a metabolic disease of a heterogeneous nature, often familial, associated with abnormal deposits of urate in tissues and characterized initially by a recurring acute arthritis, usually monoarticular, and later by chronic deforming arthritis. Urate deposition occurs when serum uric acid is supersaturated (ie, at levels greater than 6.8 mg/dL [404.5 μmol/L]). Hyperuricemia is due to overproduction or underexcretion of uric acid—sometimes both. The disease is especially common in Pacific islanders, eg, Filipinos and Samoans. Primary gout has a heritable component, and genome-wide surveys have linked risk of gout to several genes whose products regulate urate handling by the kidney. Secondary gout, which may have a heritable component, is related to acquired causes of hyperuricemia, eg, medication use (especially diuretics, low-dose aspirin, cyclosporine, and niacin), myeloproliferative disorders, plasma cell myeloma, hemoglobinopathies, chronic kidney disease (CKD), hypothyroidism, psoriasis, sarcoidosis, and lead poisoning (Table 20-4). Alcohol ingestion promotes hyperuricemia by increasing urate production and decreasing the renal excretion of uric acid. Finally, hospitalized patients frequently suffer attacks of gout because of changes in diet, fluid intake, or medications that lead either to rapid reductions or increases in the serum urate level.

About 90% of patients with primary gout are men, usually over 30 years of age. In women, the onset is typically postmenopausal. The characteristic lesion is the tophus, a nodular deposit of monosodium urate monohydrate crystals with an associated foreign body reaction. Tophi are found in cartilage, subcutaneous and periarticular tissues, tendon, bone, the kidneys, and elsewhere. Urates have been

Table 20-4. Origin of hyperuricemia.

Primary hyperuricemia

- Increased production of purine
- Idiopathic
- Specific enzyme defects (eg, Lesch-Nyhan syndrome, glycogen storage diseases)
- Decreased renal clearance of uric acid (idiopathic)

Secondary hyperuricemia

- Increased catabolism and turnover of purine
- Myeloproliferative disorders
- Carcinoma and sarcoma (disseminated)
- Chronic hemolytic anemias
- Cytotoxic drugs
- Psoriasis
- Down syndrome
- Decreased renal clearance of uric acid
- Chronic kidney disease
- Drug-induced (eg, thiazides, low-dose aspirin, cyclosporine, niacin)
- Ketoacidemia (eg, diabetic ketoacidosis, starvation)
- Hypothyroidism
- Preeclampsia
- Functional impairment of tubular transport
- Hyperlacticacidemia
- Diabetes insipidus (vasopressin-resistant)
- Bartter syndrome
- Sarcoidosis
- Lead poisoning

Modified, with permission, from Rodnan GP. Gout and other crystalline forms of arthritis. *Postgrad Med.* 1975;58:6. <http://www.tandfonline.com>.

demonstrated in the synovial tissues (and fluid) during acute arthritis; indeed, the acute inflammation of gout is believed to be initiated by the ingestion of uncoated urate crystals by monocytes and synoviocytes. The precise relationship of hyperuricemia to gouty arthritis is still obscure, since chronic hyperuricemia is found in people who never develop gout or uric acid stones. Rapid fluctuations in serum urate levels, either increasing or decreasing, are important factors in precipitating acute gout. The mechanism of the late, chronic stage of gouty arthritis is better understood. This is characterized pathologically by tophaceous invasion of the articular and periarticular tissues, with structural derangement and secondary degeneration (osteoarthritis).

Uric acid kidney stones are present in 5–10% of patients with gouty arthritis. Hyperuricemia correlates highly with the likelihood of developing stones, with the risk of stone formation reaching 50% in patients with a serum urate level greater than 13 mg/dL. Chronic urate nephropathy is caused by the deposition of monosodium urate crystals in the renal medulla and pyramids. Although progressive CKD occurs in a substantial percentage of patients with chronic gout, the role of hyperuricemia in causing this outcome is controversial, because many patients with gout have numerous confounding risk factors for CKD (eg, hypertension, NSAID use, alcohol use, lead exposure, and other risk factors for vascular disease). In a 2020 randomized, controlled trial in patients with CKD and a high risk of its progression, urate-lowering treatment with

allopurinol did not slow the decline in estimated glomerular filtration rate compared with placebo.

► Clinical Findings

A. Symptoms and Signs

Acute gouty arthritis is sudden in onset and frequently nocturnal. It may develop without apparent precipitating cause or may follow rapid increases or decreases in serum urate levels. Common precipitants are alcohol excess (particularly beer), changes in medications that affect urate metabolism, and, in the hospitalized patient, fasting before medical procedures. The MTP joint of the great toe is the most susceptible joint ("podagra"), although others, especially those of the feet, ankles, and knees, are commonly affected (Figure 20–2). Gouty attacks may develop in periaricular soft tissues such as the arch of the foot. Hips and shoulders are rarely affected. More than one joint may occasionally be affected during the same attack; in such cases, the distribution of the arthritis is usually asymmetric. As the attack progresses, the pain becomes intense. The involved joints are swollen and exquisitely tender and the overlying skin tense, warm, and dusky red. Fever is common and may reach 39°C. Tophi may be found in the pinna of the ears, feet, olecranon and prepatellar bursae, and hands. They usually develop years after the initial attack of gout.

Asymptomatic periods of months or years commonly follow the initial acute attack. After years of recurrent severe monoarthritis attacks of the lower extremities and untreated hyperuricemia, gout can evolve into a chronic, deforming polyarthritis of upper and lower extremities that mimics rheumatoid arthritis.

Chronic lead intoxication may result in attacks of gouty arthritis (saturnine gout).

B. Laboratory Findings

Although serial measurements of the serum uric acid detect hyperuricemia in 95% of patients, a single uric acid determination during an acute flare of gout is normal in up

to 25% of cases. A normal serum uric acid level, therefore, does not exclude gout, especially in patients taking urate-lowering drugs. During an acute attack, the peripheral blood white cell count (neutrophilia) is frequently elevated. Identification of sodium urate crystals in joint fluid or material aspirated from a tophus establishes the diagnosis. The crystals, which may be extracellular or found within neutrophils, are needle-like and negatively birefringent when examined by polarized light microscopy.

C. Imaging

Early in the disease, radiographs show no changes. Later, punched-out erosions with an overhanging rim of cortical bone ("rat bite") develop. When these are adjacent to a soft tissue tophus, they are diagnostic of gout. Ultrasonography can be used to confirm the diagnosis of gout. Tophi that are too small to appreciate on physical examination and smaller deposits of urate crystals can frequently be imaged by ultrasonography.

► Differential Diagnosis

Acute gout is often confused with cellulitis. Bacteriologic studies usually exclude acute pyogenic arthritis but rarely, acute gout and pyogenic arthritis can co-exist. Pseudogout is distinguished by the identification of calcium pyrophosphate crystals (positive birefringence) in the joint fluid, usually normal serum uric acid, and the radiographic appearance of chondrocalcinosis.

Chronic tophaceous arthritis may resemble chronic rheumatoid arthritis; gout is suggested by an earlier history of monoarthritis and is established by the demonstration of urate crystals in a suspected tophus. Likewise, hips and shoulders are generally spared in tophaceous gout. Biopsy may be necessary to distinguish tophi from rheumatoid nodules.

► Treatment

A. Asymptomatic Hyperuricemia

As a general rule, uric acid-lowering drugs should not be instituted until acute gout, renal calculi, or tophi become apparent.

B. Acute Attack

Treatment of the acute attack focuses on reducing inflammation, not lowering serum uric acid. Indeed, sudden reduction of serum uric acid often precipitates further episodes of gouty arthritis.

1. NSAIDs—Oral NSAIDs in full dose (eg, naproxen 500 mg twice daily or indomethacin 25–50 mg every 8 hours; see Table 5–5) are effective treatment for acute gout and should be continued until the symptoms have resolved (usually 5–10 days). Contraindications include active peptic ulcer disease, impaired kidney function, and a history of allergic reaction to NSAIDs.

2. Colchicine—Oral colchicine is an appropriate treatment option for acute gout, provided the duration of the attack is less than 36 hours. For acute gout, colchicine should be



▲ **Figure 20–2.** Typical inflammatory changes of gout at first MTP joint (podagra). (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw Hill, 2019.)

administered orally as follows: a loading dose of 1.2 mg followed by a dose of 0.6 mg 1 hour later for a total dose of 1.8 mg the first day; thereafter 0.6 mg twice per day is used until resolution. Patients who are already taking prophylactic doses of colchicine and have an acute flare of gout may receive the full loading dose (1.2 mg) followed by 0.6 mg 1 hour later (before resuming the usual 0.6 mg once or twice daily) provided they have not received this regimen within the preceding 14 days (in which case, NSAIDs or corticosteroids should be used). Colchicine dose should be reduced or avoided altogether if there is significant kidney or liver impairment. The use of oral colchicine during the intercritical period to prevent gout attacks is discussed below.

3. Corticosteroids—Corticosteroids often give dramatic symptomatic relief in acute episodes of gout and will control most attacks. They are especially useful in patients with contraindications to the use of NSAIDs. Corticosteroids may be given intravenously (eg, methylprednisolone, 40 mg/day) or orally (eg, prednisone, 40–60 mg/day). Corticosteroids can be given at the suggested dose for 5–10 days and then simply discontinued or given at the suggested initial dose for 2–5 days and then tapered over 7–10 days. If the patient's gout is monoarticular or oligoarticular, intra-articular administration of the corticosteroid (eg, triamcinolone, 10–40 mg depending on the size of the joint) is very effective. Because gouty and septic arthritis can coexist, albeit rarely, joint aspiration and Gram stain with culture of synovial fluid should be performed when intra-articular corticosteroids are given.

4. Interleukin-1 inhibitors—Anakinra (an interleukin-1 receptor antagonist) and canakinumab (a monoclonal antibody against interleukin-1 beta) have efficacy for the management of acute gout, but these drugs have not been approved by the FDA for this indication.

C. Management Between Attacks

Treatment during symptom-free periods is intended to minimize urate deposition in tissues and to reduce the frequency and severity of recurrences. Potentially reversible causes of hyperuricemia are a high-purine diet, obesity, alcohol consumption, and use of certain medications (Table 20–4). Patients with a single episode of gout who have normal kidney function and are able to lose weight and stop drinking alcohol are at low risk for another attack and may not require long-term medical therapy. In contrast, individuals with mild CKD or with a history of multiple attacks of gout are likely to benefit from pharmacologic treatment. In general, the higher the uric acid level and the more frequent the attacks, the more likely that long-term medical therapy will be beneficial. All patients with tophaceous gout should receive urate-lowering therapy.

1. Diet—Excessive alcohol consumption can precipitate attacks and should be avoided. Beer consumption appears to confer a higher risk of gout than does whiskey or wine. Although dietary purines usually contribute only 1 mg/dL to the serum uric acid level, moderation in eating foods with high purine content is advisable. Patients should avoid

organ meats and beverages sweetened with high fructose corn syrup. A high liquid intake and, more importantly, a daily urinary output of 2 L or more will aid urate excretion and minimize urate precipitation in the kidney.

2. Avoidance of hyperuricemic medications—Thiazide and loop diuretics inhibit renal excretion of uric acid and, if possible, should be avoided in patients with gout. Similarly, niacin can raise serum uric acid levels and should be discontinued if there are therapeutic alternatives. Low doses of aspirin also aggravate hyperuricemia.

3. Colchicine prophylaxis—Colchicine can be used when urate-lowering therapy is started to suppress attacks precipitated by abrupt changes in the serum uric acid level. The usual dose is 0.6 mg orally either once or twice a day. Colchicine is renally cleared. Patients who have coexisting moderate CKD should take colchicine only once a day or once every other day in order to avoid peripheral neuropathy and other complications of colchicine toxicity. In patients with concomitant coronary artery disease, chronic colchicine use can reduce major cardiovascular events.

4. Reduction of serum uric acid—Indications for urate-lowering therapy in a person with gout include frequent acute arthritis (two or more episodes per year), tophaceous deposits, or CKD (stage 2 or worse). The American College of Rheumatology guidelines recommend a treat-to-target approach for urate-lowering therapy. The minimum goal of urate-lowering therapy is a serum uric acid at or below 6 mg/dL or 357 mcmol/L (ie, below the level at which serum is supersaturated with uric acid, thereby allowing urate crystals to solubilize); in some cases, control of gout may require lowering serum uric acid to less than 5 mg/dL or 297.4 mcmol/L. Lowering serum uric acid levels is not of benefit for the treatment of an acute gout flare.

Three classes of agents may be used to lower the serum uric acid—xanthine oxidase inhibitors (allopurinol or febuxostat), uricosuric agents, and uricase (pegloticase).

A. XANTHINE OXIDASE INHIBITORS—Allopurinol and febuxostat are the preferred first-line agents for lowering urate. They reduce plasma uric acid levels by blocking the final enzymatic steps in the production of uric acid. Allopurinol and febuxostat should not be used together, but they can be tried sequentially if the initial agent fails to lower serum uric acid to the target level or if it is not tolerated. The most frequent adverse effect with either medication is the precipitation of an acute gouty attack; thus, patients generally should be receiving prophylactic doses of colchicine.

Hypersensitivity to allopurinol occurs in 2% of cases, usually within the first few months of therapy, and it can be life-threatening. The most common initial sign of hypersensitivity is a pruritic rash that may progress to toxic epidermal necrolysis, particularly if allopurinol is continued; vasculitis and hepatitis are other manifestations. Patients should be instructed to stop allopurinol immediately if a rash develops. CKD and concomitant thiazide therapy are risk factors. There is a strong association between allopurinol hypersensitivity and HLA-B*5801, which is a prevalent allele in certain East Asian populations.

Current recommendations are to screen for HLA-B*5801 prior to initiating allopurinol in all persons of Han Chinese and Thai descent and in Koreans with stage 3 or worse CKD.

The initial daily dose of allopurinol is 100 mg/day orally (50 mg/day for those with stage 4 or worse CKD); the dose of allopurinol should be titrated upward every 2–5 weeks to achieve the target serum uric acid level. A typical dose of allopurinol is 300 mg, but most patients require greater than 300 mg daily to achieve the target uric acid level. The maximum daily dose is 800 mg.

Allopurinol interacts with other drugs. The combined use of allopurinol and ampicillin causes a drug rash in 20% of patients. Allopurinol can increase the half-life of probenecid, while probenecid increases the excretion of allopurinol. Thus, a patient taking both drugs may need to use slightly higher than usual doses of allopurinol and lower doses of probenecid.

Febuxostat can also rarely cause hypersensitivity reactions, and those with previous hypersensitivity to allopurinol appear to have slightly higher risk. It can be given without dose adjustment to patients with mild to moderate kidney disease. However, abnormal liver tests may develop in 2–3% of patients taking febuxostat. Despite initial concern that febuxostat was associated with more cardiovascular events than allopurinol, a large, randomized, controlled trial in 2020 showed that the two drugs have similar cardiovascular safety. The initial dose of febuxostat is 40 mg/day orally. If the target serum uric acid is not reached in 4 weeks, the dose of febuxostat can be increased to 80 mg/day and then to the maximum dose of 120 mg/day.

B. URICOSURIC DRUGS—Uricosuric drugs lower serum uric acid levels by blocking the tubular reabsorption of filtered urate, thereby increasing uric acid excretion by the kidney. Probenecid (0.5 g/day orally) is the uricosuric available in the United States; lesinurad (200 mg/day orally) is also available in some countries. These drugs are typically reserved for patients who cannot achieve a serum uric acid of less than or equal to 6.0 mg/dL with allopurinol or febuxostat alone. Probenecid should not be used in patients with a creatinine clearance of less than 50 mL/min due to limited efficacy; contraindications include a history of nephrolithiasis (uric acid or calcium stones) and evidence of high uric acid excretion (ie, greater than 800 mg of uric acid in a 24-hour urine collection). To reduce the development of uric acid stones (which occur in up to 11%), patients should be advised to increase their fluid intake and clinicians should consider prescribing an alkalinizing agent (eg, potassium citrate, 30–80 mEq/day orally) to maintain a urinary pH > 6.0.

C. URICASE—Pegloticase, a recombinant uricase that must be administered intravenously (8 mg every 2 weeks), is indicated for the rare patient with refractory chronic tophaceous gout. Pegloticase carries an FDA black box warning, which advises administering the drug only in health care settings and by health care professionals prepared to manage anaphylactic and other serious infusion reactions.

D. Chronic Tophaceous Arthritis

With rigorous medical compliance, allopurinol, febuxostat, and pegloticase shrink tophi and in time can lead to their disappearance. Resorption of extensive tophi requires maintaining a serum uric acid below 6 mg/dL. Surgical excision of large tophi offers mechanical improvement in selected deformities.

E. Gout in the Transplant Patient

Hyperuricemia and gout commonly develop in many transplant patients because they have decreased kidney function and require drugs that inhibit uric acid excretion (especially cyclosporine and diuretics). Treating acute gout in these patients is challenging. Often the best approach for monoarticular gout—after excluding infection—is injecting corticosteroids into the joint. For polyarticular gout, increasing the dose of systemic corticosteroid may be the only alternative. Since transplant patients often have multiple attacks of gout, long-term relief requires lowering the serum uric acid with allopurinol or febuxostat. (Kidney dysfunction seen in many transplant patients makes uricosuric agents ineffective.) Both allopurinol and febuxostat inhibit the metabolism of azathioprine and should be avoided in patients who take azathioprine.

▶ Prognosis

Without treatment, the acute attack may last from a few days to several weeks. The intervals between acute attacks vary up to years, but the asymptomatic periods often become shorter if the disease progresses. Chronic gouty arthritis occurs after repeated attacks of acute gout, but only after inadequate treatment. The younger the patient at the onset of disease, the greater the tendency to a progressive course. Destructive arthropathy is rarely seen in patients whose first attack is after age 50.

Badve SV et al; CKD-FIX Study Investigators. Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med.* 2020;382:2504. [PMID: 32579811]

Mackenzie IS et al; FAST Study Group. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *Lancet.* 2020;396:1745. [PMID: 33181081]

Nidorf SM et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med.* 2020; 383:1838. [PMID: 32865380]

2. Calcium Pyrophosphate Deposition

Calcium pyrophosphate deposition (CPPD) in fibrocartilage and hyaline cartilage (chondrocalcinosis) can cause an acute crystal-induced arthritis ("pseudogout"), a degenerative arthropathy, and a chronic inflammatory polyarthritides ("pseudorheumatoid arthritis"). CPPD also can be an asymptomatic condition detected as incidental chondrocalcinosis on radiographs. The prevalence of CPPD increases with age. Hyperparathyroidism, familial hypocalciuric hypercalcemia, hemochromatosis, and hypomagnesemia confer risk of CPPD, but most cases have no associated condition.

Pseudogout is most often seen in persons aged 60 or older, is characterized by acute, recurrent and rarely chronic arthritis involving large joints (most commonly the knees and the wrists) and is almost always accompanied by radiographic chondrocalcinosis of the affected joints. The crowned dens syndrome, caused by pseudogout of the atlantoaxial junction associated with “crown-like” calcifications around the dens, manifests with severe neck pain, rigidity, and high fever that can mimic meningitis or polymyalgia rheumatica. Pseudogout, like gout, frequently develops 24–48 hours after major surgery. Identification of weakly positively birefringent calcium pyrophosphate crystals in joint aspirates is diagnostic. NSAIDs are helpful in the treatment of acute episodes. Colchicine, 0.6 mg orally once or twice daily, is more effective for prophylaxis than for acute attacks. Aspiration of the inflamed joint and intra-articular injection of triamcinolone, 10–40 mg, depending on the size of the joint, are also of value in resistant cases. In patients with contraindications to other therapies, the use of anakinra, an IL-1 inhibitor, is an option.

The degenerative arthropathy associated with CPPD can involve joints not usually affected by osteoarthritis (eg, glenohumeral joint, wrist, patellofemoral compartment of the knee). The “pseudorheumatoid arthritis” of CPPD affects the metacarpophalangeal joints and wrists. In both conditions, radiographs demonstrate chondrocalcinosis and degenerative changes such as asymmetric joint space narrowing and osteophyte formation.

Cipolletta E et al. Biologics in the treatment of calcium pyrophosphate deposition disease: a systematic literature review. *Clin Exp Rheumatol*. 2020;38:1001. [PMID: 32359034]

Lee JS et al. Clinical features and risk of recurrence of acute calcium pyrophosphate crystal arthritis. *Clin Exp Rheumatol*. 2019;37:254. [PMID: 30148438]

AUTOIMMUNE DISEASES

RHEUMATOID ARTHRITIS



ESSENTIALS OF DIAGNOSIS

- Usually insidious onset with morning stiffness and joint pain.
- Symmetric polyarthritis with predilection for small joints of the hands and feet; deformities common with progressive disease.
- Radiographic findings: juxta-articular osteoporosis, joint erosions, and joint space narrowing.
- Rheumatoid factor and antibodies to cyclic citrullinated peptides (anti-CCP) are present in 70–80%.
- Extra-articular manifestations: subcutaneous nodules, interstitial lung disease, pleural effusion, pericarditis, splenomegaly with leukopenia, scleritis, and vasculitis.

► General Considerations

Rheumatoid arthritis is a chronic systemic inflammatory disease whose major manifestation is synovitis of multiple joints. It has a prevalence of 1% and is more common in women than men (female:male ratio of 3:1). Rheumatoid arthritis can begin at any age, but the peak onset is in the fourth or fifth decade for women and the sixth to eighth decades for men. The cause is not known. Susceptibility to rheumatoid arthritis is genetically determined with multiple genes contributing. Inheritance of HLA-DRB1 alleles encoding a distinctive five-amino-acid sequence known as the “shared epitope” is the best characterized genetic risk factor. Untreated, rheumatoid arthritis causes joint destruction with consequent disability and shortens life expectancy. Early, aggressive treatment is the standard of care.

The pathologic findings in the joint include chronic synovitis with formation of a pannus, which erodes cartilage, bone, ligaments, and tendons. Effusion and other manifestations of inflammation are common.

► Clinical Findings

A. Symptoms and Signs

1. Joint symptoms—The clinical manifestations of rheumatoid arthritis are highly variable, but joint symptoms usually predominate. Although acute presentations may occur, the onset of articular signs of inflammation is usually insidious, with prodromal symptoms of vague periarthritis pain or stiffness. Symmetric swelling of multiple joints with tenderness and pain is characteristic. Monoarticular disease is occasionally seen initially. Stiffness persisting for longer than 30 minutes (and usually many hours) is prominent in the morning. Stiffness may recur after daytime inactivity and be much more severe after strenuous activity. Although any diarthrodial joint may be affected, PIP joints of the fingers, MCP joints (Figure 20–3), wrists, knees, ankles, and MTP joints are most often involved. Synovial cysts and rupture of tendons may occur. Entrapment syndromes are common—particularly of the median nerve at the carpal tunnel of the wrist. Rheumatoid arthritis can affect the neck but spares the other components of the spine and does not involve the sacroiliac joints. In advanced disease, atlantoaxial (C1–C2) subluxation can lead to myelopathy.

2. Rheumatoid nodules—Twenty percent of patients have subcutaneous rheumatoid nodules, most commonly situated over bony prominences but also observed in the bursae and tendon sheaths (Figure 20–4). Nodules are occasionally seen in the lungs, the sclerae, and other tissues. Nodules correlate with the presence of rheumatoid factor in serum (“seropositivity”), as do most other extra-articular manifestations.

3. Ocular symptoms—Dryness of the eyes, mouth, and other mucous membranes is found especially in advanced disease (see Sjögren syndrome). Other ocular manifestations include episcleritis, scleritis, scleromalacia due to scleral nodules, and peripheral ulcerative keratitis.



▲ **Figure 20–3.** Rheumatoid arthritis with ulnar deviation at the metacarpophalangeal (MCP) joints. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw Hill, 2019.)

4. Other symptoms—Interstitial lung disease is not uncommon (estimates of prevalence vary widely according to method of detection) and manifests clinically as cough and progressive dyspnea. Pericarditis and pleural disease are usually silent clinically but symptomatic effusions can occur. Occasionally, a small vessel vasculitis develops and



▲ **Figure 20–4.** Rheumatoid nodules over the extensor surface of the forearm. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw Hill, 2019.)

manifests as tiny hemorrhagic infarcts in the nail folds or finger pulps. Necrotizing arteritis is well reported but rare. A small subset of patients with rheumatoid arthritis have Felty syndrome, the occurrence of splenomegaly and neutropenia, usually in the setting of severe, destructive arthritis. Felty syndrome must be distinguished from large granular lymphoproliferative disorder, with which it shares many features.

B. Laboratory Findings

Anti-CCP antibodies and rheumatoid factor, an IgM antibody directed against the Fc region of IgG, are present in 70–80% of patients with established rheumatoid arthritis. Rheumatoid factor has a sensitivity of only 50% in early disease. Anti-CCP antibodies are the most specific blood test for rheumatoid arthritis (specificity ~95%). Rheumatoid factor can occur in other autoimmune diseases and in chronic infections, including hepatitis C, syphilis, subacute bacterial endocarditis, and tuberculosis. The prevalence of rheumatoid factor positivity also rises with age in healthy individuals. Approximately 20% of rheumatoid arthritis patients have antinuclear antibodies.

The ESR and levels of C-reactive protein (CRP) are typically elevated in proportion to disease activity. Anemia of chronic disease is common. The white cell count is normal or slightly elevated, but leukopenia may occur, often in the presence of splenomegaly (eg, Felty syndrome). The platelet count is often elevated, roughly in proportion to the severity of overall joint inflammation. Initial joint fluid examination confirms the inflammatory nature of the arthritis (see Table 20–2).

Arthrocentesis is needed to diagnose superimposed septic arthritis, which is a common complication of rheumatoid arthritis and should be considered whenever a patient with rheumatoid arthritis has one joint inflamed out of proportion to the rest.

C. Imaging

Of all the laboratory tests, radiographic changes are the most specific for rheumatoid arthritis. Radiographs obtained during the first 6 months of symptoms, however, are usually normal. The earliest changes occur in the hands or feet and consist of soft tissue swelling and juxta-articular demineralization. Later, diagnostic changes of uniform joint space narrowing and erosions develop. The erosions are often first evident at the ulnar styloid and at the juxta-articular margin, where the bony surface is not protected by cartilage. Characteristic changes also occur in the cervical spine, with C1–2 subluxation, but these changes usually take many years to develop. Although both MRI and ultrasonography are more sensitive than radiographs in detecting bony and soft tissue changes in rheumatoid arthritis, their value in early diagnosis relative to that of plain radiographs has not been established.

Differential Diagnosis

The differentiation of rheumatoid arthritis from other joint conditions and immune-mediated disorders can be

difficult. In contrast to rheumatoid arthritis, osteoarthritis spares the wrist and the MCP joints. Osteoarthritis is not associated with constitutional manifestations, and the joint pain is characteristically relieved by rest, unlike the morning stiffness of rheumatoid arthritis. Signs of articular inflammation, prominent in rheumatoid arthritis, are usually minimal in degenerative joint disease. CPPD disease can cause a degenerative arthropathy of the MCPs and wrists; radiographs are usually diagnostic. Although gouty arthritis is almost always intermittent and monoarticular in the early years, it may evolve with time into a chronic polyarticular process that mimics rheumatoid arthritis. Gouty tophi can resemble rheumatoid nodules but are not associated with rheumatoid factor, whose sensitivity for rheumatoid nodules approaches 100%. The early history of intermittent monoarthritis and the presence of synovial urate crystals are distinctive features of gout.

Spondyloarthropathies, particularly earlier in their course, can be a source of diagnostic uncertainty; predilection for lower extremities and involvement of the spine and sacroiliac joints point to the correct diagnosis. Chronic Lyme arthritis typically involves only one joint, most commonly the knee, and is associated with positive serologic tests (see Chapter 34). Acute viral infections, most notably with Chikungunya virus and parvovirus B19, can cause a polyarthritis that mimics early-onset rheumatoid arthritis. However, fever is common, the arthritis usually resolves within weeks, and serologic studies confirm recent infection. Chronic infection with hepatitis C can cause a chronic nonerosive polyarthritis associated with rheumatoid factor; tests for anti-CCP antibodies are negative.

Malar rash, photosensitivity, discoid skin lesions, alopecia, high titer antibodies to double-stranded DNA or Smith, glomerulonephritis, and central nervous system abnormalities point to the diagnosis of SLE. Polymyalgia rheumatica occasionally causes polyarthralgias in patients over age 50, but these patients remain rheumatoid factor-negative and have chiefly proximal muscle pain and stiffness, centered on the shoulder and hip girdles. Joint pain that can be confused with rheumatoid arthritis presents in a substantial minority of patients with granulomatosis with polyangiitis. This diagnostic error can be avoided by recognizing that, in contrast to rheumatoid arthritis, the arthritis of granulomatosis with polyangiitis preferentially involves larger joints (eg, hips, ankles, wrists) and usually spares the small joints of the hand. Rheumatic fever is characterized by the migratory nature of the arthritis, an elevated antistreptolysin titer, and a more dramatic and prompt response to aspirin; carditis and erythema marginatum may occur in adults, but chorea and subcutaneous nodules virtually never do. Finally, a variety of cancers produce paraneoplastic syndromes, including polyarthritis. One form is hypertrophic pulmonary osteoarthropathy most often produced by lung and gastrointestinal carcinomas, characterized by a rheumatoid-like arthritis associated with clubbing, periosteal new bone formation, and a negative rheumatoid factor. Diffuse swelling of the hands with palmar fasciitis occurs in a variety of cancers, especially ovarian carcinoma.

► Treatment

The primary objectives in treating rheumatoid arthritis are reduction of inflammation and pain, preservation of function, and prevention of deformity. Disease-modifying antirheumatic drugs (DMARDs) should be started as soon as the diagnosis of rheumatoid disease is certain and then adjusted with the aim of suppressing disease activity. NSAIDs provide some symptomatic relief in rheumatoid arthritis but do not prevent erosions or alter disease progression. They are not appropriate for monotherapy and should only be used in conjunction with DMARDs, if at all. The American College of Rheumatology recommends using standardized assessments, such as the Disease Activity Score 28 Joints (www.das-score.nl/das28/en/) or the Clinical Disease Activity Index, to gauge therapeutic responses, with the target of low disease activity or remission by these measures.

A. Corticosteroids

Low-dose corticosteroids (eg, oral prednisone 5–10 mg daily) produce a prompt anti-inflammatory effect and slow the rate of articular erosion. These are often used as a “bridge” to reduce disease activity until the slower acting DMARDs take effect or as adjunctive therapy for active disease that persists despite treatment with DMARDs. No more than 10 mg of prednisone or equivalent per day is appropriate for articular disease. Higher doses are used to manage serious extra-articular manifestations (eg, pericarditis, necrotizing scleritis). When corticosteroids are to be discontinued, they should be tapered gradually on a planned schedule appropriate to the duration of treatment. All patients receiving long-term corticosteroid therapy should take measures to prevent osteoporosis (Table 26–16).

Intra-articular corticosteroids may be helpful for symptom control if one or two joints are the chief source of difficulty. Intra-articular triamcinolone, 10–40 mg depending on the size of the joint to be injected, may be given but not more than four times a year.

B. DMARDs

1. Synthetic DMARDs—

A. METHOTREXATE—Methotrexate is usually the initial synthetic DMARD of choice for patients with rheumatoid arthritis. It is generally well tolerated and often produces a beneficial effect in 2–6 weeks. The usual initial dose is 7.5 or 10 mg of methotrexate orally once weekly. If the patient has tolerated methotrexate but has not responded in 1 month, the dose can be increased to 15 mg orally weekly. The maximal oral dose is usually 20 mg weekly. The most frequent side effects are gastric irritation and stomatitis. Cytopenia, most commonly leukopenia or thrombocytopenia but rarely pancytopenia due to bone marrow suppression, is another important potential problem. The risk of developing pancytopenia is much higher in patients whose serum creatinine is greater than 2 mg/dL (176.8 mcmol/L). Hepatotoxicity with fibrosis and cirrhosis is an important toxic effect that correlates with cumulative dose and is uncommon with appropriate monitoring of

liver biochemical tests. Methotrexate is contraindicated in a patient with any form of chronic hepatitis, in pregnant women, and in any patient with significant kidney dysfunction (estimated glomerular filtration rate less than 30 mL/min/1.73 m²). Heavy alcohol use increases the hepatotoxicity, so patients should be advised to drink alcohol in extreme moderation, if at all. Diabetes mellitus, obesity, and kidney disease also increase the risk of hepatotoxicity. Liver biochemical tests should be monitored at least every 12 weeks, along with a complete blood count. The dose of methotrexate should be reduced if aminotransferase levels are elevated, and the drug should be discontinued if abnormalities persist despite dosage reduction. All patients should be prescribed either daily folate (1 mg orally) or weekly leucovorin calcium (2.5–5 mg taken orally 24 hours after the dose of methotrexate) to reduce gastric irritation, stomatitis, cytopenias, and hepatotoxicity. Hypersensitivity to methotrexate can cause an acute or subacute interstitial pneumonitis that can be life-threatening but which usually responds to cessation of the drug and institution of corticosteroids. Because methotrexate is teratogenic, women of childbearing age must use effective contraception while taking the medication. Methotrexate is associated with an increased risk of B-cell lymphomas, some of which resolve following the discontinuation of the medication as well as all types of skin cancer. The combination of methotrexate and other folate antagonists, such as trimethoprim-sulfamethoxazole, should be used cautiously since pancytopenia can result. Amoxicillin can decrease renal clearance of methotrexate, leading to toxicity. Probenecid also increases methotrexate drug levels and toxicity and should be avoided.

B. SULFASALAZINE—This drug is a second-line agent for rheumatoid arthritis. It is usually introduced at a dosage of 500 mg orally twice daily and then increased each week by 500 mg until the patient improves or the daily dose reaches 3000 mg. Side effects, particularly neutropenia and thrombocytopenia, occur in 10–25% and are serious in 2–5%. Sulfasalazine also causes hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, so a G6PD level should be checked before initiating sulfasalazine. Patients with aspirin sensitivity should not be given sulfasalazine. Patients taking sulfasalazine should have complete blood counts monitored every 2–4 weeks for the first 3 months, then every 3 months.

C. LEFLUNOMIDE—Leflunomide, a pyrimidine synthesis inhibitor, is FDA-approved for the treatment of rheumatoid arthritis and is administered orally as a single daily dose of 20 mg. The most frequent side effects are diarrhea, rash, reversible alopecia, and hepatotoxicity. Some patients experience dramatic unexplained weight loss. The drug is teratogenic and has a half-life of 2 weeks, but active metabolites can be detected for up to 2 years. Thus, it is strongly contraindicated in premenopausal women who wish to bear children.

D. ANTIMALARIALS—Hydroxychloroquine sulfate is the antimalarial agent most often used in rheumatoid arthritis. Monotherapy with hydroxychloroquine should be reserved

for patients with very mild disease because only a small percentage will respond and often only after 3–6 months of therapy. Hydroxychloroquine is often used in combination with other conventional DMARDs, particularly methotrexate and sulfasalazine (so called “triple therapy”). The advantage of hydroxychloroquine is its comparatively low toxicity, especially at a dosage of 200–400 mg/day orally (not to exceed 5 mg/kg/day). The prevalence of the most important adverse effect, retinal toxicity that can lead to visual loss, is a function of duration of therapy, occurring in less than 2% of patients (dosed properly) during the first 10 years of use but rising to 20% after 20 years of treatment. Ophthalmologic examinations every 12 months are required. Rare reactions include neuropathies and myopathies of both skeletal and cardiac muscle, which usually improve when the drug is withdrawn.

E. JANUS KINASE INHIBITORS—Tofacitinib, baricitinib, and upadacitinib, inhibitors of Janus kinase, are used to manage severe rheumatoid arthritis that is refractory to methotrexate or other agents. Janus kinase inhibitors are oral agents that can be used either as monotherapy or in combination with methotrexate. Tofacitinib is administered in a dose of 5 mg twice daily; baricitinib is 2 mg or 4 mg daily, and upadacitinib is 15 mg daily. Patients should be screened and treated for latent tuberculosis prior to receiving these drugs. Vaccination against varicella is also recommended.

2. Biologic DMARDs—

A. TUMOR NECROSIS FACTOR INHIBITORS—Inhibitors of tumor necrosis factor (TNF)—a pro-inflammatory cytokine—are frequently added to the treatment of patients who have not responded adequately to methotrexate and can be used as initial therapy in combination with methotrexate for patients with poor prognostic factors.

Five TNF inhibitors are in use: etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. Etanercept, a soluble recombinant TNF receptor:Fc fusion protein, is usually administered at a dosage of 50 mg subcutaneously once per week. Infliximab, a chimeric monoclonal antibody, is administered at a dosage of 3–10 mg/kg intravenously; infusions are repeated after 2, 6, 10, and 14 weeks and then are administered every 8 weeks. Adalimumab, a human monoclonal antibody that binds to TNF, is given at a dosage of 40 mg subcutaneously every other week. The dose for golimumab, a human anti-TNF monoclonal antibody, is 50 mg subcutaneously once monthly. Certolizumab pegol is a PEGylated Fab fragment of an anti-TNF monoclonal antibody; the dose is 200–400 mg subcutaneously every 2 to 4 weeks. Each drug produces substantial improvement in more than 60% of patients and is usually well tolerated. Minor irritation at injection sites is the most common side effect of etanercept and adalimumab. Rarely, nonrecurrent leukopenia develops in patients. TNF inhibitors have been associated with a several-fold increased risk of serious bacterial infections and a striking increase in granulomatous infections, particularly reactivation of tuberculosis. Screening for latent tuberculosis (see Chapter 9) is mandatory before the

initiation of TNF blockers. It is prudent to suspend TNF blockers when a fever or other manifestations of a clinically important infection develops. Demyelinating neurologic complications that resemble multiple sclerosis have been reported rarely in patients taking TNF inhibitors, but the true magnitude of this risk—likely quite small—has not been determined with precision. A majority of observational studies have not found a higher risk of malignancy with TNF inhibitors, but the FDA has issued a safety alert about case reports of malignancies, including leukemias. Infliximab was associated with increased morbidity in a heart failure trial, therefore, TNF inhibitors should be used with extreme caution in patients with heart failure. Infliximab can rarely cause anaphylaxis and induce anti-DNA antibodies (but rarely clinically evident SLE).

B. ABATACEPT—Abatacept, a recombinant protein made by fusing a fragment of the Fc domain of human IgG with the extracellular domain of a T-cell inhibitory receptor (CTLA4), blocks T-cell costimulation and produces clinically meaningful responses in approximately 50% of individuals whose disease does not respond to the combination of methotrexate and a TNF inhibitor.

C. RITUXIMAB—Rituximab, a humanized mouse monoclonal antibody that depletes B cells, can be used in combination with methotrexate or leflunomide for patients whose disease has been refractory to treatment with a TNF inhibitor.

D. TOCILIZUMAB AND SARILUMAB—Tocilizumab and sarilumab are monoclonal antibodies that block the receptor for IL-6, an inflammatory cytokine involved in the pathogenesis of rheumatoid arthritis. They are used most often in combination with methotrexate for patients whose disease has been refractory to treatment with a TNF inhibitor. Tocilizumab has been associated with gastrointestinal perforations, although this adverse event is rare.

3. Combination DMARDs—As a general rule, DMARDs have greater efficacy when administered in combination than when used individually. The most commonly used combination is methotrexate with one of the TNF inhibitors. Still, most patients who require DMARD therapy are given methotrexate monotherapy initially because this regimen is effective in up to one-third of patients and is less expensive and less toxic than combination therapy. The combination of methotrexate, sulfasalazine, and hydroxychloroquine (“triple therapy”) is economical, effective, and not inferior to the combination of methotrexate plus etanercept for those who have not responded to methotrexate monotherapy. *Biologic DMARDs should not be combined.*

► Course & Prognosis

After months or years, deformities may occur; the most common are ulnar deviation of the fingers, boutonnière deformity (hyperextension of the DIP joint with flexion of the PIP joint), “swan-neck” deformity (flexion of the DIP joint with extension of the PIP joint), valgus deformity of the knee, and volar subluxation of the MTP joints. The

excess mortality associated with rheumatoid arthritis is largely due to cardiovascular disease that is unexplained by traditional risk factors and that appears to be a result of deleterious effects of chronic systemic inflammation on the vascular system.

► When to Refer

Early referral to a rheumatologist is essential for diagnosis and the timely introduction of effective therapy.

Boleto G et al. Safety of combination therapy with two bDMARDs in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum.* 2019;49:35. [PMID: 30638975]

Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79:685. [PMID: 31969328]

Solomon DH et al. Adverse effects of low-dose methotrexate: a randomized trial. *Ann Intern Med.* 2020;172:369. [PMID: 32066146]

ADULT STILL DISEASE

Still disease is a systemic form of juvenile chronic arthritis in which high spiking fevers are much more prominent, especially at the outset, than arthritis. This rare syndrome also occurs in adults. Most adults are in their 20s or 30s; onset after age 60 is rare. The fever is dramatic, often with daily spikes to 40°C, associated with sweats and chills, and then plunging to normal or several degrees below normal in the absence of antipyretics. Many patients initially complain of sore throat. An evanescent salmon-colored non-pruritic rash, chiefly on the chest and abdomen, is a characteristic feature. The rash can easily be missed since it often appears only with the fever spike. Many patients also have lymphadenopathy and pericardial effusions. Joint symptoms are mild or absent in the beginning, but a destructive arthritis, especially of the wrists, may develop months later. Anemia and leukocytosis, with white blood counts sometimes exceeding 40,000/mcL ($40 \times 10^9/L$), are the rule. Serum ferritin levels are often strikingly elevated (greater than 3000 mg/mL or 6741 pmol/L). (Other conditions, including viral infections, malignancy, and multiple blood transfusions, can also cause extreme elevations in ferritin levels.) The diagnosis of adult Still disease is suggested by the quotidian fever pattern, sore throat, and the classic rash but requires exclusion of other causes of fever. About half of the patients respond to NSAIDs, and half require prednisone, sometimes in doses greater than 60mg/day orally. Targeting IL-1 with anakinra or canakinumab or IL-6 with tocilizumab can be effective for patients with refractory disease. The course of adult Still disease can be monophasic, intermittent, or chronic. Macrophage activation syndrome is a life-threatening complication of adult Still disease and manifests as fever; splenomegaly; cytopenias; hypertriglyceridemia; hypofibrinogenemia; marked elevation of serum ferritin; elevated soluble CD25; depressed natural killer cell activity; and hemophagocytosis in bone marrow, spleen, and lymph nodes.

Kedor C et al. Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Ann Rheum Dis.* 2020;79:1090. [PMID: 32404342]

SYSTEMIC LUPUS ERYTHEMATOSUS



ESSENTIALS OF DIAGNOSIS

- ▶ Occurs mainly in young women.
- ▶ Rash over areas exposed to sunlight.
- ▶ Joint symptoms in 90% of patients.
- ▶ Anemia, leukopenia, thrombocytopenia.
- ▶ Glomerulonephritis, central nervous system disease, and complications of antiphospholipid antibodies are major sources of disease morbidity.
- ▶ Serologic findings: antinuclear antibodies (100%), anti-double-stranded DNA antibodies (approximately two-thirds), and low serum complement levels (particularly during disease flares).

► General Considerations

SLE is an inflammatory autoimmune disorder characterized by autoantibodies to nuclear antigens. It can affect multiple organ systems. Many of its clinical manifestations are secondary to the trapping of antigen-antibody complexes in capillaries of visceral structures or to autoantibody-mediated destruction of host cells (eg, thrombocytopenia). The clinical course is marked by spontaneous remission and relapses. The severity may vary from a mild episodic disorder to a rapidly fulminant, life-threatening illness.

The incidence of SLE is influenced by many factors, including sex, race, and genetic inheritance. About 85% of patients are women. Sex hormones play a role; most cases develop after menarche and before menopause. Among older individuals, the sex distribution is more equal. Race is also a factor, as SLE occurs in 1:1000 White women but in 1:250 Black women. Familial occurrence of SLE has been repeatedly documented, and the disorder is concordant in 25–70% of identical twins. If a mother has SLE, her daughters' risks of developing the disease are 1:40 and her sons' risks are 1:250. Aggregation of serologic abnormalities (positive antinuclear antibody) is seen in asymptomatic family members, and the prevalence of other rheumatic diseases is increased among close relatives of patients.

The diagnosis of SLE should be suspected in patients having a multisystem disease with a positive test for anti-nuclear antibodies. It is imperative to ascertain that the condition has not been induced by a drug (see Drug-Induced Lupus below).

The diagnosis of SLE can be made with reasonable probability if at least 4 of the 11 criteria set forth in Table 20–5 are met. The updated 2019 version of these

Table 20–5. Criteria for the classification of SLE.
(A patient is classified as having SLE if any 4 or more of 11 criteria are met.)

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
7. Kidney disease
 - a. $> 0.5 \text{ g/day}$ proteinuria, or
 - b. $\geq 3+$ dipstick proteinuria, or
 - c. Cellular casts
8. Neurologic disease
 - a. Seizures, or
 - b. Psychosis (without other cause)
9. Hematologic disorders
 - a. Hemolytic anemia, or
 - b. Leukopenia ($< 4000/\text{mCL}$ [$4.0 \times 10^9/\text{L}$]), or
 - c. Lymphopenia ($< 1500/\text{mCL}$ [$1.5 \times 10^9/\text{L}$]), or
 - c. Thrombocytopenia ($< 100,000/\text{mCL}$ [$100 \times 10^9/\text{L}$])
10. Immunologic abnormalities
 - a. Antibody to native DNA, or
 - b. Antibody to Sm, or
 - c. Antibodies to antiphospholipid antibodies based on (1) IgG or IgM anticardiolipin antibodies, (2) lupus anticoagulant, or (3) false-positive serologic test for syphilis
11. Positive ANA

ANA, antinuclear antibody; SLE, systemic lupus erythematosus. Modified and reproduced, with permission, from Tan EM et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheumatol.* 1982;25:1271, and data from Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheumatol.* 1997;40:1725.

criteria requires an ANA titer of 80 or more, highlighting that SLE should almost never be diagnosed in the absence of an ANA (Table 20–6). Criteria are developed as guidelines for the inclusion of patients in research studies and do not supplant clinical judgment in the diagnosis of SLE.

► Clinical Findings

A. Symptoms and Signs

The systemic features include fever, anorexia, malaise, and weight loss. Most patients have skin lesions at some time; the characteristic “butterfly” (malar) rash affects less than half of patients. Other cutaneous manifestations are panniculitis (lupus profundus), discoid lupus and typical fingertip lesions (periungual erythema, nail fold infarcts, and splinter hemorrhages). Alopecia is common. Mucous membrane lesions tend to occur during periods of exacerbation. Raynaud phenomenon, present in about 20% of patients, often antedates other features of the disease.

Joint symptoms, with or without active synovitis, occur in over 90% of patients and are often the earliest manifestation. The arthritis can lead to reversible swan-neck deformities, but radiographic erosions and subcutaneous nodules are rare.

Table 20–6. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus.

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of $\geq 1:80$ at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature $> 38.3^{\circ}\text{C}$
Leukopenia	White blood cell count $< 4000/\text{mCL}$ ($4.0 \times 10^9/\text{L}$)
Thrombocytopenia	Platelet count $< 100,000/\text{mCL}$ ($100 \times 10^9/\text{L}$)
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LD, and positive direct antiglobulin (Coombs) test
Delirium	Characterized by: (1) change in consciousness or level of arousal with reduced ability to focus, (2) symptom development over hours to < 2 days, (3) symptom fluctuation throughout the day, (4) either acute/subacute change in cognition (eg, memory deficit or disorientation) or change in behavior, mood, or affect (eg, restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by delusions or hallucinations or both without insight and absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure
Nonscarring alopecia	Nonscarring alopecia observed by a clinician ¹
Oral ulcers	Oral ulcers observed by a clinician ¹
Subacute cutaneous or discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician ¹ : Annular or papulosquamous (psoriasisiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted). or Discoid lupus erythematosus observed by a clinician ¹ : Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition may be noted)
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician ¹ If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course)
Pleural or pericardial effusion	Imaging evidence (such as ultrasonography, radiography, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	Presence of two or more of the following: (1) Pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward) (2) Pericardial rub (3) ECG with new widespread ST elevation or PR depression (4) New or worsened pericardial effusion on imaging (such as ultrasonography, radiography, CT scan, MRI)
Joint involvement	Presence of either synovitis involving > 2 joints characterized by swelling or effusion or tenderness in > 2 joints and at least 30 minutes of morning stiffness
Proteinuria	$> 0.5 \text{ g}/24 \text{ hours}$ by 24-hour urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	<i>Class II:</i> Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy but not by light microscopy <i>Class V:</i> Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations

(continued)

Table 20–6. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. (continued)

Criteria	Definition
Class III or IV lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	<p><i>Class III:</i> Focal lupus nephritis: active or inactive focal, segmental, or global endocapillary, or extracapillary glomerulonephritis involving < 50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations</p> <p><i>Class IV:</i> Diffuse lupus nephritis: active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥ 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation</p>
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (> 40 APL, GPL, or MPL, or > 99th percentile) or positive anti-beta-2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below the lower limits of normal
Anti-dsDNA antibodies or anti-Sm antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥ 90% specificity for SLE against relevant disease controls or anti-Sm antibodies

¹This may include physical examination or review of a photograph.

anti-beta-2GPI, anti-beta-2-glycoprotein 1; anti-dsDNA, anti-double-stranded DNA; CT, computed tomography; ECG, electrocardiography; Ig, immunoglobulin; ISN, International Society of Nephrology; LD, lactate dehydrogenase; MRI, magnetic resonance imaging; RPS, Renal Pathology Society; SLE, systemic lupus erythematosus.

Modified, with permission, from Aringer M et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol.* 2019;71:1400. © 2019 American College of Rheumatology.

Ocular manifestations include keratoconjunctivitis sicca and retinal vasculopathy (cotton-wool spots, episcleritis, scleritis and optic neuropathy). Pleurisy and pleural effusion are common. Pneumonitis, interstitial lung disease, and pulmonary hypertension can rarely occur. Alveolar hemorrhage is uncommon but life-threatening.

The pericardium is affected in the majority of patients. Heart failure may result from myocarditis and hypertension. Cardiac arrhythmias are common. Atypical verrucous endocarditis of Libman-Sacks is usually clinically silent but occasionally can produce acute or chronic valvular regurgitation—most commonly mitral regurgitation.

Neurologic complications of SLE include psychosis, cognitive impairment, seizures, peripheral and cranial neuropathies, transverse myelitis, and strokes. Severe depression and psychosis are sometimes exacerbated by the administration of large doses of corticosteroids.

Several forms of glomerulonephritis may occur, including mesangial, focal proliferative, diffuse proliferative, and membranous (see Chapter 22). Some patients may also have interstitial nephritis. With appropriate therapy, the survival rate even for patients with serious kidney disease (proliferative glomerulonephritis) is favorable, albeit a substantial portion of patients with severe lupus nephritis develop end-stage kidney disease.

Hematologic manifestations include leukopenia, autoimmune hemolytic anemia, immune thrombocytopenia, and thrombotic thrombocytopenic purpura.

B. Laboratory Findings

(Tables 20–7 and 20–8.) SLE is characterized by the production of many different autoantibodies. Antinuclear antibody tests based on immunofluorescence assays using HEp-2 cells (a human cell line) as a source of nuclei are nearly 100% sensitive for SLE but not specific—ie, they are positive in low titer in up to 20% of healthy adults and also in many patients with other immune-mediated conditions such as rheumatoid arthritis, thyroid disease, systemic sclerosis (scleroderma), and Sjögren syndrome. False-negative results can occur with tests for antinuclear antibodies based on multiplex assays that use specific nuclear antigens rather than cell lines. Antibodies to double-stranded DNA and to Sm are specific for SLE but not sensitive, since they are present in only 60% and 30% of patients, respectively. Depressed serum complement—a finding suggestive of disease activity—often returns toward normal in remission. Anti-double-stranded DNA antibody levels also correlate with disease activity in some patients; anti-Sm levels do not. Other autoantibodies commonly seen in SLE include antibodies to SS-A/Ro, SS-B/La, ribonucleoprotein (RNP), and phospholipid. Antibodies to SS-A/Ro are associated with subacute cutaneous lupus; during pregnancy these autoantibodies can cross the placenta and damage the developing fetal conduction system, producing congenital heart block.

During disease flares, elevations in the ESR are common, but the serum CRP is usually normal unless there is

Table 20–7. Frequency (%) of autoantibodies in rheumatic diseases.¹

	ANA	Anti-Native DNA	Rheumatoid Factor	Anti-Sm	Anti-SS-A	Anti-SS-B	Anti-SCL-70	Anti-Centromere	Anti-Jo-1	ANCA
Rheumatoid arthritis	30–60	0–5	70	0	0–5	0–2	0	0	0	0
Systemic lupus erythematosus	95–100	60	20	10–25	15–20	5–20	0	0	0	0–1
Sjögren syndrome	95	0	75	0	65	65	0	0	0	0
Diffuse systemic sclerosis	> 95	0	30	0	0	0	33	1	0	0
Limited systemic sclerosis (CREST syndrome)	> 95	0	30	0	0	0	20	50	0	0
Polymyositis/dermatomyositis	80	0	33	0	0	0	0	0	20–30	0
Granulomatosis with polyangiitis	0–15	0	50	0	0	0	0	0	0	93–96 ¹

¹Frequency for generalized, active disease.

ANA, antinuclear antibodies; Anti-Sm, anti-Smith antibody; Anti-SCL-70, anti-scleroderma antibody; ANCA, antineutrophil cytoplasmic antibody; CREST, calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia.

serositis or arthritis. Abnormality of urinary sediment, including hematuria with or without casts, and proteinuria (varying from mild to nephrotic range) can indicate active lupus nephritis.

Differential Diagnosis

Differential diagnosis includes drug-induced lupus, rheumatoid arthritis, systemic vasculitis, systemic sclerosis,

primary antiphospholipid syndrome, inflammatory myopathies, viral hepatitis, sarcoidosis, and acute drug reactions.

Treatment

Since the various manifestations of SLE affect prognosis differently and since SLE activity often waxes and wanes, drug therapy—both the choice of agents and the intensity of their use—must be tailored to match disease severity. Patients should be cautioned against sun exposure and should apply broad-spectrum UVA/UVB sunscreen while outdoors. Milder skin lesions often respond to the topical administration of corticosteroids. Minor joint symptoms can usually be alleviated by NSAIDs.

Antimalarials (hydroxychloroquine) may be helpful in treating lupus rashes or joint symptoms. They also reduce the incidence of disease flares and prolong survival in SLE. The dose of hydroxychloroquine is 200 or 400 mg/day orally and should not exceed 5 mg/kg/day; annual monitoring for retinal changes is recommended. Neuropathy and myopathy are rare adverse effects of hydroxychloroquine and may be erroneously ascribed to the underlying disease.

Corticosteroids are required for the control of certain complications. (Systemic corticosteroids are not usually given for minor skin rashes, leukopenia, or the anemia associated with chronic disease.) Glomerulonephritis, hemolytic anemia, myocarditis, alveolar hemorrhage, central nervous system involvement, and severe thrombocytopenia all require corticosteroid treatment and often other interventions as well. For serious manifestations, either methylprednisolone 250–1000 mg given intravenously over 30 minutes daily for 3 days or prednisone 40–60 mg orally is needed initially; however, the lowest dose of corticosteroid that controls the condition should be used over time (Table 26–16). Immunosuppressive agents

Table 20–8. Frequency (%) of laboratory abnormalities in systemic lupus erythematosus.

Anemia	60%
Leukopenia	45%
Thrombocytopenia	30%
Antiphospholipid antibodies	
Anti-cardiolipin antibody	25%
Lupus anticoagulant	7%
Anti-beta-2-glycoprotein 1	25%
Direct Coombs-positive	30%
Proteinuria	30%
Hematuria	30%
Hypocomplementemia	60%
ANA	95–100%
Anti-double stranded DNA	50%
Anti-Sm	20%

ANA, antinuclear antibody; Anti-Sm, anti-Smith antibody.

Modified and reproduced, with permission, from Hochberg MC et al. Systemic lupus erythematosus: a review of cliniclaboratory features and immunologic matches in 150 patients with emphasis on demographic subsets. Medicine (Baltimore). 1985;64:285.

(such as cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, or tacrolimus) are used for long-term control of disease. Belimumab, a monoclonal antibody that inhibits the activity of a B-cell growth factor, is FDA approved for treating antibody-positive SLE patients with active disease who have not responded to standard therapies (eg, NSAIDs, antimalarials, or immunosuppressive therapies).

Treatment of lupus nephritis includes an induction phase and a maintenance phase. Mycophenolate mofetil (1000 mg or 1500 mg orally twice daily) and cyclophosphamide are first-line induction treatments for lupus nephritis and are generally given with corticosteroids to achieve disease control. Cyclophosphamide is usually administered using the Euro-Lupus regimen (500 mg intravenously every 2 weeks for six doses) but can also be administered according to the National Institutes of Health regimen (3–6 monthly intravenous pulses [0.5–1 g/m²] for induction followed by maintenance infusions every 3 months). Belimumab, the first FDA approved drug for lupus nephritis, can improve renal response when added to cyclophosphamide or mycophenolate mofetil. Mycophenolate mofetil or azathioprine is typically used for maintenance therapy for lupus nephritis. Very close follow-up is needed to watch for potential side effects when immunosuppressants are given; these agents should be administered by clinicians experienced in their use. When higher doses of cyclophosphamide are required, gonadotropin-releasing hormone analogs can be given to protect a woman against the risk of premature ovarian failure. Rituximab is usually reserved for life-threatening or organ-threatening manifestations that have failed conventional therapies.

Course & Prognosis

Ten-year survival rates exceeding 85% are routine. In most patients, the illness pursues a relapsing and remitting course. Prednisone, often needed in doses of 40 mg/day orally or more during severe flares, can usually be tapered to low doses (5–10 mg/day) or be discontinued when the disease is inactive. However, there are some in whom the disease pursues a virulent course, leading to serious impairment of vital structures such as lungs, heart, brain, or kidneys, and the disease may lead to death. Mortality in SLE shows a bimodal pattern. In the early years after diagnosis, infections—especially with opportunistic organisms—are the leading cause of death, followed by active SLE, chiefly due to kidney or central nervous system disease. In later years, accelerated atherosclerosis, linked to chronic inflammation, becomes a major cause of death. Indeed, the incidence of myocardial infarction is five times higher in persons with SLE than in the general population. Therefore, it is especially important for SLE patients to avoid smoking and to minimize other conventional risk factors for atherosclerosis (eg, hypercholesterolemia, hypertension, obesity, and inactivity).

Fertility is normal in SLE. Women can pursue pregnancy under close supervision and when SLE is well-controlled and no teratogenic medications are being used. Since SLE patients have a higher risk of developing malignancy (especially lymphoma, lung cancer, and cervical cancer), preventive cancer screening recommendations

should be followed assiduously. With more patients living longer, avascular necrosis of bone, affecting most commonly the hips and knees, is responsible for substantial morbidity. Nonetheless, the outlook for most patients with SLE is increasingly favorable.

When to Refer

- Appropriate diagnosis and management of SLE requires the active participation of a rheumatologist.
- The severity of organ involvement dictates referral to other subspecialists, such as nephrologists and pulmonologists.

When to Admit

- Rapidly progressive glomerulonephritis, pulmonary hemorrhage, transverse myelitis, and other severe organ-threatening manifestations of lupus usually require in-patient assessment and management.
- Severe infections, particularly in the setting of immunosuppressant therapy, should prompt admission.

Aringer M et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol.* 2019;71:1400. [PMID: 31385462]

Durcan L et al. Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet.* 2019;393:2332. [PMID: 31180030]

DRUG-INDUCED LUPUS

Drug-induced lupus shares several clinical and serologic features with SLE but is due to ongoing exposure to a drug and resolves when the offending drug is discontinued. In contrast to SLE, the sex ratio is nearly equal. As a general rule, drug-induced lupus presents with fever, arthralgia, myalgia, and serositis but not renal involvement, neurologic symptoms, or other features of SLE. Serologic testing reveals elevated titers of antinuclear antibodies in all patients, but antibodies to DNA, Sm, RNP, SS-A, and SS-B are rare. Antibodies to histones are common but also are seen in SLE and thus do not distinguish drug-induced lupus from SLE. Complement levels are usually normal. The list of drugs implicated as possible causes of drug-induced lupus in observational studies and case reports is extensive. There are definite associations between the development of drug-induced lupus and the use of hydralazine, isoniazid, and minocycline as well as several medications no longer commonly prescribed (procainamide, quinidine, methyldopa, chlorpromazine). The incidence of drug-induced lupus in patients taking hydralazine for a year or longer is as high as 5–8%; for most other medications, the risk is considerably lower (less than 1%). TNF inhibitors can induce antibodies to DNA, but the incidence of lupus-like syndromes resulting from these medications is low (0.5–1%).

Kawka L et al. Characterization of drug-induced cutaneous lupus: analysis of 1994 cases using the WHO pharmacovigilance database. *Autoimmun Rev.* 2021;20:102705. [PMID: 33188917]

ANTIPHOSPHOLIPID SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Hypercoagulability; recurrent arterial or venous thromboses.
- ▶ Thrombocytopenia is common.
- ▶ Recurrent fetal loss.
- ▶ Recurrent events are frequent; lifetime anticoagulation with warfarin is recommended.

► General Considerations

The clinical features of primary antiphospholipid syndrome (APS) are venous or arterial occlusions or certain pregnancy complications. Laboratory criteria include the identification of at least one of the following three antiphospholipid antibodies: IgG or IgM anticardiolipin, IgG or IgM antibodies to beta-2-glycoprotein 1, and lupus anticoagulant. In less than 1% of patients with antiphospholipid antibodies, a potentially devastating syndrome known as the “**catastrophic antiphospholipid syndrome**” occurs, leading to diffuse thromboses, thrombotic microangiopathy, and multiorgan system failure. Catastrophic APS has a mortality rate approaching 50%.

► Clinical Findings

A. Symptoms and Signs

Patients are often asymptomatic until suffering a thrombotic complication of this syndrome or a pregnancy loss. Thrombotic events may occur in either the arterial or venous circulations. Thus, deep venous thromboses, pulmonary emboli, and cerebrovascular accidents are typical clinical events. Budd-Chiari syndrome, cerebral sinus vein thrombosis, myocardial or digital infarctions, hemorrhagic infarction of the adrenal glands (due to adrenal vein thrombosis), and other thrombotic events also occur. Other symptoms and signs of APS include thrombocytopenia, mental status changes, livedo reticularis, skin ulcers, microangiopathic nephropathy, and cardiac valvular thickening or vegetations. Pregnancy losses include unexplained fetal death after 10 weeks’ gestation; one or more premature births before 34 weeks because of eclampsia, preeclampsia, or placental insufficiency; or three or more unexplained miscarriages before 10 weeks’ gestation.

B. Laboratory Findings

Thrombocytopenia occurs in 22–42% of patients, and it is usually moderate (platelet counts above 50,000/mcL [$50 \times 10^9/L$]). The presence of thrombocytopenia does not reduce the risk of thrombosis.

Three types of antiphospholipid antibodies are associated with this syndrome: (1) anti-cardiolipin antibodies, (2) antibodies to beta-2-glycoprotein, and (3) a “lupus

anticoagulant” that prolongs certain phospholipid-dependent coagulation tests (see below). Antibodies to cardiolipin and to beta-2-glycoprotein are typically measured with enzyme immunoassays. Anti-cardiolipin antibodies can produce a biologic false-positive test for syphilis (ie, a positive rapid plasma reagent but negative specific anti-treponemal assay). In general, IgG anti-cardiolipin antibodies are believed to be more pathologic than IgM. In case-control studies, 3.1% of patients in the general population who experienced a venous thrombotic event (in the absence of cancer) tested positive for the lupus anticoagulant (versus 0.9% of controls, yielding an odds ratio of 3.6). For women younger than 50 years in whom stroke developed, the odds ratio for having the lupus anticoagulant is 43.1. Presence of the lupus anticoagulant is a stronger risk factor for thrombosis or pregnancy loss than is the presence of antibodies to either beta-2-glycoprotein 1 or anti-cardiolipin. A clue to the presence of a lupus anticoagulant, which may occur in individuals who do not have SLE, may be detected by a prolongation of the partial thromboplastin time (which, paradoxically, is associated with a thrombotic tendency rather than a bleeding risk). Testing for the lupus anticoagulant involves phospholipid-dependent functional assays of coagulation, such as the Russell viper venom time (RVVT).

► Differential Diagnosis

The exclusion of other autoimmune disorders, particularly those in the SLE spectrum, is essential because such disorders may be associated with additional complications requiring alternative treatments. Other genetic or acquired conditions associated with hypercoagulability such as protein C, protein S, or antithrombin deficiency and factor V Leiden should be excluded. Catastrophic APS has a broad differential, including sepsis, pulmonary-renal syndromes, systemic vasculitis, disseminated intravascular coagulation, and thrombotic thrombocytopenic purpura.

► Treatment

Patients should be given warfarin to maintain an INR of 2.0–3.0. Available evidence suggests direct-acting oral anticoagulants are less effective than warfarin. Patients who have recurrent thrombotic events while taking warfarin may require higher INRs (greater than 3.0), but the bleeding risk increases substantially with this degree of anticoagulation.

For pregnancy-associated APS, the combination of prophylactic doses of low-molecular-weight heparin (Table 14–14) and low-dose aspirin (81 mg) is the usual approach to prevent pregnancy complications. In women with a history of thrombotic events outside of pregnancy, full-dose low-molecular-weight heparin is administered (Table 14–16). Anticoagulation is typically continued through pregnancy and the early postpartum period for thromboprophylaxis. The benefit of using corticosteroids and intravenous immunoglobulin in these patients is unclear; neither treatment is recommended.

However, in patients with catastrophic APS, either intravenous immunoglobulin or plasmapheresis plus intravenous heparin and high doses of corticosteroids are administered. Resistant disease may require biologic therapy with monoclonal antibodies against CD20 on B cells (rituximab) or against complement component C5 (eculizimab), although data to support these therapies are limited to case series.

Tektonidou MG et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019;78:1296. [PMID: 31092409]

RAYNAUD PHENOMENON



ESSENTIALS OF DIAGNOSIS

- ▶ Paroxysmal bilateral digital pallor and cyanosis followed by rubor.
- ▶ Precipitated by cold or emotional stress; relieved by warmth.
- ▶ **Primary form:** benign course; usually affects young women.
- ▶ **Secondary form:** more severe, sometimes causing digital ulceration or gangrene.

putting the extremity in warm water. The patient is usually asymptomatic between attacks. Sensory changes that often accompany vasomotor manifestations include numbness, tingling, diminished sensation, and aching pain.

Primary RP appears first between ages 15 and 30, almost always in women. It tends to be mildly progressive and, unlike secondary RP (which may be unilateral and may involve only one or two fingers), symmetric involvement of the fingers of both hands is the rule. Spasm becomes more frequent and prolonged. Unlike secondary RP, primary RP does not cause digital pitting, ulceration, or gangrene.

Nailfold capillary abnormalities are among the earliest clues that a person has secondary rather than primary RP. The nailfold capillary pattern can be visualized by placing a drop of grade B immersion oil at the patient's cuticle and then viewing the area with an ophthalmoscope set to 20–40 diopters. Dropout of capillaries and dilation of the remaining capillary loops indicate the patient has a secondary form of RP, most commonly systemic sclerosis (Figure 20-5) (Table 20-9). While highly specific for secondary RP, nailfold capillary changes have a low sensitivity. Digital pitting or ulceration or other abnormal physical findings (eg, skin tightening, loss of extremity pulse, rash, swollen joints) can also provide evidence of secondary RP.

Primary RP must be differentiated from the numerous causes of secondary RP (Table 20-9). The history and examination may suggest the diagnosis of systemic sclerosis, SLE, or mixed connective tissue disease; RP is often the first manifestation of limited systemic sclerosis (CREST syndrome). The diagnosis of many of these rheumatic diseases is supported with specific serologic tests.

RP may occur in patients with the thoracic outlet syndromes. In these disorders, involvement is generally unilateral, and symptoms referable to brachial plexus compression tend to dominate the clinical picture. Carpal tunnel syndrome should also be considered, and nerve conduction tests are appropriate in selected cases.

Differential Diagnosis

The differentiation from Buerger disease (thromboangiitis obliterans) is usually not difficult, since thromboangiitis obliterans is generally a disease of men, particularly smokers; peripheral pulses are often diminished or absent; and, when RP occurs in association with thromboangiitis obliterans, it is usually in only one or two digits.

In acrocytosis, cyanosis of the hands is permanent and diffuse; the sharp and paroxysmal line of demarcation with pallor does not occur with acrocytosis. Frostbite may lead to chronic RP.

Treatment

A. General Measures

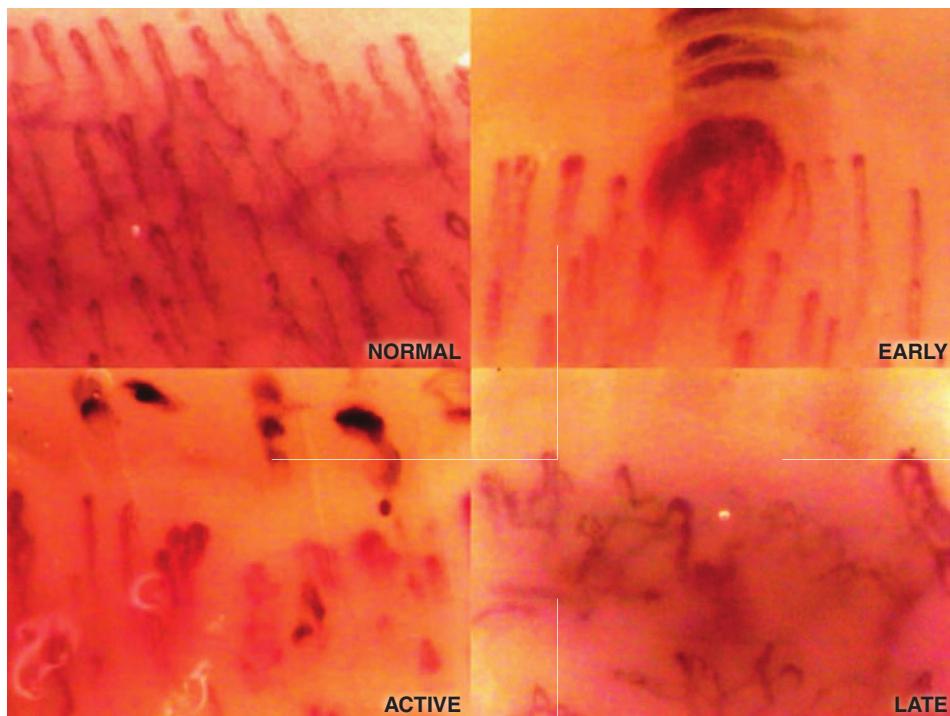
Patients should wear gloves or mittens whenever in temperatures that precipitate attacks. Keeping the body warm is also a cornerstone of initial therapy. Wearing warm shirts, coats, and hats will help prevent the exaggerated vasospasm that causes RP and that is not prevented by

General Considerations

Raynaud phenomenon (RP) is a syndrome of paroxysmal digital ischemia, most commonly caused by an exaggerated response of digital arterioles to cold or emotional stress. The initial phase of RP, mediated by excessive vasoconstriction, consists of well-demarcated digital pallor or cyanosis; the subsequent (recovery) phase of RP, caused by vasodilation, leads to intense hyperemia and rubor. Although RP chiefly affects fingers, it can also affect toes and other acral areas such as the nose and ears. RP is classified as primary (idiopathic or Raynaud disease) or secondary. Nearly one-third of the population reports being “sensitive to the cold” but does not experience the paroxysms of digital pallor, cyanosis, and erythema characteristic of RP. Primary RP occurs in 2–6% of adults, is especially common in young women, and poses more of a nuisance than a threat to good health. In contrast, secondary RP is less common, is chiefly associated with rheumatic diseases (especially systemic sclerosis [scleroderma]), and can be severe enough to cause digital ulceration or gangrene.

Clinical Findings

In early attacks of RP, only one or two fingertips may be affected; as it progresses, all fingers down to the distal palm may be involved. The thumbs are rarely affected. During recovery there may be intense rubor, throbbing, paresthesia, pain, and slight swelling. Attacks usually terminate spontaneously or upon returning to a warm room or



▲ **Figure 20-5.** The systemic sclerosis (scleroderma) pattern: early, active, and late nailfold videocapillaroscopy patterns versus normal. (Reproduced, with permission, from Cutolo M et al. Capillaroscopy. Best Pract Res Clin Rheumatol. 2008;22(6):1093–1108. Copyright © Elsevier.)

warming only the hands. The hands should be protected from injury at all times; wounds heal slowly, and infections are consequently hard to control. Softening and lubricating lotion to control fissured dry skin should be applied to the hands frequently. Cigarette smoking should be stopped and sympathomimetic drugs (eg, decongestants, diet pills, and amphetamines) should be avoided. For most patients with primary RP, general measures alone are sufficient to control symptoms. Medical or surgical therapy should be considered in patients who have severe symptoms or are experiencing tissue injury from digital ischemia.

B. Medications

Calcium channel blockers are first-line therapy for RP. Calcium channel blockers produce a modest benefit and are more effective in primary RP than secondary RP. Slow-release nifedipine (30–180 mg/day orally), amlodipine (5–20 mg/day orally), felodipine, isradipine, and nisoldipine are popular and more effective than verapamil, nicardipine, and diltiazem. Other medications that are sometimes effective in treating RP include angiotensin II receptor blockers, topical nitrates, phosphodiesterase inhibitors (eg, sildenafil, tadalafil, and vardenafil), selective serotonin reuptake inhibitors (fluoxetine), statins, or endothelin-receptor inhibitors (ie, bosentan). Severe or refractory episodes in which there is a threat of digital loss may require treatment with intravenous infusions of prostacyclin or prostacyclin analogs (eg, epoprostenol, iloprost, treprostinil).

C. Surgical Measures

Sympathectomy may be indicated when attacks have become frequent and severe, when they interfere with work and well-being, and particularly when trophic changes have developed and medical measures have failed. Digital sympathectomy may improve secondary RP.

► Prognosis

Primary RP is benign and largely a nuisance for affected individuals who are exposed to cold winters or excessive air conditioning. The prognosis of secondary RP depends on underlying disease; unfortunately, severe pain from ulceration and gangrene is not rare with systemic sclerosis.

► When to Refer

Appropriate management of patients with secondary RP often requires consultation with a rheumatologist.

► When to Admit

Patients with critical digital ischemia as evidenced by severe pain and demarcation should be admitted for intensive therapy.

Hughes M et al. Raynaud phenomenon and digital ulcers in systemic sclerosis. Nat Rev Rheumatol. 2020;16:208. [PMID: 32099191]

Table 20–9. Causes of secondary Raynaud phenomenon.

Rheumatic diseases
Systemic sclerosis (scleroderma)
Systemic lupus erythematosus
Mixed connective tissue disease
Dermatomyositis/polymyositis
Sjögren syndrome
Vasculitis (polyarteritis nodosa, Takayasu disease, Buerger disease)
Neurovascular compression and occupational
Carpal tunnel syndrome
Thoracic outlet obstruction
Vibration injury
Drugs and substances
Beta-blockers
Serotonin agonists (sumatriptan)
Sympathomimetic drugs (decongestants)
Chemotherapy (bleomycin, vinblastine)
Ergotamine
Caffeine
Nicotine
Cocaine
Epoxy resins
Hematologic disorders
Cryoglobulinemia
Polycythemia vera
Paraproteinemia
Cold agglutinins
Endocrine disorders
Hypothyroidism
Pheochromocytoma
Miscellaneous
Atherosclerosis
Embolic disease
Migraine
Sequelae of frostbite

SYSTEMIC SCLEROSIS (Scleroderma)



ESSENTIALS OF DIAGNOSIS

- ▶ **Limited disease (CREST syndrome):** skin thickening confined to face, neck, and distal extremities.
- ▶ **Diffuse disease (20%):** widespread thickening of skin, including truncal involvement, with areas of increased pigmentation and depigmentation.
- ▶ Raynaud phenomenon and antinuclear antibodies are present in virtually all patients.
- ▶ **Systemic features:** gastroesophageal reflux, gastrointestinal hypomotility, pulmonary fibrosis, pulmonary hypertension, renal involvement.

► General Consideration

Systemic sclerosis (scleroderma) is a rare chronic disorder characterized by diffuse fibrosis of the skin and internal organs. Symptoms usually appear in the third to fifth

decades, and women are affected two to three times as frequently as men.

Two forms of systemic sclerosis are generally recognized: limited (80% of patients) and diffuse (20%). In limited systemic sclerosis, which often has one or more features of the CREST syndrome (representing calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia), the hardening of the skin (scleroderma) is limited to the face, neck, and skin distal to the elbows and knees. In contrast, in diffuse systemic sclerosis, the skin changes also involve the trunk and proximal extremities. Tendon friction rubs over the forearms and shins occur uniquely (but not universally) in diffuse systemic sclerosis. In general, patients with limited systemic sclerosis have better outcomes than those with diffuse disease, largely because life-threatening lung or kidney disease is rare. Cardiac disease is also more characteristic of diffuse systemic sclerosis. Patients with limited disease, however, are more susceptible to digital ischemia, leading to finger loss, and to life-threatening pulmonary hypertension. Small and large bowel hypomotility, which may occur in either form of systemic sclerosis, can cause constipation alternating with diarrhea, malabsorption due to bacterial overgrowth, pseudoobstruction, and severe bowel distention with rupture.

► Clinical Findings

A. Symptoms and Signs

Raynaud phenomenon is usually the initial manifestation and can precede other signs and symptoms by years in cases of limited systemic sclerosis. Polyarthralgia, weight loss, and malaise are common early features of diffuse systemic sclerosis but are infrequent in limited disease. Cutaneous disease usually, but not always, develops before visceral involvement and can manifest initially as non-pitting subcutaneous edema associated with pruritus. With time the skin becomes thickened and hidebound, with loss of normal folds. Telangiectasia, pigmentation, and depigmentation are characteristic. Ulceration of the fingertips and subcutaneous calcification are seen. Dysphagia and symptoms of reflux due to esophageal dysfunction are common and result from abnormalities in motility and later from fibrosis. Fibrosis and atrophy of the gastrointestinal tract cause hypomotility. Large-mouthed diverticuli occur in the jejunum, ileum, and colon. Diffuse pulmonary fibrosis and pulmonary vascular disease are reflected in restrictive lung physiology and low diffusing capacities. Cardiac abnormalities include pericardial effusions, heart block, myocardial fibrosis, and right heart failure secondary to pulmonary hypertension. Systemic sclerosis-associated renal crisis, resulting from intimal proliferation of smaller renal arteries and usually associated with hypertension, is a life-threatening emergency. Many cases can be treated effectively with angiotensin-converting enzyme inhibitors.

B. Laboratory Findings

Mild anemia is often present. In renal crisis, the peripheral blood smear shows findings consistent with a microangiopathic hemolytic anemia (due to mechanical damage to red

cells from diseased small vessels). Elevation of the ESR is unusual. Mild proteinuria with few cells or casts can occur. Antinuclear antibody tests are nearly always positive, frequently in high titers (Table 20–7). The scleroderma antibody (anti-SCL-70), directed against topoisomerase III, is found in one-third of patients with diffuse systemic sclerosis and in 20% of those with limited disease. Although present in only a small number of patients with diffuse systemic sclerosis, anti-SCL-70 antibodies may portend a poor prognosis, with a high likelihood of serious internal organ involvement (eg, interstitial lung disease). Anticentromere antibodies are seen in 50% of those with limited systemic sclerosis and in 5% of individuals with diffuse disease (Table 20–7). Anticentromere antibodies are highly specific for limited systemic sclerosis, but they also occur occasionally in overlap syndromes. Anti-RNA polymerase III antibodies develop in 10–20% of systemic sclerosis patients overall and are associated with rapidly progressive skin disease, renal crisis, and a higher risk of concomitant solid cancers, especially breast cancer.

Differential Diagnosis

Early in its course, systemic sclerosis can cause diagnostic confusion with other causes of Raynaud phenomenon, particularly SLE, mixed connective tissue disease, and the inflammatory myopathies. Eosinophilic fasciitis is a rare disorder presenting with skin hardening that resembles diffuse systemic sclerosis. The inflammatory abnormalities, however, are limited to the fascia rather than the dermis and epidermis. Moreover, patients with eosinophilic fasciitis are distinguished from those with systemic sclerosis by the presence of peripheral blood eosinophilia, the absence of Raynaud phenomenon, a good response to prednisone, and an association (in some cases) with paraproteinemias. Diffuse skin thickening and visceral involvement are features of scleromyxedema; the presence of a paraprotein, the absence of Raynaud phenomenon, and distinct skin histology point to scleromyxedema. Diabetic cheiropathy typically develops in longstanding, poorly controlled diabetes mellitus and can mimic sclerodactyly. Morphea and linear scleroderma cause sclerodermatosus changes limited to circumscribed areas of the skin and usually have excellent outcomes.

Treatment

Treatment of systemic sclerosis focuses on the organ systems involved. There is no effective therapy for the underlying disease process. However, interventions for management of specific organ manifestations of this disease have improved substantially. Treatment for Raynaud phenomenon is discussed above. The hypertensive crises in scleroderma renal crisis must be treated early and aggressively (in the hospital) with angiotensin-converting enzyme inhibitors, eg, captopril, initiated at 25 mg orally every 6 hours and titrated up as tolerated to a maximum of 100 mg every 6 hours. Patients with severe esophageal disease should take medications in liquid or crushed form. Esophageal reflux can be reduced and the risk of scarring diminished by avoidance of late-night meals and by the use

of proton pump inhibitors (eg, omeprazole, 20–40 mg/day orally), which achieve near-complete inhibition of gastric acid production and are effective for refractory esophagitis. Patients with delayed gastric emptying maintain their weight better if they eat small, frequent meals and remain upright for at least 2 hours after eating. Oral prokinetic agents such as metoclopramide (10 mg four times daily) or cisapride (10–20 mg four times daily) can improve dysphagia caused by esophageal hypomotility. Erythromycin (250 mg three times daily) can be used if prokinetic agents fail. Since erythromycin impairs the metabolism of cisapride, combined use of these two agents is contraindicated. Long-term octreotide (0.1 mg subcutaneously twice daily), a somatostatin analog, helps some patients with bacterial overgrowth and pseudoobstruction. Malabsorption due to bacterial overgrowth responds to antibiotics, eg, rifaximin, 550 mg three times orally daily, often prescribed cyclically. Apart from the patient with myositis, prednisone has little or no role in the treatment of systemic sclerosis; doses higher than 15 mg/day have been associated with scleroderma renal crisis. In patients with early diffuse systemic sclerosis (scleroderma), methotrexate can be used in the treatment of skin disease, arthritis, and myositis. The usual initial dose is 7.5 mg of methotrexate orally once weekly. If the patient has tolerated methotrexate but has not responded in 1 month, the dose can be increased to 15 mg orally once per week. The maximal dose is usually 20 mg/wk. For patients who require treatment for interstitial lung disease, mycophenolate mofetil (1000–1500 mg orally twice daily) can improve dyspnea and pulmonary function tests modestly. Cyclophosphamide has similar efficacy but greater toxicity; this drug should only be administered by physicians familiar with its use. In patients who do not respond to or cannot take mycophenolate mofetil or cyclophosphamide, nintedanib (an inhibitor of multiple tyrosine kinases) can slow the progression of systemic sclerosis-associated lung disease and is FDA approved for this indication. Bosentan, an endothelin receptor antagonist, improves exercise capacity and cardio-pulmonary hemodynamics in patients with pulmonary hypertension and helps prevent digital ulceration. Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil), a guanylate cyclase stimulant (riociguat), endothelin-1 receptor antagonists (bosentan, macitentan), and an endothelin-A receptor antagonist (ambrisentan) are used to treat pulmonary hypertension. Refractory pulmonary hypertension may require prostacyclin pathway agonists (epoprostenol, treprostinal, iloprost). For patients with severe, diffuse systemic sclerosis, myeloablation followed by autologous stem cell transplantation is superior to immunosuppression with cyclophosphamide but has greater toxicity.

The 9-year survival rate in systemic sclerosis averages approximately 40%. The prognosis tends to be worse in those with diffuse disease, in Blacks, in men, and in older patients. Lung disease—in the form of pulmonary fibrosis or pulmonary arterial hypertension—is the leading cause of mortality. Those persons in whom severe internal organ involvement does not develop in the first 3 years have a substantially better prognosis, with 72% surviving at least 9 years. Studies conducted in a small number of patients

with simultaneous onset of cancer and systemic sclerosis have demonstrated that the disease developed as a consequence of an immune response directed at the cancer.

► When to Refer

- Appropriate management of systemic sclerosis requires frequent consultations with a rheumatologist.
- Severity of organ involvement dictates referral to cardiologists, pulmonologists, gastroenterologists, or nephrologists.

Distler O et al; SENSCIS Trial Investigators. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med.* 2019;380:2518. [PMID: 31112379]
 Kowal-Bielecka O et al; EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis.* 2017;76:1327. [PMID: 27941129]
 Roofeh D et al. Management of systemic sclerosis-associated interstitial lung disease. *Curr Opin Rheumatol.* 2019;31:241. [PMID: 30870216]

IMMUNE-MEDIATED INFLAMMATORY MYOPATHIES



ESSENTIALS OF DIAGNOSIS

- ▶ Progressive muscle weakness.
- ▶ **Dermatomyositis:** characteristic cutaneous manifestations (Gottron papules, heliotrope rash); increased risk of malignancy.
- ▶ Elevated creatine kinase, myositis-specific antibodies, diagnostic muscle biopsy.
- ▶ Mimics include infectious, metabolic, or drug-induced myopathies.

► General Considerations

Idiopathic inflammatory myopathies include polymyositis, dermatomyositis, myositis resulting from a rheumatic disease or overlap syndrome, inclusion body myositis (IBM), and immune-mediated necrotizing myopathy. These disorders are characterized by progressive muscle weakness, and all but IBM demonstrate an inflammatory infiltrate in muscle tissue.

Polymyositis and dermatomyositis are systemic disorders of unknown cause whose principal manifestation is muscle weakness. Although their clinical presentations (aside from the presence of certain skin findings in dermatomyositis, some of which are pathognomonic) and treatments are similar, the two diseases are pathologically quite distinct. They affect persons of any age group, but the peak incidence is in the fifth and sixth decades of life. Women are affected twice as commonly as men, and the diseases (particularly polymyositis) also occur more often among Blacks than Whites. There is an increased risk of malignancy, especially in dermatomyositis. Indeed, up to one

patient in four with dermatomyositis has an occult malignancy. Malignancies may be evident at the time of presentation with the muscle disease but may not be detected until months afterward in some cases. The malignancies most commonly associated with dermatomyositis are lung, ovarian, breast, colorectal, cervical, bladder, nasopharyngeal, esophageal, pancreatic, and renal cancer. Patients may have skin disease without overt muscle involvement, a condition termed dermatomyositis sine myositis; these patients can have aggressive interstitial lung disease. Myositis may also overlap with other connective tissue diseases, especially systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, and Sjögren syndrome.

IBM affects older men and is characterized by more distal weakness in the upper extremities and is generally less symmetric. Immune-mediated necrotizing myopathies include those associated with the signal recognition particle or with anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (anti-HMGCR) autoantibodies in the setting of statin use.

► Clinical Findings

A. Symptoms and Signs

Polymyositis may begin abruptly, but the usual presentation is one of progressive muscle weakness over weeks to months. The weakness chiefly involves proximal muscle groups of the upper and lower extremities as well as the neck. Leg weakness (eg, difficulty in rising from a chair or climbing stairs) typically precedes arm symptoms. In contrast to myasthenia gravis, polymyositis and dermatomyositis do not cause facial or ocular muscle weakness. In contrast to polymyalgia rheumatica (PMR), pain and tenderness of affected muscles occur in one-fourth of cases, but these are rarely the chief complaints. About one-fourth of patients have dysphagia. In contrast to systemic sclerosis, which affects the smooth muscle of the lower esophagus and can cause a “sticking” sensation below the sternum, polymyositis or dermatomyositis involves the striated muscles of the upper pharynx and can make initiation of swallowing difficult. Clinically significant myocarditis is uncommon even though there is often creatine kinase-MB elevation. Respiratory muscle weakness can be severe enough to cause CO₂ retention and respiratory failure.

Dermatomyositis has a characteristic rash that is dusky red and may appear in a malar distribution, mimicking the classic rash of SLE. Facial erythema beyond the malar distribution is also characteristic of dermatomyositis. Erythema also occurs over other areas of the face, neck, shoulders, and upper chest and back (“shawl sign”). Periorbital edema and a purplish (heliotrope) suffusion over the eyelids are typical signs (Figure 20–6). Coloration of the heliotrope and other rashes of dermatomyositis can be affected by skin tone. In Blacks, the rashes may appear more hyperpigmented than erythematous or violaceous. Periungual erythema, dilations of nailfold capillaries, Gottron papules (raised violaceous lesions overlying the dorsa of DIP, PIP, and MCP joints), and Gottron sign (erythematous rash on the extensors surfaces of the fingers, elbows, and knees) are highly suggestive. Scalp involvement by dermatomyositis may mimic psoriasis.



▲ Figure 20–6. Bilateral heliotrope rash, which is a pathognomonic sign of dermatomyositis. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw Hill, 2019.)

Infrequently, the cutaneous findings of this disease precede the muscle inflammation by weeks or months. Diagnosing polymyositis in patients over age 70 years can be difficult because weakness may be overlooked or attributed erroneously to idiopathic frailty. A subset of patients with polymyositis and dermatomyositis have the “**antisynthetase syndrome**,” a group of findings including inflammatory nonerosive arthritis, fever, Raynaud phenomenon, “mechanic’s hands” (hyperkeratosis along the radial and palmar aspects of the fingers), interstitial lung disease, and often severe muscle disease associated with certain autoantibodies (eg, anti-Jo-1 antibodies).

IBM, because of its tendency to mimic polymyositis, is a common cause of “treatment-resistant polymyositis.” In contrast to polymyositis, the typical patient with IBM is a White, male over the age of 50 years. The onset of IBM is more insidious than that of polymyositis or dermatomyositis (eg, occurring over years rather than months), and the distal motor weakness is commonly asymmetric. Creatine kinase levels are often minimally elevated and are normal in 25%. Electromyography may show a mixed picture of myopathic and neurogenic abnormalities. The disease is associated with antibodies to cytoplasmic 5'-nucleotidase 1A (cN1A). IBM is less likely to respond to therapy.

Immune-mediated necrotizing myopathy, although similar to polymyositis, is distinct because of the presence of muscle necrosis. Autoantibodies aid in diagnosis; anti-SRP antibodies are associated with severe muscle weakness, pain, and cardiac involvement. Anti-HMGCR antibodies occur in the setting of statin use and are associated with proximal muscle weakness and marked creatine kinase elevations. Unlike statin-induced myopathy, anti-HMGCR myositis does not resolve when statins are stopped. Instead, many patients have a severe and unrelenting disease course with persistent weakness.

B. Laboratory Findings

Measurement of serum levels of muscle enzymes, especially creatine kinase and aldolase, is most useful in diagnosis and

in assessment of disease activity. Inflammatory myositis can be misdiagnosed as hepatitis because of elevations in serum levels of muscle-derived alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Anemia is uncommon. The ESR and CRP are often normal and are not reliable indicators of disease activity. Rheumatoid factor is found in a minority of patients. Antinuclear antibodies can be present, especially when there is an associated connective tissue disease. A number of autoantibodies are seen exclusively in patients with myositis and are associated with distinctive clinical features (Table 20–10). Examples of myositis-specific antibodies include (1) anti-Jo-1 antibody (seen in the subset of patients who have antisynthetase syndrome), (2) anti-Mi-2 (associated with dermatomyositis), (3) anti-155/140 (strongly associated with dermatomyositis with malignancy), and (4) anti-MDA5 (melanocyte differentiation-associated protein 5, linked to dermatomyositis with cutaneous ulcerations and rapidly progressive interstitial lung disease). Chest radiographs are usually normal unless there is associated interstitial lung disease. Electromyographic abnormalities can point toward a myopathic, rather than a neurogenic, cause of weakness. MRI can detect early and patchy muscle involvement, can guide biopsies, and often is more useful than electromyography. The search for an occult malignancy should begin with a history and physical examination, supplemented with a complete blood count, comprehensive biochemical panel, and urinalysis and should include age- and risk-appropriate cancer screening tests. Given the especially strong association of ovarian carcinoma and dermatomyositis,

Table 20–10. Myositis-specific antibodies.

Antibody	Clinical Association
Anti-Jo-1 and other anti-tRNA synthetase antibodies	Polymyositis or dermatomyositis with interstitial lung disease, arthritis, mechanic’s hands
Anti-Mi-2	Dermatomyositis with rash more than myositis, good prognosis
Anti-MDA5 (anti-CADM 140)	Dermatomyositis with rapidly progressive lung disease, cutaneous ulcers
Anti-TIF-1 (p155/140)	Cancer-associated dermatomyositis
Anti-NXP-2	Juvenile dermatomyositis
Anti-SAE	Cancer-associated dermatomyositis, dermatomyositis with pulmonary arterial hypertension
Anti-signal recognition particle	Severe, acute necrotizing myopathy
Anti-HMG CoA reductase	Necrotizing myopathy related to statin use
PM-Scl, Ku, U 1-3 RNP	Polymyositis/dermatomyositis overlap syndromes

Adapted, with permission, from Imboden JB, Hellmann DB, Stone JH (editors): *Current Diagnosis & Treatment Rheumatology*, 3rd ed. McGraw-Hill, 2013.

transvaginal ultrasonography, CT scanning, and CA-125 levels may be useful in women. No matter how extensive the initial screening, some malignancies will not become evident for months after the initial presentation.

C. Muscle Biopsy

Biopsy of clinically involved muscle is often required. The pathology findings in polymyositis and dermatomyositis are distinct. In dermatomyositis, the cellular infiltrate is mostly perifascicular and perivascular, while in polymyositis, the inflammatory infiltrate involves the fascicle itself. The presence of prominent necrosis with a paucity of inflammatory cells suggests an immune-mediated necrotizing myopathy. Muscle biopsy in IBM shows characteristic intracellular vacuoles by light microscopy and either tubular or filamentous inclusions in the nucleus or cytoplasm by electron microscopy. False-negative biopsies sometimes occur in these disorders because of the sometimes patchy distribution of pathologic abnormalities.

Differential Diagnosis

Muscle inflammation may occur as a component of SLE, systemic sclerosis, Sjögren syndrome, and overlap syndromes. In those cases, associated findings usually permit the precise diagnosis of the primary condition.

Hypothyroidism is a common cause of proximal muscle weakness associated with elevations of serum creatine kinase. Hyperthyroidism and Cushing disease may both be associated with proximal muscle weakness with normal levels of creatine kinase. Patients with polymyalgia rheumatica are over the age of 50 and—in contrast to patients with polymyositis—have pain but no objective weakness; creatine kinase levels are normal. Disorders of the peripheral and central nervous systems (eg, chronic inflammatory polyneuropathy, multiple sclerosis, myasthenia gravis, Lambert-Eaton disease, and amyotrophic lateral sclerosis) can produce weakness but are distinguished by characteristic symptoms and neurologic signs and often by distinctive electromyographic abnormalities. A number of systemic vasculitides (polyarteritis nodosa, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, and mixed cryoglobulinemia) can produce profound weakness through vasculitic neuropathy. The muscle weakness associated with these disorders, however, is typically distal and asymmetric, at least in the early stages.

Limb-girdle muscular dystrophy can present in early adulthood with a clinical picture that mimics polymyositis: proximal muscle weakness, elevations in serum levels of creatine kinase, and inflammatory changes on muscle biopsy. Failure to respond to treatment for polymyositis or the presence of atypical clinical features such as scapular winging or weakness of ankle plantar flexors should prompt genetic testing for limb-girdle muscular dystrophy.

Many drugs, including corticosteroids, alcohol, clofibrate, penicillamine, tryptophan, and hydroxychloroquine, can produce proximal muscle weakness. Long-term use of colchicine at doses as low as 0.6 mg twice a day in patients

with moderate CKD can produce a mixed neuropathy-myopathy that mimics polymyositis. The weakness and muscle enzyme elevation reverse with cessation of the drug. HIV is associated with a myopathy indistinguishable from polymyositis.

Statins can cause myopathy and rhabdomyolysis, in addition to the anti-HMGCR myopathy described above. Although only about 0.1% of patients taking a statin drug alone develop myopathy, concomitant administration of other drugs (especially gemfibrozil, cyclosporine, niacin, macrolide antibiotics, azole antifungals, and protease inhibitors) increases the risk.

The use of immune checkpoint inhibitors to treat cancer can cause rheumatic and musculoskeletal symptoms, including myalgia and myositis.

Treatment

Most patients respond to corticosteroids. Often a daily dose of 40–60 mg or more of oral prednisone is required initially. The dose is then adjusted downward while monitoring muscle strength and serum levels of muscle enzymes. Long-term use of corticosteroids is often needed, and the disease may recur when they are withdrawn. Patients with an associated neoplasm have a poor prognosis, although remission may follow treatment of the tumor; corticosteroids may or may not be effective in these patients. Immunosuppressive drugs like methotrexate or azathioprine are often started to reduce cumulative corticosteroid exposure. Intravenous immune globulin is effective for dermatomyositis resistant to prednisone and anti-HMGCR myopathy. Mycophenolate mofetil (1–1.5 g orally twice daily) may also be useful as a steroid-sparing agent. Rituximab is effective in some patients with inflammatory myositis unresponsive to prednisone. Since the rash of dermatomyositis is often photosensitive, patients should limit sun exposure. Hydroxychloroquine (200–400 mg/day orally not to exceed 5 mg/kg) can also help ameliorate the skin disease.

When to Refer

- All patients with myositis should be referred to a rheumatologist or neurologist.
- Severe lung disease may require consultation with a pulmonologist.

When to Admit

- Signs of rhabdomyolysis.
- New onset of dysphagia.
- Respiratory insufficiency with hypoxia or carbon dioxide retention.

Allenbach Y et al. Immune-mediated necrotizing myopathy: clinical features and pathogenesis. *Nat Rev Rheumatol*. 2020;16:689. [PMID: 33093664]

Wolstencroft PW et al. Dermatomyositis clinical and pathological phenotypes associated with myositis-specific autoantibodies. *Curr Rheumatol Rep*. 2018;20:28. [PMID: 29637414]

MIXED CONNECTIVE TISSUE DISEASE & OVERLAP SYNDROMES

Many patients with symptoms and signs of a connective tissue disease have features of more than one type of rheumatic disease. Special attention has been drawn to a subset of antinuclear antibody–positive patients who have high titers of RNP autoantibodies and overlapping features of SLE, systemic sclerosis, rheumatoid arthritis and inflammatory myositis. Swollen or puffy hands are a common early feature of this disease, referred to as mixed connective tissue disease. Raynaud phenomenon, arthralgias, and myalgias are common. Unlike patients with SLE, renal or central nervous system disease is uncommon. A key reason to identify this subset of patients is that pulmonary hypertension and interstitial lung disease are major causes of mortality, and regular screening for these manifestations is required. Some patients have features of more than one connective tissue disease (eg, rheumatoid arthritis and SLE, SLE and systemic sclerosis) in the absence of high-titer anti-RNP antibodies and are referred to as having an “overlap syndrome.” Treatments are guided more by the distribution and severity of patients’ organ system involvement than by therapies specific to these overlap syndromes.

Reiseter S et al. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. *Rheumatology (Oxford)*. 2018;57:255. [PMID: 28379478]

SJÖGREN SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Women (average age 50 years) compose 90% of patients.
- ▶ Dryness of eyes and dry mouth (sicca components) are the most common features; they occur alone or with rheumatoid arthritis or other connective tissue disease.
- ▶ Rheumatoid factor and antinuclear antibodies are common.
- ▶ Increased incidence of lymphoma.

General Considerations

Sjögren syndrome is a systemic autoimmune disorder whose clinical presentation is usually dominated by dryness of the eyes and mouth due to immune-mediated dysfunction of the lacrimal and salivary glands. The disorder is predominantly seen in women, with a ratio of 9:1; most cases develop between the ages of 40 and 60 years. Sjögren syndrome can occur in isolation (“primary” Sjögren syndrome) or in association with another rheumatic disease. Sjögren syndrome is most frequently associated with rheumatoid arthritis but also occurs with SLE, primary biliary

cholangitis, systemic sclerosis, polymyositis, Hashimoto thyroiditis, polyarteritis, and interstitial pulmonary fibrosis.

Clinical Findings

A. Symptoms and Signs

Keratoconjunctivitis sicca results from inadequate tear production caused by lymphocyte and plasma cell infiltration of the lacrimal glands. Ocular symptoms are usually mild. Burning, itching, and the sensation of having a foreign body or a grain of sand in the eye occur commonly. For some patients, the initial manifestation is the inability to tolerate wearing contact lenses. Many patients with more severe ocular dryness noticeropy secretions across their eyes, especially in the morning. For most patients, symptoms of dryness of the mouth (xerostomia) dominate those of dry eyes. Patients frequently complain of a “cotton mouth” sensation and difficulty swallowing foods, especially dry foods like crackers, unless they are washed down with liquids. The persistent oral dryness causes most patients to carry water bottles or other liquid dispensers from which they sip constantly. A few patients have such severe xerostomia that they have difficulty speaking. Persistent xerostomia results in rampant dental caries; caries at the gum line strongly suggest Sjögren syndrome. Some patients are most troubled by loss of taste and smell. Parotid enlargement, which may be chronic or relapsing, develops in one-third of patients. Dryness may involve the nose, throat, larynx, bronchi, vagina, and skin.

Systemic manifestations include dysphagia, small vessel vasculitis, pleuritis, obstructive airways disease and interstitial lung disease (in the absence of smoking), neuropsychiatric dysfunction (most commonly peripheral neuropathies), and pancreatitis; they may be related to the associated diseases noted above. Renal tubular acidosis (type I, distal) occurs in 20% of patients. Chronic interstitial nephritis, which may result in impaired kidney function, may be seen.

B. Laboratory Findings

Laboratory findings include mild anemia, leukopenia, and eosinophilia. Polyclonal hypergammaglobulinemia, rheumatoid factor positivity (70%), and antinuclear antibodies (95%) are all common findings. Antibodies against SS-A and SS-B are often present in primary Sjögren syndrome and tend to correlate with the presence of extra-glandular manifestations (Table 20–7).

Useful ocular diagnostic tests include the Schirmer test, which measures the quantity of tears secreted. Lip biopsy, a simple procedure, reveals characteristic lymphoid foci in accessory salivary glands. Biopsy of the parotid gland should be reserved for patients with atypical presentations such as unilateral gland enlargement that suggest a neoplastic process.

Differential Diagnosis

Isolated complaints of dry mouth are most commonly due to medication side effects. Chronic hepatitis C can cause sicca symptoms and rheumatoid factor positivity. Minor

salivary gland biopsies reveal lymphocytic infiltrates but not to the extent of Sjögren syndrome, and tests for anti-SS-A and anti-SS-B are negative. Diffuse infiltration of CD8 T cells producing parotid gland enlargement can develop in HIV-infected individuals. Involvement of the lacrimal or salivary glands, or both in sarcoidosis can mimic Sjögren syndrome; biopsies reveal noncaseating granulomas. IgG₄-related systemic disease (characterized by high serum IgG₄ levels and infiltration of tissues with IgG₄⁺ plasma cells) can result in lacrimal and salivary gland enlargement that mimics Sjögren syndrome.

Treatment & Prognosis

Treatment of sicca symptoms is symptomatic and supportive. Artificial tears applied frequently will relieve ocular symptoms and avert further desiccation. Topical ocular 0.05% cyclosporine also improves ocular symptoms and signs of dryness. The mouth should be kept well lubricated. Sipping water frequently or using sugar-free gums and hard candies usually relieves dry mouth symptoms. Pilocarpine (5 mg orally four times daily) and the acetylcholine derivative cevimeline (30 mg orally three times daily) may improve xerostomia symptoms. Atropinic drugs and decongestants decrease salivary secretions and should be avoided. A program of oral hygiene, including fluoride treatment, is essential in order to preserve dentition. If there is an associated rheumatic disease, its systemic treatment is not altered by the presence of Sjögren syndrome. Extraglandular disease, including arthritis, vasculitis, or pulmonary manifestations, is treated with similar immunosuppressive medications as SLE or rheumatoid arthritis.

Although Sjögren syndrome may compromise patients' quality of life significantly, the disease is usually associated with a normal life span. Poor prognoses are influenced mainly by the presence of systemic features associated with underlying disorders, the development in some patients of lymphocytic vasculitis, the occurrence of a painful peripheral neuropathy, and the complication (in a minority of patients) of lymphoma. Severe systemic inflammatory manifestations are treated with prednisone or various immunosuppressive medications. The patients at greatest risk for developing lymphoma are those with severe exocrine dysfunction, marked parotid gland enlargement, splenomegaly, vasculitis, peripheral neuropathy, anemia, and mixed monoclonal cryoglobulinemia (3–10% of the total Sjögren population).

When to Refer

- Presence of systemic symptoms or signs.
- Ocular dryness not responsive to artificial tears.

When to Admit

Presence of severe systemic signs such as vasculitis unresponsive to outpatient management.

Ramos-Casals M et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis. 2020;79:3. [PMID: 31672775]

IgG₄-RELATED DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Predominantly affects men (75% of patients); average age older than 50 years.
- ▶ Protean manifestations from lymphoplasmacytic infiltrates causing tumors or fibrosis in any organ or tissue
- ▶ Subacute onset; fever, constitutional symptoms rare.
- ▶ Diagnostic histopathology.

General Considerations

IgG₄-related disease is a systemic disorder of unknown cause marked by highly characteristic fibroinflammation that contains IgG₄ plasma cells and can infiltrate virtually any organ. Elevations of serum IgG₄ levels occur often but are not diagnostic. The disorder chiefly affects men over the age of 50 years.

Clinical Findings

A. Symptoms and Signs

IgG₄-related disease can affect any organ of the body, can be localized or generalized, demonstrates the same distinctive histopathology at all sites of involvement, produces protean manifestations depending on location and extent of involvement, and causes disease that ranges in severity from asymptomatic to organ- or life-threatening. The inflammatory infiltration in IgG₄-related disease frequently produces tumefactive masses that can be found during physical examination or on imaging. Some of the common presenting manifestations include enlargement of submandibular glands, proptosis from periorbital infiltration, retroperitoneal fibrosis, mediastinal fibrosis, inflammatory aortic aneurysm, and pancreatic mass with autoimmune pancreatitis. IgG₄-related disease can also affect the thyroid (formerly Riedel thyroiditis), kidney, meninges, pituitary, sinuses, lung, prostate, breast, and bone. Most symptomatic patients with IgG₄-related disease present subacutely; fever and constitutional symptoms are usually absent. Nearly half of the patients with IgG₄-related disease also have allergic disorders such as sinusitis or asthma.

B. Laboratory Findings

The infiltrating lesions in IgG₄-related disease often produce tumors or fibrotic changes that are evident on CT or MRI imaging. However, the cornerstone of diagnosis is histopathology. The key pathological findings are a dense

lymphoplasmacytic infiltrate rich in IgG₄ plasma cells, storiform (matted and irregularly whorled) fibrosis, and obliterative phlebitis. Serum IgG₄ levels are usually, but not invariably, elevated so this finding cannot be used as the sole diagnostic criterion.

Differential Diagnosis

IgG₄-related disease can mimic many disorders including sarcoidosis, Sjögren syndrome (lacrimal gland enlargement), pancreatic cancer (pancreatic mass), chronic infections (eg, HIV, hepatitis C), and granulomatosis with polyangiitis (proptosis). Some cases of retroperitoneal fibrosis and mediastinal fibrosis are caused by IgG₄-related disease. Lymphoma can mimic some of the histopathologic features of IgG₄-related disease.

Treatment & Prognosis

Patients who are asymptomatic and have no organ-threatening disease can be monitored carefully. Spontaneous resolution can occur. Initial therapy is usually oral prednisone 0.6 mg/kg/day, tapered over weeks or months depending on response. Given that corticosteroid monotherapy may fail to control the disease and can cause significant long-term toxicity, immunosuppressants, such as rituximab, mycophenolate mofetil, or azathioprine, are often used. The degree of fibrosis in affected organs determines the patient's responsiveness to treatment.

When to Refer

- Presence of systemic symptoms or signs.
- Symptoms or signs not responsive to prednisone.

When to Admit

Presence of severe systemic signs unresponsive to outpatient management.

Lu H et al. Differences in clinical characteristics of IgG₄-related disease across age groups: a prospective study of 737 patients. *Rheumatology (Oxford)*. 2020. [Epub ahead of print] [PMID: 33211878]

Wallace ZS et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG₄-related disease. *Arthritis Rheumatol*. 2020;72:7. [PMID: 31793250]

Zhang W et al. Management of IgG₄-related disease. *Lancet Rheumatol*. 2019;1:e55. [https://doi.org/10.1016/S2665-9913\(19\)30017](https://doi.org/10.1016/S2665-9913(19)30017).

VASCULITIS SYNDROMES

"Vasculitis" is a heterogeneous group of disorders characterized by inflammation within the walls of affected blood vessels. The major forms of primary systemic vasculitis are listed in Table 20–11. The first consideration in classifying cases of vasculitis is the size of the major vessels involved: large, medium, or small. The presence of the clinical signs and symptoms shown in Table 20–12 helps distinguish among these three groups. After determining the size of

Table 20–11. Classification scheme of primary vasculitides according to size of predominant blood vessels involved.

Predominantly large-vessel vasculitides

Takayasu arteritis
Giant cell arteritis (temporal arteritis)
Behçet disease¹

Predominantly medium-vessel vasculitides

Polyarteritis nodosa
Buerger disease
Primary angiitis of the central nervous system

Predominantly small-vessel vasculitides

Cutaneous leukocytoclastic angiitis ("hypersensitivity vasculitis")
Immune-complex mediated
IgA vasculitis (Henoch-Schönlein purpura)
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
Essential cryoglobulinemia²
"ANCA-associated" vasculitis³
Granulomatosis with polyangiitis²
Microscopic polyangiitis²
Eosinophilic granulomatosis with polyangiitis²

¹May involve small-, medium-, and large-sized blood vessels.

²Frequent overlap of small- and medium-sized blood vessel involvement.

³Not all forms of these disorders are always associated with ANCA. ANCA, antineutrophil cytoplasmic antibodies.

the major vessels involved, other issues that contribute to the classification include the following:

- Does the process involve arteries, veins, or both?
- What are the patient's demographic characteristics (age, sex, ethnicity, cigarette smoking status)?
- Which organs are involved?
- Is there hypocomplementemia or other evidence of immune complex deposition?

Table 20–12. Typical clinical manifestations of large-, medium-, and small-vessel vasculitis.

Large Vessel	Medium vessel	Small vessel
Fever, weight loss, malaise, arthralgias/ arthritis	Fever, weight loss, malaise, arthralgias/ arthritis	Fever, weight loss, malaise, arthralgias/ arthritis
Limb claudication	Cutaneous nodules	Purpura
Asymmetric blood pressures	Ulcers	Vesiculobullous lesions
Absence of pulses	Livedo reticularis	Urticaria
Bruits	Digital gangrene	Glomerulonephritis
Aortic dilation	Mononeuritis multiplex	Alveolar hemorrhage
	Microaneurysms	Cutaneous extravascular necrotizing granulomas
		Splinter hemorrhages
		Uveitis
		Episcleritis
		Scleritis

- Is there granulomatous inflammation on tissue biopsy?
- Are antineutrophil cytoplasmic antibodies (ANCA) present?

In addition to the disorders considered to be primary vasculitides, there are also multiple forms of vasculitis that are associated with other known underlying conditions. These “secondary” forms of vasculitis occur in the setting of chronic infections (eg, hepatitis B or C, subacute bacterial endocarditis), connective tissue disorders, inflammatory bowel disease, malignancies, and reactions to medications. Only the major primary forms of vasculitis are discussed here.

Felicetti M et al. One year in review 2020: vasculitis. *Clin Exp Rheumatol*. 2020;38:3. [PMID: 32359039]

POLYMYALGIA RHEUMATICA & GIANT CELL ARTERITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Age over 50 years.
- ▶ Markedly elevated ESR and CRP.
- ▶ **Polymyalgia rheumatica:** pain and stiffness in shoulders and hips lasting for several weeks without other explanation.
- ▶ **Giant cell arteritis:** headache, jaw claudication, polymyalgia rheumatica; without treatment, permanent blindness may occur.

► General Considerations

Polymyalgia rheumatica and giant cell arteritis probably represent a spectrum of one disease. Both affect the same population (patients over the age of 50), and the incidence of the disease increases with each decade of life. Both show preference for the same HLA haplotypes, and show similar patterns of cytokines in blood and arteries. Giant cell arteritis is a systemic panarteritis affecting medium-sized and large vessels. Giant cell arteritis was previously called temporal arteritis because the temporal artery is frequently involved, as are other extracranial branches of the carotid artery. However, the aorta and its major branches may be involved in giant cell arteritis as well. Polymyalgia rheumatica and giant cell arteritis frequently coexist. The important differences between the two conditions are that polymyalgia rheumatica alone is not a systemic vasculitis, does not cause blindness, and responds to low-dose (10–20 mg/day orally) prednisone; giant cell arteritis can cause blindness, aortitis, and large artery complications which requires high-dose (40–60 mg/day) prednisone.

► Clinical Findings

A. Polymyalgia Rheumatica

Polymyalgia rheumatica is a clinical diagnosis based on pain and stiffness of the shoulder and pelvic girdle areas,

frequently in association with fever, malaise, and weight loss. In approximately two-thirds of cases, polymyalgia occurs in the absence of giant cell arteritis. Because of the stiffness and pain in the shoulders, hips, and lower back, patients have trouble combing their hair, putting on a coat, or rising from a chair. In contrast to polymyositis and polyarteritis nodosa, polymyalgia rheumatica does not cause muscular weakness either through primary muscle inflammation or secondary to nerve infarction.

B. Giant Cell Arteritis

The mean age at onset is approximately 79 years. About 50% of patients with giant cell arteritis also have polymyalgia rheumatica. The classic symptoms suggesting that a patient has arteritis are headache, scalp tenderness, visual symptoms (particularly amaurosis fugax or diplopia), jaw claudication, or throat pain. Of these symptoms, jaw claudication has the highest positive predictive value. The temporal artery can be normal on physical examination but may be nodular, enlarged, tender, or pulseless. Blindness usually results from anterior ischemic optic neuropathy, caused by occlusive arteritis of the posterior ciliary branch of the ophthalmic artery. The ischemic optic neuropathy of giant cell arteritis may produce no fundoscopic findings for the first 24–48 hours after the onset of blindness.

Asymmetry of pulses in the arms, a murmur of aortic regurgitation, or bruits heard near the clavicle resulting from subclavian artery stenoses identify patients in whom giant cell arteritis has affected the aorta or its major branches. Clinically evident large vessel involvement—characterized chiefly by aneurysm of the thoracic aorta or stenosis of the subclavian, vertebral, carotid, and basilar arteries—occurs in approximately 25% of patients with giant cell arteritis, sometimes years after the diagnosis. Subclinical large artery disease is the rule; positron emission tomography scans reveal inflammation in the aorta and its major branches in nearly 85% of untreated patients. Forty percent of patients with giant cell arteritis have nonclassical symptoms at presentation, including large artery involvement causing chiefly aortic regurgitation or arm claudication, respiratory tract problems (most frequently dry cough), mononeuritis multiplex (most frequently with painful paralysis of a shoulder), or fever of unknown origin. Giant cell arteritis accounts for 15% of all cases of fever of unknown origin in patients over the age of 65. The fever can be as high as 40°C and is frequently associated with rigors and sweats. Thus, in an older patient with fever of unknown origin and marked elevations of acute-phase reactants in the absence of an infectious source, giant cell arteritis must be considered even in the absence of specific features such as headache or jaw claudication. In some cases, instead of having the well-known symptom of jaw claudication, patients complain of vague pain affecting other locations, including the tongue, nose, or ears. Indeed, unexplained head or neck pain in an older patient may signal the presence of giant cell arteritis.

C. Laboratory Findings

1. Polymyalgia rheumatica—Anemia and elevated acute-phase reactants (generally ESR higher than 30 mm/h and CRP more than 0.5 mg/dL) are present universally.

2. Giant cell arteritis—Nearly 90% of patients with giant cell arteritis have ESRs higher than 50 mm/h. The ESR in this disorder is often more than 100 mm/h, but cases in which the ESR is lower or even normal do occur. In one series, 5% of patients with biopsy-proven giant cell arteritis had ESRs below 40 mm/h. Although the CRP is slightly more sensitive, patients with biopsy-proven giant cell arteritis with normal CRP have also been described. Most patients also have a mild normochromic, normocytic anemia and thrombocytosis. The alkaline phosphatase (liver source) is elevated in 20% of patients with giant cell arteritis.

► Differential Diagnosis

The differential diagnosis of malaise, anemia, and striking acute-phase reactant elevations includes rheumatic diseases (such as rheumatoid arthritis or systemic vasculitides), plasma cell myeloma, other malignant disorders, and chronic infections (such as bacterial endocarditis and osteomyelitis).

► Treatment

A. Polymyalgia Rheumatica

Patients with isolated polymyalgia rheumatica (ie, those not having “above the neck” symptoms of headache, jaw claudication, scalp tenderness, or visual symptoms) are treated with prednisone, 10–20 mg/day orally. If the patient does not experience a dramatic improvement within 72 hours, the diagnosis should be revisited. Usually after 2–4 weeks of treatment, slow tapering of prednisone can be attempted. Most patients require some dose of prednisone for a minimum of approximately 1 year; 6 months is too short in most cases. Care must be taken to prevent corticosteroid side effects (Table 26–16). Disease flares are common (50% or more) as prednisone is tapered, which may necessitate increasing prednisone. Tapering of prednisone should be based on symptoms and not solely on laboratory values because the ESR can fluctuate and it is not specific for polymyalgia rheumatica disease activity. The addition of weekly methotrexate may increase the chance of successfully tapering prednisone in some patients.

B. Giant Cell Arteritis

The urgency of early diagnosis and treatment in giant cell arteritis relates to the prevention of blindness. Once blindness develops, it is usually permanent. Therefore, when a patient has symptoms and findings suggestive of cranial involvement from giant cell arteritis, therapy with prednisone (1 mg/kg/daily or 60 mg/day orally) should be initiated immediately, and a temporal artery biopsy performed promptly thereafter. For patients who seek medical attention for visual loss, intravenous pulse methylprednisolone (eg, 1 g daily for 3 days) has been advocated; unfortunately, few patients recover vision no matter what the initial treatment. Although it is prudent to obtain a temporal artery biopsy as soon as possible after instituting treatment, diagnostic findings of giant cell arteritis may still be present 2 weeks (or even considerably longer) after starting corticosteroids.

Typically, a positive biopsy shows inflammatory infiltrate in the media and adventitia with lymphocytes, histiocytes, plasma cells, and giant cells. An adequate biopsy specimen is essential (at least 2 cm in length is ideal), because the disease may be segmental. Unilateral temporal artery biopsies are positive in approximately 80–85% of patients, but bilateral biopsies add incrementally to the yield (10–15% in some studies, less in others). The presence of a “halo sign” on temporal artery ultrasonography may obviate the need for temporal artery biopsy, although biopsy remains the gold standard for giant cell arteritis diagnosis. Temporal artery biopsy is abnormal in only 50% of patients with *large artery* giant cell arteritis. In these patients, magnetic resonance angiography or CT angiography will establish the diagnosis by demonstrating long stretches of narrowing, thickening, or aneurysmal dilation of the aorta, subclavian and/or axillary arteries. Thoracic aortic aneurysms occur 17 times more frequently in patients with giant cell arteritis than in normal individuals and can result in aortic regurgitation, dissection, or rupture. The aneurysms can develop at any time but typically occur 7 years after the diagnosis of giant cell arteritis is made; hence, routine screening for this complication is recommended.

Prednisone should be continued in a dosage of 60 mg/day orally for about 1 month before tapering. After 1 month of high-dose prednisone, almost all patients will have a normal ESR. When tapering and adjusting the dosage of prednisone, the ESR (or CRP) is a useful, but not absolute, guide to disease activity. A common error is treating the ESR rather than the patient. The ESR often rises slightly as the prednisone is tapered, even as the disease remains quiescent. Because elderly individuals often have baseline ESRs that are above the normal range, mild ESR elevations should not be an occasion for renewed treatment with prednisone in patients who are asymptomatic. Tocilizumab, an inhibitor of the IL-6 receptor, is FDA approved for giant cell arteritis and can reduce the prolonged use of prednisone and decrease the risk of disease flare. Clinical trials demonstrate that patients with new or relapsing giant cell arteritis with cranial and/or large vessel involvement treated initially with both tocilizumab and prednisone can taper off of prednisone more rapidly and successfully than patients treated with prednisone alone. After 1 year of treatment, tocilizumab achieves corticosteroid-free remission in approximately 50% of patients. Methotrexate has been less promising; it was modestly effective in one double-blind, placebo-controlled treatment trial but ineffective in another.

Calderón-Goercke M et al. Tocilizumab in giant cell arteritis: differences between the GiACTA trial and a multicentre series of patients from the clinical practice. *Clin Exp Rheumatol*. 2020;38:112. [PMID: 32441643]

Hellmich B et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2020;79:19. [PMID: 31270110]

Schmidt WA et al. Imaging in large-vessel vasculitis. *Best Pract Res Clin Rheumatol*. 2020;34:101589. [PMID: 32948434]

Serling-Boyd N et al. Recent advances in the diagnosis and management of giant cell arteritis. *Curr Opin Rheumatol*. 2020;32:201. [PMID: 32168069]

TAKAYASU ARTERITIS

Takayasu arteritis is a granulomatous vasculitis of the aorta and its major branches. Rare in North America but more prevalent in the Far East, it primarily affects women and typically has its onset in early adulthood. Takayasu arteritis can present with nonspecific constitutional symptoms of malaise, fever, and weight loss or with manifestations of vascular inflammation and damage: diminished pulses, unequal blood pressures in the arms, carotidynia (tenderness over the carotid arteries), bruits over carotid and subclavian arteries, retinopathy, limb claudication, and hypertension. There are no specific laboratory abnormalities; the ESR and the CRP level are elevated in most cases. The diagnosis is established by imaging studies, usually MRI, which can detect inflammatory thickening of the walls of affected vessels, or CT angiography, which can provide images of the stenoses, occlusions, and dilations characteristic of arteritis. Corticosteroids (eg, oral prednisone, 1 mg/kg for 1 month, followed by a taper over several months to 10 mg daily) are the mainstays of treatment. The addition of methotrexate, azathioprine, or mycophenolate mofetil to prednisone may be more effective than the prednisone alone. Case series suggest that biologic therapy with either inhibitors of TNF (eg, infliximab) or the IL-6 receptor (tocilizumab) may be effective for patients refractory to prednisone. Takayasu arteritis has a chronic relapsing and remitting course that requires ongoing monitoring and adjustment of therapy.

Gribbons KB et al. Patterns of arterial disease in Takayasu arteritis and giant cell arteritis. *Arthritis Care Res (Hoboken)*. 2020;72:1615. [PMID: 31444857]

Michailidou D et al. Clinical symptoms and associated vascular imaging findings in Takayasu's arteritis compared to giant cell arteritis. *Ann Rheum Dis*. 2020;79:262. [PMID: 31649025]

POLYARTERITIS NODOSA



ESSENTIALS OF DIAGNOSIS

- ▶ Medium-sized arteries are affected.
- ▶ Clinical findings depend on the arteries involved; lungs are spared.
- ▶ Common features include fever, abdominal pain, extremity pain, livedo reticularis, mononeuritis multiplex.
- ▶ Kidney involvement causes renin-mediated hypertension.
- ▶ Anemia and elevated acute-phase reactants (ESR or CRP or both).
- ▶ Associated with hepatitis B (10% of cases).

► General Considerations

Polyarteritis nodosa is a necrotizing arteritis of medium-sized vessels that has a predilection for involving the skin,

peripheral nerves, mesenteric vessels (including renal arteries), heart, and brain but spares the lungs. Polyarteritis nodosa is relatively rare, with a prevalence of about 30 per 1 million people. Approximately 10% of cases of polyarteritis nodosa are caused by hepatitis B. Most cases of hepatitis B-associated disease occur within 6 months of hepatitis B infection. Mutations in the gene for adenosine deaminase 2 have been identified in early-onset familial polyarteritis.

► Clinical Findings

A. Symptoms and Signs

The clinical onset is usually insidious, with fever, malaise, weight loss, and other symptoms developing over weeks to months. Pain in the extremities is often a prominent early feature caused by arthralgia, myalgia (particularly affecting the calves), or neuropathy. The combination of mononeuritis multiplex (with the most common finding being foot-drop) and features of a systemic illness is one of the earliest specific clues to the presence of an underlying vasculitis. Polyarteritis nodosa is among the forms of vasculitis most commonly associated with vasculitic neuropathy.

In polyarteritis nodosa, the typical skin findings—livedo reticularis, subcutaneous nodules, and skin ulcers—reflect the involvement of deeper, medium-sized blood vessels. Digital gangrene is common. The most common cutaneous presentation is lower extremity ulcerations, usually occurring near the malleoli. Involvement of the renal arteries leads to a renin-mediated hypertension (much less characteristic of vasculitides involving smaller blood vessels). For unclear reasons, classic polyarteritis nodosa seldom (if ever) involves the lung, with the occasional exception of the bronchial arteries.

Abdominal pain—particularly diffuse periumbilical pain precipitated by eating—is common but often difficult to attribute to mesenteric vasculitis in the early stages. Nausea and vomiting are common symptoms. Infarction compromises the function of major viscera and may lead to acalculous cholecystitis or appendicitis. Some patients present dramatically with an acute abdomen caused by mesenteric vasculitis and gut perforation or with hypotension resulting from rupture of a microaneurysm in the liver, kidney, or bowel.

Newly acquired hypertension from renin-mediated kidney disease frequently occurs. Subclinical cardiac involvement is common in polyarteritis nodosa, and overt cardiac dysfunction occasionally occurs (eg, myocardial infarction secondary to coronary vasculitis, or myocarditis).

B. Laboratory Findings

Most patients with polyarteritis nodosa have anemia, and leukocytosis is common. Acute-phase reactants are often (but not always) strikingly elevated. A major challenge in making the diagnosis of polyarteritis nodosa, however, is the absence of a disease-specific serologic test (eg, an autoantibody). Patients with classic polyarteritis nodosa are ANCA-negative but may have low titers of rheumatoid factor or antinuclear antibodies, both of which are nonspecific findings. Tests for active hepatitis B infection (HBsAg, HBeAg, hepatitis B viral load) should be performed.

Patients with childhood onset of polyarteritis nodosa should undergo genetic evaluation for mutations in the genes for adenosine deaminase 2.

C. Biopsy and Angiography

The diagnosis of polyarteritis nodosa requires confirmation with either a tissue biopsy or an angiogram. Biopsies of symptomatic sites such as skin (from the edge of an ulcer or the center of a nodule), nerve, or muscle have sensitivities of approximately 70%. The least invasive tests should usually be obtained first, but biopsy of an involved organ is essential. If performed by experienced clinicians, tissue biopsies normally have high benefit-risk ratios because of the importance of establishing the diagnosis. Patients in whom polyarteritis nodosa is suspected—eg, on the basis of mesenteric ischemia or new-onset hypertension occurring in the setting of a systemic illness—may be diagnosed by the angiographic finding of aneurysmal dilations in the renal, mesenteric, or hepatic arteries.

► Differential Diagnosis

Genetic collagen vascular disorders (such as Ehlers-Danlos and Loey-Dietz syndromes), fibromuscular dysplasia, and segmental arterial mediolysis should be considered when imaging findings suggest polyarteritis nodosa in the absence of other clinical features of the disorder.

► Treatment

For polyarteritis nodosa, corticosteroids in high doses (up to 60 mg of oral prednisone daily) may control fever and constitutional symptoms and heal vascular lesions. Pulse methylprednisolone (eg, 1 g intravenously daily for 3 days) may be necessary for patients who are critically ill at presentation. The addition of cyclophosphamide lowers the risk of disease-related death and morbidity among patients who have severe disease. Methotrexate or azathioprine are used to maintain remissions induced by cyclophosphamide. For patients with polyarteritis nodosa associated with hepatitis B, the preferred treatment regimen is a short course of prednisone accompanied by anti-HBV therapy and plasmapheresis (three times a week for up to 6 weeks). Inhibitors of TNF are first-line therapy for the polyarteritis associated with deficiency of adenosine deaminase 2.

► Prognosis

Without treatment, the 5-year survival rate in this disorder is about 10%. With appropriate therapy, remissions are possible in many cases and the 5-year survival rate has improved to 60–90%. Poor prognostic factors are CKD with serum creatinine greater than 1.6 mg/dL (141 μmol/L), proteinuria greater than 1 g/day, gastrointestinal ischemia, central nervous system disease, and cardiac involvement. In the absence of any of these five factors, 5-year survival is nearly 90%. Survival at 5 years drops to 75% with one poor prognostic factor present and to about 50% with two or more factors. Substantial morbidity and even death may result from adverse effects of cyclophosphamide and corticosteroids (Table 26–16).

Consequently, these therapies require careful monitoring and expert management. In contrast to many other forms of systemic vasculitis, disease relapses in polyarteritis following the successful induction of remission occur in only about 20% of cases.

Huang Z et al. Polyarteritis nodosa and deficiency of adenosine deaminase 2—shared genealogy, generations apart. *Clin Immunol*. 2020;215:108411. [PMID: 32276138]

Karadag O et al. Polyarteritis nodosa revisited: a review of historical approaches, subphenotypes, and a research agenda. *Clin Exp Rheumatol*. 2018;36:135. [PMID: 29465365]

GRANULOMATOSIS WITH POLYANGIITIS

ESSENTIALS OF DIAGNOSIS

- ▶ Classic triad of upper and lower respiratory tract disease and glomerulonephritis.
- ▶ Suspect if upper respiratory tract symptoms (eg, nasal congestion, sinusitis) are refractory to usual treatment.
- ▶ Kidney disease often rapidly progressive.
- ▶ Venous thromboembolism commonly occurs.
- ▶ ANCA (90% of patients), usually directed against proteinase-3 (but may be directed against myeloperoxidase).
- ▶ Tissue biopsy usually necessary for diagnosis.

► General Considerations

Granulomatosis with polyangiitis, which has an estimated incidence of approximately 12 cases per million individuals per year, is the prototype of diseases associated with anti-neutrophil cytoplasmic antibodies (ANCA). Other “ANCA-associated vasculitides” include microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. Granulomatosis with polyangiitis is a disease of predominantly small arteries. It is characterized in its full expression by vasculitis of small arteries, arterioles, and capillaries, necrotizing granulomatous lesions of both upper and lower respiratory tract, glomerulonephritis, and other organ manifestations. Without treatment, generalized disease is invariably fatal, with most patients surviving less than 1 year after diagnosis. It occurs most commonly in the fourth and fifth decades of life and affects men and women with equal frequency.

► Clinical Findings

A. Symptoms and Signs

The disorder usually develops over 4–12 months. Upper respiratory tract symptoms develop in 90% of patients and lower respiratory tract symptoms develop in 60% of patients; some patients may have both upper and lower respiratory tract symptoms. Upper respiratory tract



▲ Figure 20–7. Scleritis in a patient with granulomatosis with polyangiitis. (Used, with permission, from Everett Allen, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw Hill, 2019.)

symptoms can include nasal congestion, sinusitis, otitis media, mastoiditis, inflammation of the gums, or stridor due to subglottic stenosis. Since many of these symptoms are common, the underlying disease is not often suspected until the patient develops systemic symptoms or the original problem is refractory to treatment. The lungs are affected initially in 40% and eventually in 80%, with symptoms including cough, dyspnea, and hemoptysis. Other early symptoms can include a migratory oligoarthritis with a predilection for large joints; a variety of symptoms related to ocular disease (unilateral proptosis from orbital pseudotumor; red eye from scleritis [Figure 20–7], episcleritis, anterior uveitis, or peripheral ulcerative keratitis); purpura or other skin lesions; and dysesthesia due to neuropathy. Renal involvement, which develops in three-fourths of the cases, may be subclinical until kidney disease is advanced. Fever, malaise, and weight loss are common.

Physical examination can be remarkable for congestion, crusting, ulceration, bleeding, and even perforation of the nasal septum. Destruction of the nasal cartilage with “saddle nose” deformity occurs late. Otitis media, proptosis, scleritis, episcleritis, and conjunctivitis are other common findings. Newly acquired hypertension, a frequent feature of polyarteritis nodosa, is rare in granulomatosis with polyangiitis. Venous thrombotic events (eg, deep venous thrombosis and pulmonary embolism) are a common occurrence in granulomatosis with polyangiitis. Although limited forms of granulomatosis with polyangiitis have been described in which the kidney is spared initially, kidney disease will develop in the majority of untreated patients.

B. Laboratory Findings

1. Serum tests and urinalysis—Most patients have an anemia, mild leukocytosis, and elevated acute-phase reactants. If there is kidney involvement, proteinuria occurs and the

urinary sediment contains red cells, and often has red cell casts.

Serum tests for ANCA help in the diagnosis of granulomatosis with polyangiitis and related forms of vasculitis (Table 20–7). Several different types of ANCA are recognized, but the two subtypes relevant to systemic vasculitis are those directed against proteinase-3 (PR3) and myeloperoxidase (MPO). Antibodies to these two antigens are termed “PR3-ANCA” and “MPO-ANCA,” respectively. The cytoplasmic pattern of immunofluorescence (c-ANCA) caused by PR3-ANCA has a high specificity (more than 90%) for either granulomatosis with polyangiitis or a closely related disease, microscopic polyangiitis (or, less commonly, eosinophilic granulomatosis with polyangiitis). In the setting of active disease, particularly cases in which the disease is severe and generalized to multiple organ systems, the sensitivity of PR3-ANCA is greater than 95%. A substantial percentage of patients with “limited” granulomatosis with polyangiitis—disease that does not pose an immediate threat to life and is often confined to the respiratory tract—are ANCA-negative. Furthermore, ANCA levels correlate erratically with disease activity, and changes in titer should not dictate changes in therapy in the absence of supporting clinical data. The perinuclear (p-ANCA) pattern, caused by MPO-ANCA, is more likely to occur in microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis but may also be found in granulomatosis with polyangiitis. Approximately 10–25% of patients with classic granulomatosis with polyangiitis have MPO-ANCA. All positive immunofluorescence assays for ANCA should be confirmed by enzyme immunoassays for the specific autoantibodies directed against PR3 or MPO.

2. Histologic findings—Although ANCA testing may be helpful when used properly, there remains the need in most cases for confirmation of the diagnosis by tissue biopsy. Histologic features of granulomatosis with polyangiitis include vasculitis, granulomatous inflammation, geographic necrosis, and acute and chronic inflammation. The full range of pathologic changes is usually evident only on thoracoscopic lung biopsy; granulomas, observed only rarely in kidney biopsy specimens, are found much more commonly on lung biopsy specimens. Nasal biopsies often do not show vasculitis but may show chronic inflammation and other changes which rule out nasopharyngeal cancer or infection. Kidney biopsy discloses a segmental necrotizing glomerulonephritis with multiple crescents; this is characteristic but not diagnostic. Pathologists characterize the kidney lesion of granulomatosis with polyangiitis (and other forms of “ANCA-associated vasculitis”) as a pauci-immune glomerulonephritis because of the relative absence (compared with immune complex-mediated disorders) of IgG, IgM, IgA, and complement proteins within glomeruli.

C. Imaging

Chest CT is more sensitive than chest radiography; lesions include infiltrates, nodules, masses, and cavities. Pleural effusions are uncommon. Often the radiographs prompt concern about lung cancer. Hilar adenopathy large enough

to be evident on chest film is unusual in granulomatosis with polyangiitis; if present, sarcoidosis, tumor, or infection is more likely. Other common radiographic abnormalities include extensive sinusitis and even bony sinus erosions.

► Differential Diagnosis

In most patients with granulomatosis with polyangiitis, refractory sinusitis or otitis media is initially suspected. When upper respiratory tract inflammation persists and is accompanied by additional systemic inflammatory signs (eg, red eye from scleritis, joint pain, and swelling), the diagnosis of granulomatosis with polyangiitis should be considered. Initial complaints of joint pain can lead to a misdiagnosis of rheumatoid arthritis. Arriving at the correct diagnosis is aided by awareness that rheumatoid arthritis typically involves small joints of the hand, whereas granulomatosis with polyangiitis favors large joints, such as the hip, knee, elbow, and shoulder. Lung cancer may be the first diagnostic consideration for some middle-aged patients in whom cough, hemoptysis, and lung masses are presenting symptoms and signs; typically, evidence of glomerulonephritis, a positive ANCA or, ultimately, the lung biopsy findings will point to the proper diagnosis. Granulomatosis with polyangiitis shares with SLE, anti-glomerular basement membrane disease, and microscopic polyangiitis the ability to cause an acute pulmonary-renal syndrome. Approximately 10–25% of patients with classic granulomatosis with polyangiitis have MPO-ANCA. Owing to involvement of the same types of blood vessels, similar patterns of organ involvement, and the possibility of failing to identify granulomatous pathology on tissue biopsies because of sampling error, granulomatosis with polyangiitis is often difficult to differentiate from microscopic polyangiitis. The crucial distinctions between the two disorders are the tendencies for granulomatosis with polyangiitis to involve the upper respiratory tract (including the ears) and to cause granulomatous inflammation. Cocaine use can cause destruction of midline tissues—the nose and palate—that mimics granulomatosis with polyangiitis. Indeed, distinguishing between the two conditions can be challenging because patients with cocaine-mediated midline destructive disease frequently have positive tests for PR-3-ANCA and lesional biopsies that demonstrate vasculitis. In contrast to granulomatosis with polyangiitis, cocaine-mediated midline destructive disease does not cause pulmonary or kidney disease. IgG₄-related disease may mimic some of the manifestations of granulomatosis with polyangiitis.

► Treatment

Early treatment is crucial in preventing the devastating end-organ complications of this disease, and often in preserving life. While granulomatosis with polyangiitis may involve the sinuses or lung for months, once proteinuria or hematuria develops, progression to advanced CKD can be rapid (over several weeks). Current practice divides treatment into two phases: induction of remission and maintenance of remission. Choice of induction therapy is dictated by whether the patient has mild disease (ie, no significant

kidney dysfunction or immediately life-threatening disease) or severe disease (ie, life- or organ-threatening disease such as rapidly progressive glomerulonephritis or pulmonary hemorrhage). Plasma exchange does not reduce the incidence of end-stage kidney disease or death in severe ANCA-associated vasculitis.

A. Induction of Remission

For patients with severe disease, the treatment options for inducing remission are corticosteroids plus either rituximab or cyclophosphamide. Although the standard induction regimen of corticosteroids in ANCA-associated vasculitis is 1 mg/kg orally daily, regimens with faster corticosteroid dose reductions have demonstrated equal efficacy with fewer corticosteroid-related complications, such as infections.

1. Rituximab plus prednisone—Rituximab, a B-cell-depleting antibody, is FDA approved in combination with corticosteroids (prednisone 1 mg/kg orally daily) for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis. Studies demonstrate that rituximab is as effective as cyclophosphamide for remission induction in these conditions. Indeed, post-hoc analysis of one clinical trial demonstrated that rituximab is more effective than cyclophosphamide for treating relapses of granulomatosis with polyangiitis and microscopic polyangiitis.

2. Cyclophosphamide and prednisone—Remissions can be induced in more than 90% of patients treated with prednisone (1 mg/kg daily) plus cyclophosphamide (2 mg/kg/day orally with adjustments required for acute or CKD and patients over age 70). Intermittent high-dose intravenous cyclophosphamide is associated with a higher relapse risk compared to daily oral cyclophosphamide, but there is no increase in mortality or long-term morbidity. To minimize toxicity, patients are treated with cyclophosphamide for only 3–6 months; once remission is achieved, the patient is switched to a non-cyclophosphamide maintenance regimen.

Both rituximab and cyclophosphamide increase the risk of developing life-threatening opportunistic infections (including progressive multifocal leukoencephalopathy [PML]). *Whenever cyclophosphamide or rituximab is used, Pneumocystis jirovecii prophylaxis with single-strength oral trimethoprim-sulfamethoxazole daily is essential.*

B. Maintenance of Remission

Options for maintaining remission in patients with normal or near normal kidney function after rituximab or cyclophosphamide induction include azathioprine (up to 2 mg/kg/day orally), methotrexate (20–25 mg/wk administered either orally or intramuscularly), or rituximab (500 mg administered intravenously when remission is achieved, repeated in 14 days, then repeated as a single dose approximately every 6 months). Mycophenolate mofetil is an option for maintenance remission if there are intolerances or failure of other regimens. Methotrexate should not be used in patients with kidney dysfunction. One randomized, controlled trial comparing rituximab and azathioprine for maintenance of remission showed that the

risk of relapse over 28 months was 5% with rituximab and 29% with azathioprine. After 60 months of follow-up, the patients treated with rituximab maintenance had significantly longer relapse-free survival rates and overall better survival.

Because of its superior side-effect profile, methotrexate is viewed as an appropriate substitute for cyclophosphamide or rituximab for initial and maintenance treatment in patients who have mild disease (usually defined as mild sinonasal or skin disease, or both) and normal kidney function.

Charles P et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med.* 2020;173:179. [PMID: 32479166]

Merkel PA et al. Long-term safety of rituximab in granulomatosis with polyangiitis or microscopic polyangiitis. *Arthritis Care Res (Hoboken).* 2020. [Epub ahead of print] [PMID: 32475029]

Walsh M et al; PEXIVAS Investigators. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med.* 2020;382:622. [PMID: 32053298]

MICROSCOPIC POLYANGIITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Necrotizing vasculitis of small- and medium-sized arteries and veins.
- ▶ Most common cause of pulmonary-renal syndrome (diffuse alveolar hemorrhage and glomerulonephritis).
- ▶ ANCA in 75% of cases.

General Considerations

Microscopic polyangiitis is a pauci-immune nongranulomatous necrotizing vasculitis that (1) affects small blood vessels (capillaries, venules, or arterioles), (2) often causes glomerulonephritis and pulmonary capillaritis, and (3) is often associated with ANCA on immunofluorescence testing (directed against MPO, a constituent of neutrophil granules). Because microscopic polyangiitis may involve medium-sized as well as small blood vessels and because it tends to affect capillaries within the lungs and kidneys, its spectrum overlaps those of both polyarteritis nodosa and granulomatosis with polyangiitis.

In rare instances, medications, particularly propylthiouracil, hydralazine, allopurinol, penicillamine, minocycline, and sulfasalazine, induce a systemic vasculitis associated with high titers of p-ANCA and features of microscopic polyangiitis.

Clinical Findings

A. Symptoms and Signs

A wide variety of findings suggesting vasculitis of small blood vessels may develop in microscopic polyangiitis. These include “palpable” (or “raised”) purpura and other

signs of cutaneous vasculitis (ulcers, splinter hemorrhages, vesiculobullous lesions).

Microscopic polyangiitis is the most common cause of pulmonary-renal syndromes, being several times more common than anti-glomerular basement membrane disease. Pulmonary hemorrhage may occur with pathologic findings typically of capillaritis. Interstitial lung fibrosis that mimics usual interstitial pneumonitis may be part of the presenting condition and conveys a poor prognosis.

Vasculitic neuropathy (mononeuritis multiplex) is also common in microscopic polyangiitis.

B. Laboratory Findings

Three-fourths of patients with microscopic polyangiitis are ANCA-positive, usually with anti-myeloperoxidase antibodies (MPO-ANCA) that cause a p-ANCA pattern on immunofluorescence testing. ANCA directed against proteinase-3 (PR3-ANCA) can also be observed.

Elevated acute-phase reactants are typical of active disease. Microscopic hematuria, proteinuria, and red blood cell casts in the urine may occur. The kidney lesion is a segmental, necrotizing glomerulonephritis, often with localized intravascular coagulation and the observation of intraglomerular thrombi upon renal biopsy.

Differential Diagnosis

Distinguishing this disease from granulomatosis with polyangiitis may be challenging. Microscopic polyangiitis is not associated with the chronic destructive upper respiratory tract disease often found in granulomatosis with polyangiitis. Moreover, as noted, a critical difference between the two diseases is the absence of granulomatous inflammation in microscopic polyangiitis. Because their treatments may differ, microscopic polyangiitis must also be differentiated from polyarteritis nodosa.

Treatment

Microscopic polyangiitis is usually treated in the same way as granulomatosis with polyangiitis: patients with severe disease, typically involving pulmonary hemorrhage and glomerulonephritis, require urgent induction treatment with corticosteroids and either cyclophosphamide or rituximab. If cyclophosphamide is chosen, it may be administered either in an oral daily regimen or via intermittent (usually monthly) intravenous pulses; following successful induction of remission, treatment should be continued with azathioprine, rituximab, or methotrexate (provided the patient has normal kidney function). In cases of drug-induced MPO-ANCA-associated vasculitis, the offending medication should be discontinued; significant organ involvement (eg, pulmonary hemorrhage, glomerulonephritis) requires immunosuppressive therapy.

Prognosis

The key to effecting good outcomes is early diagnosis. Compared with patients who have granulomatosis with polyangiitis, those who have microscopic polyangiitis are more likely to have significant fibrosis on renal biopsy.

because of later diagnosis. The likelihood of disease recurrence following remission in microscopic polyangiitis is about 33%.

Geetha D et al. ANCA-associated vasculitis: Core Curriculum 2020. *Am J Kidney Dis.* 2020;75:124. [PMID: 31358311]

Nguyen Y et al. Microscopic polyangiitis: clinical characteristics and long-term outcomes of 378 patients from the French Vasculitis Study Group Registry. *J Autoimmun.* 2020;112:102467. [PMID: 32340774]

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Eosinophilic granulomatosis with polyangiitis (previously called Churg-Strauss syndrome) is an ANCA-associated vasculitis (along with granulomatosis with polyangiitis and microscopic polyangiitis), although the presence of ANCA occurs in less than 50% of patients (usually anti-MPO). It is characterized by peripheral eosinophilia, sinusitis with polypsis, asthma, lung infiltrates, vasculitic skin involvement, glomerulonephritis, and vasculitic neuropathy. Myocarditis can lead to arrhythmias and heart failure if untreated. Eosinophilic granulomatosis with polyangiitis should be considered in patients with an unexplained peripheral eosinophilia and vasculitic features. Laboratory examination of unexplained eosinophilia should include obtaining ANCA and serum tryptase peripheral flow cytometry for PDGF receptor abnormalities and testing for helminthic infections. Eosinophilic infiltrates on tissue samples strongly suggest the diagnosis of eosinophilic granulomatosis, especially if accompanied by vasculitis (purpura, glomerulonephritis, vasculitic ulcers, mononeuritis multiplex). Corticosteroids remain first-line treatment with azathioprine and methotrexate demonstrating efficacy for mild to moderate disease. Mepolizumab, an IL-5 inhibitor, is FDA approved for the treatment of eosinophilic granulomatosis with polyangiitis, although it has not been studied for severe life- or organ-threatening vasculitic disease manifestations (which generally require cyclophosphamide).

Canzian A et al. Use of biologics to treat relapsing and/or refractory eosinophilic granulomatosis with polyangiitis: data from a European collaborative study. *Arthritis Rheumatol.* 2021; 73:498. [PMID: 33001543]

LEVAMISOLE-ASSOCIATED PURPURA

Exposure to levamisole, a prevalent adulterant of illicit cocaine in North America, can induce a distinctive clinical syndrome of retiform purpura and cutaneous necrosis affecting the extremities, ears, and skin overlying the zygomatic arch. Biopsies reveal widespread thrombosis of small cutaneous vessels with varying degrees of vasculitis. The syndrome is associated with the lupus anticoagulant, IgM antibodies to cardiolipin, and very high titers of p-ANCA (due to autoantibodies to elastase, lactoferrin, cathepsin-G, and other neutrophil components rather than to myeloperoxidase alone). There is no consensus on treatment of levamisole-induced purpura, but early lesions can resolve

with abstinence. Use of levamisole-adulterated cocaine also has been linked to neutropenia, agranulocytosis, and pauci-immune glomerulonephritis. There may be long-term sequelae of levamisole exposure, such as deforming cutaneous lesions, arthralgias, and arthritis.

Dartevel A et al. Levamisole-induced vasculopathy: a systematic review. *Semin Arthritis Rheum.* 2019;48:921. [PMID: 30166200]

Emil NS et al. Atypical chronic inflammatory ANCA-positive deforming arthritis after cocaine-levamisole exposure. *J Clin Rheumatol.* 2020;26:24. [PMID: 30273264]

CRYOGLOBULINEMIA

Cryoglobulinemia can be associated with an immune-complex mediated, small-vessel vasculitis. Chronic infection with hepatitis C is the most common underlying condition; cryoglobulinemic vasculitis also can occur with other chronic infections (such as subacute bacterial endocarditis, osteomyelitis, HIV, and hepatitis B), with connective tissue diseases (especially Sjögren syndrome), and with lymphoproliferative disorders. The cryoglobulins associated with vasculitis are cold-precipitable immune complexes consisting of rheumatoid factor and IgG (rheumatoid factor is an autoantibody to the constant region of IgG). The rheumatoid factor component can be monoclonal (type II cryoglobulins) or polyclonal (type III cryoglobulins). Type I cryoglobulins are cryoprecipitable monoclonal proteins that lack rheumatoid factor activity; these cause cold-induced hyperviscosity syndromes, not vasculitis, and are associated with B-cell lymphoproliferative diseases.

► Clinical Findings

Cryoglobulinemic vasculitis typically manifests as recurrent palpable purpura (predominantly on the lower extremities) and peripheral neuropathy. A proliferative glomerulonephritis may develop and can manifest as rapidly progressive glomerulonephritis. Abnormal liver biochemical tests, abdominal pain, digital gangrene, and pulmonary disease may also occur. The diagnosis is based on a compatible clinical picture and a positive serum test for cryoglobulins. The presence of a disproportionately low C4 level or rheumatoid factor or both can be diagnostic clues to the presence of cryoglobulinemia.

► Treatment

Antiviral regimens are first-line therapy for hepatitis C-associated cryoglobulinemic vasculitis that is neither life- nor organ-threatening. Interferon-free direct-acting antiviral agents are preferred because of the excellent long-term response in clinical trials. Patients with severe cryoglobulinemic vasculitis (eg, extensive digital gangrene, extensive neuropathy, and rapidly progressive glomerulonephritis) and hepatitis C should receive immunosuppressive therapy with corticosteroids and either rituximab or cyclophosphamide as well as antiviral treatment. Plasma exchange may provide additional benefit in selected cases. Relapse of vasculitis with cryoglobulinemia following

clearing of hepatitis C infection has been reported in a small percentage of patients.

Boleto G et al. Cryoglobulinemia after the era of chronic hepatitis C infection. *Semin Arthritis Rheum*. 2020;50:695. [PMID: 32521323]

Kolopp-Sarda MN et al. Cryoglobulinemic vasculitis: pathophysiological mechanisms and diagnosis. *Curr Opin Rheumatol*. 2021;33:1. [PMID: 33186245]

IgA VASCULITIS

IgA vasculitis (Henoch-Schönlein purpura), the most common systemic vasculitis in children, occurs in adults as well. Typical features are palpable purpura, arthritis, and hematuria. Abdominal pain occurs less frequently in adults than in children. Pathologic features include leukocytoclastic vasculitis with IgA deposition. The cause is not known.

The purpuric skin lesions are typically located on the lower extremities but may also be seen on the hands, arms, trunk, and buttocks. Joint symptoms are present in the majority of patients, with the knees and ankles being most commonly involved. Abdominal pain secondary to vasculitis of the intestinal tract is often associated with gastrointestinal bleeding. Hematuria signals the presence of a renal lesion that is usually reversible, although it occasionally may progress to CKD (see Henoch-Schönlein purpura, Chapter 22). Children tend to have more frequent and more serious gastrointestinal vasculitis, whereas adults more often suffer from CKD. Biopsy of the kidney reveals segmental glomerulonephritis with crescents and mesangial deposition of IgA. Chronic courses with persistent or intermittent skin disease are more likely to occur in adults than in children.

The value of corticosteroids has been controversial. In children, prednisone (1–2 mg/kg/day orally) does not decrease the frequency of proteinuria 1 year after onset of disease. Severe disease is often treated with aggressive immunosuppressive agents, but there is no consensus regarding the efficacy of this approach or the optimal therapeutic regimen.

Du L et al. Multisystemic manifestations of IgA vasculitis. *Clin Rheumatol*. 2021;40:43. [PMID: 32557258]

Ozen S et al. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis—the SHARE initiative. *Rheumatology (Oxford)*. 2019;58:1607. [PMID: 30879080]

RELAPSING POLYCHONDRITIS

This disease is characterized by inflammatory destructive lesions of cartilaginous structures, principally the ears, nose, trachea, and larynx. Nearly 40% of cases are associated with another disease, especially either other immunologic disorders (such as SLE, rheumatoid arthritis, or Hashimoto thyroiditis) or cancers (such as plasma cell myeloma) or hematologic disorders (such as myelodysplastic syndrome). The disease, which is usually episodic, affects males and females equally. The cartilage is painful, swollen, and tender during an attack and subsequently becomes atrophic, resulting in permanent deformity.

Biopsy of the involved cartilage shows inflammation and chondrolysis. Laryngotracheal and bronchial chondritis can lead to life-threatening airway narrowing and collapse. Noncartilaginous manifestations of the disease include fever, episcleritis, uveitis, deafness, aortic regurgitation, and rarely glomerulonephritis. In 85% of patients, a migratory, asymmetric, and seronegative arthropathy occurs, affecting both large and small joints and the costochondral junctions. Large vessel vasculitis is a frequently overlooked but potentially catastrophic complication. Diagnosing this uncommon disease is especially difficult since the signs of cartilage inflammation (such as red ears or nasal pain) may be more subtle than the fever, arthritis, rash, or other systemic manifestations.

Prednisone, 0.5–1 mg/kg/day orally, is often effective. Dapsone (100–200 mg/day orally) or methotrexate (7.5–20 mg orally per week) may also have efficacy, sparing the need for long-term high-dose corticosteroid treatment. Involvement of the tracheobronchial tree may respond to inhibitors of TNF.

Ferrada MA et al. Patient perception of disease-related symptoms and complications in relapsing polychondritis. *Arthritis Care Res (Hoboken)*. 2018;70:1124. [PMID: 29245173]

Tomelleri A et al. Large-vessel vasculitis affecting the aorta and its branches in relapsing polychondritis: case series and systematic review of the literature. *J Rheumatol*. 2020;47:1780. [PMID: 31839593]

BEHÇET DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Recurrent, painful oral and genital aphthous ulcers.
- ▶ Erythema nodosum-like lesions; follicular rash; pathergy phenomenon.
- ▶ Anterior or posterior uveitis. Posterior uveitis may be asymptomatic until significant damage to the retina has occurred.
- ▶ Neurologic lesions can mimic multiple sclerosis.

► General Considerations

Named after the Turkish dermatologist who first described it, Behçet disease is of unknown cause and most commonly occurs in persons of Asian, Turkish, or Middle Eastern background. The protean manifestations are believed to result from vasculitis that may involve all types of blood vessels: small, medium, and large, on both the arterial and venous side of the circulation.

► Clinical Findings

A. Symptoms and Signs

The hallmark of Behçet disease is painful aphthous ulcerations in the mouth. These lesions, which usually are

multiple, may be found on the tongue, gums, and inner surfaces of the oral cavity. Genital lesions, similar in appearance, are also common but do not occur in all patients. Other cutaneous lesions of Behçet disease include tender, erythematous, papular lesions that resemble erythema nodosum. On biopsy, however, many of these lesions are shown to be secondary to vasculitis rather than septal panniculitis. These erythema nodosum-like lesions have a tendency to ulcerate, which is a major difference between the lesions of Behçet disease and the erythema nodosum seen in sarcoidosis and inflammatory bowel disease. An erythematous follicular rash that occurs frequently on the upper extremities may be a subtle feature of the disease. The **pathergy phenomenon** is frequently underappreciated (unless the patient is asked); in this phenomenon, sterile pustules develop at sites where needles have been inserted into the skin (eg, for phlebotomy).

A nonerosive arthritis occurs in about two-thirds of patients, most commonly affecting the knees and ankles. Eye involvement may be one of the most devastating complications of Behçet disease. Posterior uveitis, in essence a retinal venulitis, may lead to the insidious destruction of large areas of the retina before the patient becomes aware of visual problems. Anterior uveitis, associated with the triad of photophobia, blurred vision, and a red eye, is intensely symptomatic. This complication may lead to a hypopyon, the accumulation of pus in the anterior chamber. If not treated properly with mydriatic agents to dilate the pupil and corticosteroid eyedrops to diminish inflammation, the anterior uveitis may lead to synechial formation between the iris and lens, resulting in permanent pupillary distortion.

Central nervous system involvement is another cause of major morbidity in Bechet disease. Findings include sterile meningitis (recurrent meningeal headaches associated with a lymphocytic pleocytosis), cranial nerve palsies, seizures, encephalitis, mental disturbances, and spinal cord lesions. The central nervous system lesions may mimic multiple sclerosis radiologically. Aphthous ulcerations of the ileum and cecum and other forms of gastrointestinal involvement develop in approximately a quarter of patients. Large vessel vasculitis can lead to pulmonary artery aneurysms and life-threatening pulmonary hemorrhage. Finally, patients have a hypercoagulable tendency that may lead to complicated venous thrombotic events, particularly multiple deep venous thrombosis, pulmonary emboli, cerebral sinus thrombosis, and other problems associated with clotting.

The clinical course may be chronic but is often characterized by remissions and exacerbations.

B. Laboratory Findings

There are no pathognomonic laboratory features of Behçet disease. Although acute-phase reactants are often elevated, there is no autoantibody or other assay that is distinctive. No markers of hypercoagulability specific to Behçet have been identified. Behçet disease is known to have a genetic risk factor (HLA B51), but this gene is neither necessary nor sufficient to cause the disease.

Treatment

Both colchicine (0.6 mg once to three times daily orally) and topical corticosteroids (oral dexamethasone suspension 1 mg twice daily swish and spit of 0.5 mg/5 mL) may ameliorate the mucocutaneous ulcerative symptoms. Apremilast, a selective phosphodiesterase-4 inhibitor, is FDA approved for the treatment of oral ulcers in Behcet disease. Corticosteroids (1 mg/kg/day of oral prednisone) are a mainstay of initial therapy for severe disease manifestations. Azathioprine (2 mg/kg/day orally) may be an effective steroid-sparing agent. Infliximab, cyclosporine, or cyclophosphamide is indicated for severe ocular and central nervous system complications of Behçet disease.

Hatemi G et al. 2018 update of the EULAR recommendations for the management of Behcet's syndrome. *Ann Rheum Dis*. 2018;77:808. [PMID: 29625968]

Posarelli C et al. Behcet's syndrome and ocular involvement: changes over time. *Clin Exp Rheumatol*. 2020;38:86. [PMID: 33253088]

PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

Primary angiitis of the central nervous system is a syndrome with several possible causes that produces small- and medium-sized vasculitis limited to the brain and spinal cord. Biopsy-proved cases have predominated in men who have a history of weeks to months of headaches, encephalopathy, and multifocal strokes. Systemic symptoms and signs are absent, and routine laboratory tests, including ESR and CRP, may be normal. MRI of the brain is almost always abnormal, and the spinal fluid often reveals a mild lymphocytosis and a modest increase in protein level. Angiograms classically reveal a "string of beads" pattern produced by alternating segments of arterial narrowing and dilation. However, neither the MRI nor the angiogram appearance is specific for vasculitis. Indeed, in one study, none of the patients who had biopsy-proved central nervous system vasculitis had an angiogram showing "the string of beads," and none of the patients with the classic angiographic findings had a positive brain biopsy for vasculitis. Review of many studies suggests that the sensitivity of angiography varies greatly (from 40% to 90%) and the specificity is only approximately 30%. Several conditions, including vasospasm, can produce the same angiographic pattern as vasculitis. Definitive diagnosis requires a compatible clinical picture with exclusion of infection (including subacute bacterial endocarditis), neoplasm (especially intravascular lymphoma), or drug exposure (eg, cocaine) that can mimic primary angiitis of the central nervous system and a positive brain biopsy. In contrast to biopsy-proved cases, patients with angiographically defined central nervous system vasculopathy are chiefly women who have had an abrupt onset of headaches and stroke (often in the absence of encephalopathy) with normal spinal fluid findings. Many patients who fit this clinical profile may have reversible cerebral vasoconstriction rather than true

vasculitis. Such cases are best treated with calcium channel blockers (such as nimodipine or verapamil) and possibly a short course of corticosteroids. Biopsy-proven cases usually improve with prednisone therapy and often require cyclophosphamide. Treatment response correlates with the size of arteries involved: vasculitis of small cortical and leptomeningeal vessels is associated with a better response and outcome than vasculitis of larger arteries. Cases of central nervous system vasculitis associated with cerebral amyloid angiopathy often respond well to corticosteroids, albeit the long-term natural history remains poorly defined.

Krawczyk M et al. Primary CNS vasculitis: a systematic review on clinical characteristics associated with abnormal biopsy and angiography. *Autoimmun Rev*. 2020;20:102714. [PMID: 33197577]

Salvarani C et al. Long-term remission, relapses and maintenance therapy in adult primary central nervous system vasculitis: A single-center 35-year experience. *Autoimmun Rev*. 2020;19:102497. [PMID: 32062032]

LIVEDO RETICULARIS & LIVEDO RACEMOSA

Livedo reticularis produces a mottled, purplish discoloration of the skin with reticulated cyanotic areas surrounding paler central cores. This distinctive “fishnet” pattern is caused by spasm or obstruction of perpendicular arterioles, combined with pooling of blood in surrounding venous plexuses. Idiopathic livedo reticularis is a benign condition that worsens with cold exposure, improves with warming, and primarily affects the extremities. Apart from cosmetic concerns, it is usually asymptomatic. The presence of systemic symptoms or the development of cutaneous ulcerations points to the presence of an underlying disease.

Secondary livedo reticularis, termed **livedo racemosa**, occurs in association with diseases that cause vascular obstruction or inflammation. Livedo racemosa resembles idiopathic livedo reticularis but has a wider skin distribution, including trunk, buttocks, and extremities. Its lesions are more irregular, broken, and circular. Of particular importance is the link with antiphospholipid antibody syndrome. Livedo racemosa is the presenting manifestation in 25% of patients with antiphospholipid antibody syndrome and is strongly associated with the subgroup that has arterial thromboses, including those with antiphospholipid antibody-positive Sneddon syndrome (livedo reticularis and cerebrovascular events). Other underlying causes of livedo racemosa include the vasculitides (particularly polyarteritis nodosa), cholesterol emboli syndrome, thrombocythemia, cryoglobulinemia, cold agglutinin disease, primary hyperoxaluria (due to vascular deposits of calcium oxalate), and disseminated intravascular coagulation.

Weishaupt C et al. Characteristics, risk factors and treatment reality in livedoid vasculopathy—a multicentre analysis. *J Eur Acad Dermatol Venereol*. 2019;33:1784. [PMID: 31009111]

SERONEGATIVE SPONDYLOARTROPATHIES

The seronegative spondyloarthropathies are ankylosing spondylitis, psoriatic arthritis, reactive arthritis, the arthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthritis. These disorders are noted for male predominance, onset usually before age 40, inflammatory arthritis of the spine and sacroiliac joints, asymmetric oligoarthritis of large peripheral joints, enthesopathy (inflammation of where ligaments, tendons, and joint capsule insert into bone), ocular inflammation, the absence of autoantibodies, and a striking association with HLA-B27. HLA-B27 is positive in up to 90% of patients with ankylosing spondylitis and 75% with reactive arthritis. HLA-B27 also occurs in 50% of the psoriatic and inflammatory bowel disease patients who have sacroiliitis. Patients with only peripheral arthritis in these latter two syndromes do not show an increase in HLA-B27.

ANKYLOSING SPONDYLITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Chronic low backache and stiffness in young adults, worst in the morning.
- ▶ Progressive limitation of back motion and chest expansion.
- ▶ Transient (50%) or persistent (25%) peripheral arthritis.
- ▶ Anterior uveitis in 20–25%.
- ▶ Diagnostic radiographic changes in sacroiliac joints.
- ▶ Negative serologic tests for rheumatoid factor and anti-CCP antibodies.
- ▶ HLA-B27 testing is most helpful when there is an intermediate probability of disease.

► General Considerations

Ankylosing spondylitis is a chronic inflammatory disease of the joints of the axial skeleton, manifested clinically by pain and progressive stiffening of the spine. The age at onset is usually in the late teens or early 20s. The incidence is greater in males than in females.

► Clinical Findings

A. Symptoms and Signs

The onset is usually gradual, with intermittent bouts of back pain that may radiate into the buttocks. The back pain is worse in the morning and associated with stiffness that lasts hours. Pain and stiffness improve with activity, in contrast to back pain due to mechanical causes, which improves with rest and worsens with activity. As

the disease advances, symptoms progress in a cephalad direction and back motion becomes limited, with the normal lumbar curve flattened and the thoracic curvature exaggerated. Chest expansion is often limited as a consequence of costovertebral joint involvement. In advanced cases, the entire spine becomes fused, allowing no motion in any direction. Transient acute arthritis of the peripheral joints occurs in about 50% of cases, and permanent changes in the peripheral joints—most commonly the hips, shoulders, and knees—are seen in about 25%. Enthesopathy, a hallmark of the spondyloarthropathies, can manifest as swelling of the Achilles tendon at its insertion, plantar fasciitis (producing heel pain), or dactylitis, which is fusiform “sausage” swelling of a finger or toe.

Anterior uveitis is associated in up to 25% of cases and may be a presenting feature of ankylosing spondylitis. Cardiac involvement, characterized by atrioventricular conduction defects, aortic regurgitation, or aortic root widening, occurs in 3–5% of patients with longstanding severe disease. Pulmonary fibrosis of the upper lobes, with progression to cavitation and bronchiectasis mimicking tuberculosis, may rarely occur, characteristically long after the onset of skeletal symptoms.

B. Laboratory Findings

The ESR is elevated in 85% of cases, but serologic tests for rheumatoid factor and anti-CCP antibodies are negative. Anemia of chronic disease may be present but is often mild. HLA-B27 is found in 90% of White patients and 50% of Black patients with ankylosing spondylitis. Because this antigen occurs in 8% of the healthy White population and 2% of healthy Blacks, it is not a specific diagnostic test but is most useful when there is intermediate probability of disease.

C. Imaging

The earliest radiographic changes are usually in the sacroiliac joints. In the first 2 years of the disease, sacroiliac changes may be detectable only by MRI. Indeed, patients who have symptoms and findings of ankylosing spondylitis and sacroiliitis evident by MRI but not by conventional radiographs are classified as having nonradiographic axial spondyloarthritis. With disease progression, erosion and sclerosis of the sacroiliac joints become evident on plain radiographs. The sacroiliitis of ankylosing spondylitis is bilateral and symmetric. Inflammation where the annulus fibrosus attaches to the vertebral bodies initially causes sclerosis (“the shiny corner sign”) and then characteristic squaring of the vertebral bodies. The term “bamboo spine” describes the late radiographic appearance of the spinal column in which the vertebral bodies are fused by vertically oriented, bridging syndesmophytes formed by the ossification of the annulus fibrosus and calcification of the anterior and lateral spinal ligaments.

Differential Diagnosis

Low back pain due to mechanical causes, disk disease, and degenerative arthritis is very common. Onset of back pain

prior to age 30 and an “inflammatory” quality of the back pain (ie, profound morning stiffness and pain that improve with activity) should raise the possibility of ankylosing spondylitis. In contrast to ankylosing spondylitis, rheumatoid arthritis predominantly affects multiple, small, peripheral joints of the hands and feet. Rheumatoid arthritis spares the sacroiliac joints and only affects the cervical component of the spine. Bilateral sacroiliitis indistinguishable from ankylosing spondylitis is seen with the spondylitis associated with inflammatory bowel disease. Sacroiliitis associated with reactive arthritis and psoriasis, on the other hand, is often asymmetric or even unilateral. Osteitis condensans ilii (sclerosis on the iliac side of the sacroiliac joint) is an asymptomatic, postpartum radiographic finding that is occasionally mistaken for sacroiliitis. Diffuse idiopathic skeletal hyperostosis (DISH) causes exuberant osteophytes (“enthesophytes”) of the spine that may be difficult to distinguish from the syndesmophytes of ankylosing spondylitis. The enthesophytes of DISH are thicker and more anterior than the syndesmophytes of ankylosing spondylitis, and sacroiliac joints are normal in DISH.

Treatment

NSAIDs remain first-line treatment of ankylosing spondylitis and may slow radiographic progression of spinal disease. TNF inhibitors have established efficacy for NSAID-resistant axial disease; responses are often substantial and durable. Secukinumab and ixekizumab inhibit the proinflammatory cytokine IL-17A and are also highly effective and FDA approved for the treatment of ankylosing spondylitis. Corticosteroids have minimal impact on the arthritis—particularly the spondylitis—of ankylosing spondylitis and can worsen osteopenia. All patients should be referred to a physical therapist for instruction in postural exercises and a safe exercise program.

Prognosis

Almost all patients have persistent symptoms over decades; rare individuals experience long-term remissions. The severity of disease varies greatly, with about 10% of patients having work disability after 10 years. Developing hip disease within the first 2 years of disease onset presages a worse prognosis. Biologic agents provide symptomatic relief, improve quality of life, and may slow disease progression for many patients with ankylosing spondylitis.

Koo BS et al. Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence. Ann Rheum Dis. 2020;79:1327. [PMID: 32660979]

Tahir H et al. Impact of secukinumab on patient-reported outcomes in the treatment of ankylosing spondylitis: current perspectives. Open Access Rheumatol. 2020;12:277. [PMID: 33273869]

Ward MM et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol. 2019;71:1599. [PMID: 31436036]

PSORIATIC ARTHRITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Psoriasis precedes arthritis in 80% of cases.
- ▶ **Arthritis:** usually asymmetric, with “sausage” appearance of fingers and toes (dactylitis); polyarthritis that may resemble rheumatoid arthritis.
- ▶ Sacroiliac joint involvement common.
- ▶ **Radiographic findings:** osteolysis; pencil-in-cup deformity; relative lack of osteoporosis; bony ankylosis; asymmetric sacroiliitis and atypical syndesmophytes.

► General Considerations

Although psoriasis usually precedes the onset of arthritis, arthritis may precede (by up to 2 years) or occur simultaneously with skin disease in approximately 20% of cases.

► Clinical Findings

A. Symptoms and Signs

The patterns or subsets of joint involvement in psoriatic arthritis include the following:

1. A symmetric polyarthritis that resembles rheumatoid arthritis. Usually, fewer joints are involved than in rheumatoid arthritis.
2. An oligoarthritis that may lead to considerable destruction of the affected joints.
3. A pattern of disease in which the DIP joints are primarily affected. Early, this may be monoarticular, and often the joint involvement is asymmetric. Pitting of the nails and onycholysis frequently accompany DIP involvement.
4. A severe deforming arthritis (arthritis mutilans) with osteolysis.
5. A spondylitic form in which sacroiliitis and spinal involvement predominate; 50% of these patients are HLA-B27 positive.

Arthritis is at least five times more common in patients with severe psoriatic skin disease than in those with only mild skin findings. Occasionally, however, patients may have a single patch of psoriasis (typically hidden in the scalp, gluteal cleft, or umbilicus) and are unaware of its presence. Thus, a detailed search for cutaneous lesions is essential in patients with arthritis of new onset. Also, the psoriatic lesions may have cleared when arthritis appears—in such cases, the history is most useful in diagnosing previously unexplained cases of monoarthritis or oligoarthritis. Nail pitting is sometimes a clue. “Sausage” swelling, or dactylitis, of one or more digits is a common manifestation of enthesopathy in psoriatic arthritis.

B. Laboratory Findings

The ESR is elevated in approximately 50% of patients with psoriatic arthritis; normal values do not rule out the

diagnosis. Rheumatoid factor and anti-CCP antibodies are not present. Uric acid levels may be high, reflecting the active turnover of skin affected by psoriasis.

C. Imaging

Radiographic findings are most helpful in distinguishing the disease from other forms of arthritis. There are marginal erosions of bone and irregular destruction of joint and bone, which, in the phalanx, may give the appearance of a sharpened pencil. Fluffy periosteal new bone may be marked, especially at the insertion of muscles and ligaments into bone. Such changes will also be seen along the shafts of metacarpals, metatarsals, and phalanges. Psoriatic spondylitis causes asymmetric sacroiliitis and syndesmophytes. In psoriatic arthritis as in ankylosing spondylitis, MRI is more sensitive in detecting axial abnormalities than conventional radiographs, especially in the first few years of disease onset. Ultrasoundography and MRI are more sensitive than conventional radiographs in detecting peripheral arthritis, enthesitis, and dactylitis.

► Treatment

In patients with active psoriatic arthritis, a TNF inhibitor biologic agent is recommended as first-line agent. If TNF inhibitor is contraindicated or not tolerated, methotrexate (or other oral small molecule agent, such as leflunomide, sulfasalazine, cyclosporine, or apremilast) may be effective.

Patients who do not respond to TNF inhibitors or oral small molecule agents can be treated with ustekinumab, a monoclonal antibody that inhibits IL-12 and IL-23, or secukinumab, guselkumab, or ixekizumab, which inhibit IL-17. Tofacitinib (Jak-stat inhibitor) and abatacept (CTLA4 inhibitor) may be options with failure of the above therapies. Corticosteroids are less effective in psoriatic arthritis than in other forms of inflammatory arthritis and may precipitate pustular psoriasis during tapers.

Gossec L et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79:700. [PMID: 32434812]

Singh JA et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Care Res (Hoboken). 2019;71:2. [PMID: 30499259]

REACTIVE ARTHRITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Oligoarthritis, conjunctivitis, urethritis, keratoderma blennorrhagicum, and mouth ulcers common.
- ▶ Usually follows dysentery or a sexually transmitted infection.
- ▶ HLA-B27-positive in 50–80% of patients.

► General Considerations

Reactive arthritis is precipitated by antecedent gastrointestinal and genitourinary infections and manifests as an asymmetric sterile oligoarthritis, typically of the lower extremities. It is frequently associated with enthesitis. Extra-articular manifestations are common and include urethritis, conjunctivitis, uveitis, rash (keratoderma blennorrhagicum), and mucocutaneous lesions. Reactive arthritis occurs most commonly in young men and is associated with HLA-B27 in 80% of White patients and 50–60% of Blacks.

► Clinical Findings

A. Symptoms and Signs

Most cases of reactive arthritis develop within 1–4 weeks after either a gastrointestinal infection (usually with *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter*) or a sexually transmitted infection (with *Chlamydia trachomatis* or perhaps *Ureaplasma urealyticum*). Whether the inciting infection is sexually transmitted or dysenteric does not affect the subsequent manifestations but does influence the gender ratio: The ratio is 1:1 after enteric infections but 9:1 with male predominance after sexually transmitted infections. Synovial fluid from affected joints is culture-negative. A clinically indistinguishable syndrome can occur without an apparent antecedent infection, suggesting that subclinical infection can precipitate reactive arthritis or that there are other, as yet unrecognized, triggers.

The arthritis is most commonly asymmetric and frequently involves the large weight-bearing joints (knee and ankle); sacroiliitis or ankylosing spondylitis is observed in at least 20% of patients, especially after frequent recurrences. Systemic symptoms including fever and weight loss are common at the onset of disease. The mucocutaneous lesions may include balanitis (Figure 20–8), stomatitis, and keratoderma blennorrhagicum, indistinguishable from pustular psoriasis. Involvement of the fingernails in

reactive arthritis mimics psoriatic changes. When present, conjunctivitis is mild and occurs early in the disease course. Anterior uveitis, which can develop at any time in HLA-B27-positive patients, is a more clinically significant ocular complication. Carditis and aortic regurgitation may occur. While most signs of the disease disappear within days or weeks, the arthritis may persist for several months or become chronic. Recurrences involving any combination of the clinical manifestations are common and are sometimes followed by permanent sequelae, especially in the joints (eg, articular destruction).

B. Imaging

Radiographic signs of permanent or progressive joint disease may be seen in the sacroiliac and peripheral joints.

► Differential Diagnosis

Gonococcal arthritis can initially mimic reactive arthritis, but the marked improvement after 24–48 hours of antibiotic administration in gonococcal arthritis and the culture results distinguish the two disorders. Rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis must also be considered. By causing similar oral, ocular, and joint lesions, Behçet disease may mimic reactive arthritis. The oral lesions of reactive arthritis, however, are typically painless, in contrast to those of Behçet disease.

► Treatment

NSAIDs have been the mainstay of therapy. Antibiotics given at the time of a nongonococcal sexually transmitted infection reduce the chance that the individual will develop this disorder. For chronic reactive arthritis associated with chlamydial infection, a randomized trial demonstrated that 6 months of rifampin (300 mg orally twice daily) in combination with either doxycycline (100 mg orally twice daily) or azithromycin (500 mg orally daily for 5 days then twice weekly) was more effective than placebo. Patients who do not respond to NSAIDs may respond to sulfasalazine or methotrexate. For those patients with recent-onset disease that is refractory to NSAIDs and these DMARDs, anti-TNF agents, which are effective in the other spondyloarthropathies, may be effective.

Hayes KM et al. Evolving patterns of reactive arthritis. Clin Rheumatol. 2019;38:2083. [PMID: 30919146]

Lucchino B et al. Reactive arthritis: current treatment challenges and future perspectives. Clin Exp Rheumatol. 2019;37:1065. [PMID: 31140399]

Zeidler H et al. *Chlamydia*-induced reactive arthritis: disappearing entity or lack of research? Curr Rheumatol Rep. 2019;21:63. [PMID: 31741118]



▲ Figure 20–8. Circinate balanitis due to reactive arthritis. (From Susan Lindsley, Dr. M. F. Rein, Public Health Image Library, CDC.)

INFLAMMATORY BOWEL DISEASE-ASSOCIATED SPONDYLOARTHRITIS

One-fifth of patients with inflammatory bowel disease have arthritis, which complicates Crohn disease somewhat more frequently than it does ulcerative colitis. In both diseases, two distinct forms of arthritis occur. The first is

peripheral arthritis—usually a nondeforming asymmetric oligoarthritis of large joints—in which the activity of the joint disease parallels that of the bowel disease. The arthritis usually begins months to years after the bowel disease, but occasionally the joint symptoms develop earlier and may be prominent enough to cause the patient to overlook intestinal symptoms. The second form of arthritis is a spondylitis that is indistinguishable by symptoms or radiographs from ankylosing spondylitis and follows a course independent of the bowel disease. About 50% of these patients are HLA-B27 positive.

Controlling the intestinal inflammation usually eliminates the peripheral arthritis. NSAIDs can be effective when the arthritis is mild but must be used cautiously since they can exacerbate inflammatory bowel disease. TNF inhibitors are useful therapies because they are effective both for the bowel and for the joints.

Chimenti MS et al. Use of synthetic and biological DMARDs in patients with enteropathic spondyloarthritis: a combined gastro-rheumatological approach. *Clin Exp Rheumatol*. 2019; 37:723. [PMID: 31172920]

Ribaldone DG et al. Risk factors of suspected spondyloarthritis among inflammatory bowel disease patients. *Scand J Gastroenterol*. 2019;54:1233. [PMID: 31549896]

INFECTIOUS ARTHRITIS

NONGONOCOCCAL ACUTE BACTERIAL (Septic) ARTHRITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Acute onset of inflammatory monoarticular arthritis, most often in large weight-bearing joints and wrists.
- ▶ Common risk factors include previous joint damage and injection drug use.
- ▶ Infection with causative organism commonly found elsewhere in body.
- ▶ Joint effusions are usually large; synovial fluid white blood cell counts $> 50,000/\text{mCL}$ ($50 \times 10^9/\text{L}$) are common.

General Considerations

Lyme disease is discussed in Chapter 34.

Nongonococcal acute bacterial arthritis is most often due to hematogenous seeding of the joint; direct inoculation from penetrating trauma is rare. The key risk factors are bacteremia (eg, injection drug use, endocarditis, infection at other sites), damaged joints (eg, rheumatoid arthritis), prosthetic joints, compromised immunity (eg, advanced age, diabetes mellitus, advanced CKD, alcoholism, cirrhosis, or immunosuppressive therapy), and loss of skin integrity (eg, cutaneous ulcer or psoriasis). *Staphylococcus aureus* is the most common cause of nongonococcal

septic arthritis, accounting for about 50% of all cases. Methicillin-resistant *S aureus* (MRSA) and group B *Streptococcus* are frequent and important causes of septic arthritis. Gram-negative septic arthritis causes about 10% of cases and is especially common in injection drug users and immunocompromised persons. *Escherichia coli* and *Pseudomonas aeruginosa* are the most common gram-negative isolates in adults. Pathologic changes include varying degrees of acute inflammation, with synovitis, effusion, abscess formation in synovial or subchondral tissues, and, if treatment is not adequate, articular destruction.

► Clinical Findings

A. Symptoms and Signs

The onset is usually acute, with pain, swelling, and heat of the affected joint worsening over hours. The knee is most frequently involved; other commonly affected sites are the hip, wrist, shoulder, and ankle. Unusual sites, such as the sternoclavicular or sacroiliac joint, can be involved in injection drug users. Chills and fever are common but are absent in up to 20% of patients. Infection of the hip usually does not produce apparent swelling but results in groin pain greatly aggravated by walking. More than one joint is involved in 15% of cases of septic arthritis; risk factors for multiple joint involvement include rheumatoid arthritis, associated endocarditis, and infection with group B streptococci.

B. Laboratory Findings

Synovial fluid analysis is critical for diagnosis. The leukocyte count of the synovial fluid is always inflammatory (greater than $2000/\text{mCL}$ [$2 \times 10^9/\text{L}$]), usually exceeds $50,000/\text{mCL}$ ($50 \times 10^9/\text{L}$), and often is more than $100,000/\text{mCL}$ ($100 \times 10^9/\text{L}$), with 90% or more polymorphonuclear cells (Table 20–2). Gram stain of the synovial fluid is positive in 75% of staphylococcal infections and in 50% of gram-negative infections. Synovial fluid cultures are positive in 70–90% of cases; administration of antibiotics prior to arthrocentesis reduces the likelihood of a positive culture result. Blood cultures are positive in approximately 50% of patients.

C. Imaging

Imaging tests generally add little to the diagnosis of septic arthritis. Indeed, other than demonstrating joint effusion, radiographs are usually normal early in the disease; however, evidence of demineralization may develop within days of onset. MRI and CT are more sensitive in detecting fluid in joints that are not accessible to physical examination (eg, the hip). Bony erosions and narrowing of the joint space followed by osteomyelitis and periostitis may be seen within 2 weeks.

D. Prosthetic Joint Infection

The clinical and laboratory manifestations of prosthetic joint infection is influenced by whether the infection is

early (less than 3 months after surgery), delayed (3–12 months after surgery), or late (more than 12 months after surgery). Early infections present with acute redness and swelling and are usually caused by *S aureus* and gram-negative organisms. Delayed infections often present with subtle manifestations: pain is common but only 50% of patients will have fever. Less virulent organisms, such as coagulase-negative *Staphylococcus*, *Propionibacterium acnes*, and enterococci, are most common causes of delayed infections. Late infections present with acute pain, swelling, and fever and are often caused by hematogenous seeding of *S aureus*, gram-negative bacilli, and hemolytic streptococci.

Differential Diagnosis

Gout and pseudogout can cause acute, very inflammatory monoarticular arthritis and high-grade fever; the failure to find crystals on synovial fluid analysis excludes these diagnoses. The most common articular manifestation of chronic Lyme disease is inflammatory monoarthritis of the knee, which yields synovial fluid that is Gram stain and culture negative. Acute rheumatic fever commonly involves an inflammatory migratory oligoarthritis. Pyogenic arthritis may be superimposed on other types of joint disease, notably rheumatoid arthritis. Indeed, septic arthritis must be excluded by joint fluid examination in any patient with rheumatoid arthritis who has a joint strikingly more inflamed than the other joints, especially if the patient is receiving biologic DMARD therapy.

Prevention

There is no evidence that patients with prosthetic joints undergoing procedures should receive antibiotic prophylaxis to prevent joint infection unless the patient has a prosthetic heart valve or the procedure requires antibiotics to prevent a surgical site infection. However, the topic remains controversial. The American Academy of Orthopedic Surgeons advocates prescribing antibiotic prophylaxis for any patient with a prosthetic joint replacement undergoing a procedure that can cause bacteremia.

Treatment

The effective treatment of septic arthritis requires appropriate antibiotic therapy together with drainage of the infected joint. Hospitalization is always necessary. If the likely causative organism cannot be determined clinically or from the synovial fluid Gram stain, treatment should be started with broad-spectrum antibiotic coverage effective against staphylococci, streptococci, and gram-negative organisms. The recommendation for initial treatment is to give vancomycin (1 g intravenously every 12 hours, adjusted for age, weight, and renal function) plus a third-generation cephalosporin: ceftriaxone, 1–2 g intravenously daily (or every 12 hours if concomitant meningitis or endocarditis is suspected); or ceftazidime, 1–2 g intravenously every 8 hours. Antibiotic therapy should be adjusted when culture results become available; the duration of antibiotic therapy is usually 4–6 weeks.

Early orthopedic consultation is essential. Effective drainage is usually achieved through early arthroscopic lavage and debridement. Options for treating prosthetic joint infections depend, in part, on the timing of the infection and include chronic suppression, debridement without removal of the prosthesis, or one- or two-stage exchange of the prosthesis.

Prognosis

The outcome of septic arthritis depends largely on the antecedent health of the patient, the causative organism (eg, *S aureus* bacterial arthritis is associated with a poor functional outcome in about 40% of cases), and the promptness of treatment. The mortality rate is 30% for patients with polyarticular sepsis. Bony ankylosis and articular destruction commonly also occur if treatment is delayed or inadequate.

Gjika E et al. Two weeks versus four weeks of antibiotic therapy after surgical drainage for native joint bacterial arthritis: a prospective, randomised, non-inferiority trial. Ann Rheum Dis. 2019;78:1114. [PMID: 30992295]

Goff DS et al. Review of guidelines for dental antibiotic prophylaxis for prevention of endocarditis and prosthetic joint infections and need for dental stewardship. Clin Infect Dis. 2020;71:455. [PMID: 31728507]

Mirza SZ et al. Diagnosing prosthetic joint infections in patients with inflammatory arthritis: a systematic literature review. J Arthroplasty. 2019;34:1032. [PMID: 30846314]

GONOCOCCAL ARTHRITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Prodromal migratory polyarthralgias.
- ▶ Tenosynovitis is the most common sign.
- ▶ Purulent monoarthritis in 50%.
- ▶ Characteristic skin lesions.
- ▶ Most common in young women during menses or pregnancy.
- ▶ Symptoms of urethritis frequently absent.
- ▶ Dramatic response to antibiotics.

General Considerations

In contrast to nongonococcal bacterial arthritis, gonococcal arthritis usually occurs in otherwise healthy individuals. Host factors, however, influence the expression of the disease: gonococcal arthritis is two to three times more common in women than in men, is especially common during menses and pregnancy, and is rare after age 40. Gonococcal arthritis is also common in men who have sex with men, whose high incidence of asymptomatic gonococcal pharyngitis and proctitis predisposes them to disseminated gonococcal infection. Recurrent disseminated gonococcal infection should prompt testing of the

patient's CH50 level to evaluate for a congenital deficiency of a terminal complement component (C5, C6, C7, or C8).

► Clinical Findings

A. Symptoms and Signs

One to 4 days of migratory polyarthralgias involving the wrist, knee, ankle, or elbow are common at the outset. Thereafter, two patterns emerge. The first pattern is characterized by tenosynovitis that most often affects the wrists, fingers, ankles, or toes and is seen in 60% of patients. The second pattern is purulent monoarthritis that most frequently involves the knee, wrist, ankle, or elbow and is seen in 40% of patients. Less than half of patients have fever, and less than one-fourth have any genitourinary symptoms. Most patients will have asymptomatic, but highly characteristic, skin lesions that usually consist of 2 to 10 small necrotic pustules distributed over the extremities, especially the palms and soles.

B. Laboratory Findings

The peripheral blood leukocyte count averages about 10,000 cells/mcL ($10 \times 10^9/L$) and is elevated in less than one-third of patients. The synovial fluid white blood cell count usually ranges from 30,000 to 60,000 cells/mcL ($30-60 \times 10^9/L$). The synovial fluid Gram stain is positive in one-fourth of cases and culture in less than half. Positive blood cultures are uncommon. Urethral, throat, cervical, and rectal cultures should be done in all patients, since they are often positive in the absence of local symptoms. Urinary nucleic acid amplification tests have excellent sensitivity and specificity for the detection of *Neisseria gonorrhoeae* in genitourinary sites.

C. Imaging

Radiographs are usually normal or show only soft tissue swelling.

► Differential Diagnosis

Reactive arthritis can produce acute monoarthritis, urethritis, and fever in a young person but is distinguished by negative cultures and failure to respond to antibiotics. Lyme disease involving the knee is less acute, does not show positive cultures, and may be preceded by known tick exposure and characteristic rash. The synovial fluid analysis will exclude gout, pseudogout, and nongonococcal bacterial arthritis. Rheumatic fever and sarcoidosis can produce migratory tenosynovitis but have other distinguishing features. Infective endocarditis with septic arthritis can mimic disseminated gonococcal infection. Meningococcemia occasionally presents with a clinical picture that resembles disseminated gonococcal infection; blood cultures establish the correct diagnosis. Early hepatitis B infection is associated with circulating immune complexes that can cause a rash and polyarthralgias. In contrast to disseminated gonococcal infection, the rash in hepatitis B is urticarial.

► Treatment

In most cases, patients in whom gonococcal arthritis is suspected should be admitted to the hospital to confirm the diagnosis, to exclude endocarditis, and to start treatment. The recommended initial treatment is azithromycin (1 g orally as a single dose) and a third-generation cephalosporin: ceftriaxone, 1 g intravenously daily (or every 12 hours if concomitant meningitis or endocarditis is suspected); or cefotaxime, 1 g intravenously every 8 hours; or ceftizoxime, 1 g intravenously every 8 hours. Azithromycin enhances eradication of gonorrhea and covers potential coinfection with *Chlamydia*. To mitigate against the increasing prevalence of resistant strains of gonococci, step-down treatment from parenteral to oral antibiotics is no longer recommended in the absence of culture results documenting sensitivity to the oral antibiotic being selected. Otherwise, once improvement has been achieved for 24–48 hours, patients must receive ceftriaxone 250 mg intramuscularly every 24 hours to complete a 7- to 14-day course.

► Prognosis

Generally, gonococcal arthritis responds dramatically in 24–48 hours after initiation of antibiotics, and drainage of the infected joint(s) is required infrequently. Complete recovery is the rule.

Birrell JM et al. Characteristics and impact of disseminated gonococcal infection in the "Top End" of Australia. Am J Trop Med Hyg. 2019 Oct;101(4):753–60. [PMID: 31392956]

RHEUMATIC MANIFESTATIONS OF HIV INFECTION

Infection with HIV has been associated with various rheumatic symptoms and may coexist with autoimmune rheumatic diseases, such as rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis. HIV painful articular syndrome with acute infection causes severe arthralgias in an oligoarticular, asymmetric pattern that resolve within 24 hours; the joint examination is normal. HIV-associated arthritis is an asymmetric oligoarticular process with objective findings of arthritis and a self-limited course that ranges from weeks to months. Along with antiretroviral therapies, immunosuppressive medications can be used if necessary in HIV-infected patients, though with caution. Muscle weakness associated with an elevated creatine kinase can be due to nucleoside reverse transcriptase inhibitor-associated myopathy or HIV-associated myopathy; the clinical presentations of each resemble idiopathic polymyositis but the muscle biopsies show minimal inflammation. Less commonly, an inflammatory myositis indistinguishable from idiopathic polymyositis occurs. Other rheumatic manifestations of HIV include diffuse infiltrative lymphocytosis syndrome (with parotid gland enlargement) and various forms of vasculitis.

Damba JJ et al. Incidence of autoimmune diseases in people living with HIV compared to a matched population: a cohort study. *Clin Rheumatol*. 2020. [Epub ahead of print] [PMID: 33230683]

VIRAL ARTHRITIS

Arthralgias occur frequently in the course of acute infections with many viruses, but frank arthritis is uncommon with the notable exceptions of acute parvovirus B19 infection and Chikungunya fever. Parvovirus B19 causes an acute polyarthritides in 50–60% of adult cases (infected children develop the febrile exanthem known as “slapped cheek fever”). The arthritis can mimic rheumatoid arthritis but is almost always self-limited and resolves within several weeks. The diagnosis is established by the presence of IgM antibodies specific for parvovirus B19. Chikungunya fever is an arthropod-borne viral infection that is endemic to West Africa but has spread to multiple locations including the Indian Ocean islands, the Caribbean and Central and Latin America. Clinical manifestations include high fever, rash, and incapacitating bone pain. Acute polyarthralgia and polyarthritides are common and can persist for months or years. For Chikungunya-associated chronic arthritis, treatment with methotrexate or other DMARD agents may be an option.

Self-limited polyarthritides is common in acute hepatitis B infection and typically occurs before the onset of jaundice. Urticaria or other types of skin rash may be present. Indeed, the clinical picture resembles that of serum sickness. Serum transaminase levels are elevated, and tests for hepatitis B surface antigen are positive. Serum complement levels are often low during active arthritis and become normal after remission of arthritis. The incidence of hepatitis B-associated polyarthritides has fallen substantially with the introduction of hepatitis B vaccination. Effective vaccination programs in the United States have eliminated acute rubella infections, formerly a common cause of virally induced polyarthritides.

Chronic infection with hepatitis C is associated with chronic polyarthralgia in up to 20% of cases and with chronic polyarthritides in 3–5%. This can mimic rheumatoid arthritis, and the presence of rheumatoid factor in most hepatitis C-infected individuals leads to further diagnostic confusion. Distinguishing hepatitis C-associated arthritis/arthritis from the co-occurrence of hepatitis C and rheumatoid arthritis can be difficult. Rheumatoid arthritis always causes objective arthritis (not just arthralgias) and can be erosive (hepatitis C-associated arthritis is nonerosive). The presence of anti-CCP antibodies points to the diagnosis of rheumatoid arthritis.

Adarsh MB et al. Methotrexate in early Chikungunya arthritis: a 6 month randomized controlled open-label trial. *Curr Rheumatol Rev*. 2020;16:319. [PMID: 31858912]

Amaral JK et al. The clinical features, pathogenesis and methotrexate therapy of chronic Chikungunya arthritis. *Viruses*. 2019;11:289. [PMID: 30909365]

INFECTIONS OF BONES

ACUTE PYOGENIC OSTEOMYELITIS

ESSENTIALS OF DIAGNOSIS

- Fever associated with pain and tenderness of involved bone.
- Diagnosis usually requires culture of bone biopsy.
- Elevated ESR and CRP.
- Radiographs early in the course are typically negative.

General Considerations

Osteomyelitis is a serious infection that is often difficult to diagnose and treat. Infection of bone occurs as a consequence of (1) hematogenous dissemination of bacteria, (2) invasion from a contiguous focus of infection, and (3) skin breakdown in the setting of vascular insufficiency.

Clinical Findings

A. Symptoms and Signs

1. Hematogenous osteomyelitis—Osteomyelitis resulting from bacteremia is a disease associated with sickle cell disease, injection drug users, diabetes mellitus, or older adults. Patients with this form of osteomyelitis often present with sudden onset of high fever, chills, and pain and tenderness of the involved bone. The site of osteomyelitis and the causative organism depend on the host. Among patients with hemoglobinopathies such as sickle cell anemia, osteomyelitis is caused most often by salmonellae; *S aureus* is the second most common cause. Osteomyelitis in injection drug users develops most commonly in the spine. Although in this setting *S aureus* is most common, gram-negative infections, especially *P aeruginosa* and *Serratia* species, are also frequent pathogens. Rapid progression to epidural abscess causing fever, pain, and sensory and motor loss is not uncommon. In older patients with hematogenous osteomyelitis, the most common sites are the thoracic and lumbar vertebral bodies. Risk factors for these patients include diabetes, intravenous catheters, and indwelling urinary catheters. These patients often have more subtle presentations, with low-grade fever and gradually increasing bone pain.

2. Osteomyelitis from a contiguous focus of infection

Prosthetic joint replacement, pressure injury (formerly called pressure ulcer), neurosurgery, and trauma most frequently cause soft tissue infections that can spread to bone. *S aureus* and *Staphylococcus epidermidis* are the most common organisms. Polymicrobial infections, rare in hematogenously spread osteomyelitis, are more common in osteomyelitis due to contiguous spread. Localized signs of inflammation are usually evident, but high fever and other

signs of toxicity are usually absent. Septic arthritis and cellulitis can also spread to contiguous bone.

3. Osteomyelitis associated with vascular insufficiency—

Patients with diabetes mellitus and vascular insufficiency are susceptible to developing a very challenging form of osteomyelitis. The foot and ankle are the most commonly affected sites. Infection originates from an ulcer or other break in the skin that is usually still present when the patient presents but may appear disarmingly unimpressive. Bone pain is often absent or muted by the associated neuropathy. Fever is also commonly absent. Two of the best bedside clues that the patient has osteomyelitis are the ability to easily advance a sterile probe through a skin ulcer to bone and an ulcer area larger than 2 cm².

B. Imaging and Laboratory Findings

The ESR and serum CRP are almost always elevated and can be useful parameters to follow during the course of therapy.

Plain radiographs may be sufficient to establish the diagnosis of osteomyelitis but can be falsely negative initially. Early radiographic findings include soft tissue swelling, loss of tissue planes, and periarticular demineralization of bone. About 2 weeks after onset of symptoms, erosion of bone and alteration of cancellous bone appear, followed by periostitis.

MRI, CT, and nuclear medicine bone scanning are more sensitive than conventional radiography. MRI is the most sensitive and is particularly helpful in demonstrating the extent of soft tissue involvement. Radionuclide bone scanning is most valuable when osteomyelitis is suspected but no site is obvious. Nuclear medicine studies may also detect multifocal sites of infection. Ultrasound is useful in diagnosing the presence of effusions within joints and extra-articular soft tissue fluid collections but not in detecting bone infections.

Identifying the offending organism is a crucial step in selection of antibiotic therapy. Bone biopsy for culture is required except in those with hematogenous osteomyelitis, who have positive blood cultures. Cultures from overlying ulcers, wounds, or fistulas are unreliable.

Differential Diagnosis

Acute hematogenous osteomyelitis should be distinguished from suppurative arthritis, rheumatic fever, and cellulitis. More subacute forms must be differentiated from tuberculosis or mycotic infections of bone and Ewing sarcoma or, in the case of vertebral osteomyelitis, metastatic cancer. When osteomyelitis involves the vertebrae, it commonly traverses the disk—a finding not observed in cancer. Charcot arthropathy of the foot or ankle can mimic osteomyelitis, particularly in patients with diabetes but does not cause an elevated ESR or serum CRP.

Complications

Inadequate treatment of bone infections results in chronicity of infection, and this possibility is increased by delaying diagnosis and treatment. Extension to adjacent bone or joints may complicate acute osteomyelitis. Recurrence of

bone infections often results in anemia of chronic disease, a markedly elevated ESR, weight loss, weakness and, rarely, amyloidosis or nephrotic syndrome. Pseudoepitheliomatous hyperplasia, squamous cell carcinoma, or fibrosarcoma may occasionally arise in persistently infected tissues.

Treatment

Most patients require both debridement of necrotic bone and prolonged administration of antibiotics. Patients with vertebral body osteomyelitis and epidural abscess may require urgent neurosurgical decompression. Depending on the site and extent of debridement, surgical procedures to stabilize, fill in, cover, or revascularize may be needed. Oral therapy with quinolones (eg, ciprofloxacin, 750 mg twice daily) for 6–8 weeks has been shown to be as effective as standard parenteral antibiotic therapy for chronic osteomyelitis with susceptible organisms. When treating osteomyelitis caused by *S aureus*, quinolones are usually combined with rifampin, 300 mg orally twice daily. Combined with surgical debridement, a 3-week course of antibiotics (compared to 6 weeks) may be sufficient.

Prognosis

If sterility of the lesion is achieved within 2–4 days, a good result can be expected in most cases if there is no compromise of the patient's immune system. However, progression of the disease to a chronic form may occur. It is especially common in the lower extremities and in patients in whom circulation is impaired (eg, diabetics).

Gariani K et al. Three versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: a prospective, randomized, non-inferiority pilot trial. Clin Infect Dis. 2020. [Epub ahead of print] [PMID: 33242083]

Gregori F et al. Treatment algorithm for spontaneous spinal infections: a review of the literature. J Craniovertebr Junction Spine. 2019;10:3. [PMID: 31000972]

TUBERCULOSIS OF BONES & JOINTS

SPINAL TUBERCULOSIS (Pott Disease)



ESSENTIALS OF DIAGNOSIS

- ▶ Seen primarily in immigrants from developing countries or immunocompromised patients.
- ▶ Back pain and gibbus deformity.
- ▶ Radiographic evidence of vertebral involvement.
- ▶ Evidence of *Mycobacterium tuberculosis* in aspirate or biopsies of spinal lesions.

General Considerations

In the developing world, children primarily bear the burden of musculoskeletal tuberculosis. In the United States,

however, musculoskeletal infection is more often seen in adult immigrants from countries where tuberculosis is prevalent, or it develops in the setting of immunosuppression (eg, HIV infection, therapy with biologic agent). Spinal tuberculosis (Pott disease) accounts for about 50% of musculoskeletal infection due to *M tuberculosis* (see Chapter 9). Seeding of the vertebrae may occur through hematogenous spread from the respiratory tract at the time of primary infection, with clinical disease developing years later as a consequence of reactivation, or through lymphatics from infected foci in the pleura or kidneys. The thoracic and lumbar vertebrae are the most common sites of spinal involvement; vertebral infection is associated with paravertebral cold abscesses in 75% of cases.

► Clinical Findings

A. Symptoms and Signs

Patients complain of back pain, often present for months and sometimes associated with radicular pain and lower extremity weakness. Constitutional symptoms are usually absent, and less than 20% have active pulmonary disease. Destruction of the anterior aspect of the vertebral body can produce the characteristic wedge-shaped gibbus deformity.

B. Laboratory Findings

Most patients have a positive reaction to purified protein derivative (PPD) or a positive interferon-gamma release assay. Cultures of paravertebral abscesses and biopsies of vertebral lesions are positive in up to 70–90%. Biopsies reveal characteristic caseating granulomas in most cases. Isolation of *M tuberculosis* from an extraspinal site is sufficient to establish the diagnosis in the proper clinical setting.

C. Imaging

Radiographs can reveal lytic and sclerotic lesions and bony destruction of vertebrae but are normal early in the disease course. CT scanning can demonstrate paraspinal soft tissue extensions of the infection; MRI is the imaging technique of choice to detect compression of the spinal cord or cauda equina.

► Differential Diagnosis

Spinal tuberculosis must be differentiated from subacute and chronic spinal infections due to pyogenic organisms, *Brucella*, fungi, and malignancy.

► Complications

Paraplegia due to compression of the spinal cord or cauda equina is the most serious complication of spinal tuberculosis.

► Treatment

Antimicrobial therapy should be administered for 6–9 months, usually in the form of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by

isoniazid and rifampin for an additional 4–7 months (see also Chapter 9). Medical management alone is often sufficient. Surgical intervention, however, may be indicated when there is neurologic compromise or severe spinal instability.

Guillouzouic A et al. Treatment of bone and joint tuberculosis in France: a multicentre retrospective study. *J Clin Med.* 2020;9: 2529. [PMID: 32764500]

Kim JH et al. Prognostic factors for unfavourable outcomes of patients with spinal tuberculosis in a country with an intermediate tuberculosis burden: a multicentre cohort study. *Bone Joint J.* 2019;101:1542. [PMID: 31786996]

TUBERCULOUS ARTHRITIS

Infection of peripheral joints by *M tuberculosis* usually presents as a monoarticular arthritis lasting for weeks to months (or longer), but less often, it can have an acute presentation that mimics septic arthritis. Any joint can be involved; the hip and knee are most commonly affected. Constitutional symptoms and fever are present in only a small number of cases. Tuberculosis also can cause a chronic tenosynovitis of the hand and wrist. Joint destruction occurs far more slowly than in septic arthritis due to pyogenic organisms. Synovial fluid is inflammatory but not to the degree seen in pyogenic infections, with synovial white cell counts in the range of 10,000–20,000 cells/mcL ($10\text{--}20 \times 10^9/\text{L}$). Smears of synovial fluid are positive for acid-fast bacilli in a minority of cases; synovial fluid cultures, however, are positive in 80% of cases. Because culture results may take weeks, the diagnostic procedure of choice usually is synovial biopsy, which yields characteristic pathologic findings and positive cultures in greater than 90%. Antimicrobial therapy is the mainstay of treatment. Rarely, a reactive, sterile polyarthritis associated with erythema nodosum (Poncet disease) develops in patients with active pulmonary or extrapulmonary tuberculosis.

McGuire E et al. Extrapulmonary articular tuberculosis: an 11-year retrospective study of demographic features and clinical outcomes in East London. *J Infect.* 2020;81:383. [PMID: 32579987]

MISCELLANEOUS RHEUMATOLOGIC DISORDERS

FIBROMYALGIA



ESSENTIALS OF DIAGNOSIS

- Most frequent in women aged 20–50.
- Chronic widespread musculoskeletal pain syndrome with multiple tender points.
- Fatigue, headaches, numbness common.
- Objective signs of inflammation absent; laboratory studies normal.

► General Considerations

Fibromyalgia is a common syndrome, affecting 3–10% of the general population. It shares many features with myalgic encephalomyelitis/chronic fatigue syndrome, namely, an increased frequency among women aged 20–50, absence of objective findings, and absence of diagnostic laboratory test results. While many of the clinical features of the two conditions overlap, musculoskeletal pain predominates in fibromyalgia, whereas lassitude dominates myalgic encephalomyelitis/chronic fatigue syndrome.

The cause is unknown, but aberrant perception of painful stimuli, sleep disorders, depression, and viral infections have all been proposed. Fibromyalgia can be a complication of hypothyroidism, rheumatoid arthritis or, in men, sleep apnea.

► Clinical Findings

The patient complains of chronic aching pain and stiffness, frequently involving the entire body but with prominence of pain around the neck, shoulders, low back, and hips. Fatigue, sleep disorders, subjective numbness, chronic headaches, and irritable bowel symptoms are common. Even minor exertion aggravates pain and increases fatigue. Physical examination is normal except for “trigger points” of pain produced by palpation of various areas such as the trapezius, the medial fat pad of the knee, and the lateral epicondyle of the elbow.

► Differential Diagnosis

Fibromyalgia is a diagnosis of exclusion. A detailed history and repeated physical examination can obviate the need for extensive laboratory testing. Rheumatoid arthritis and SLE present with objective physical findings or abnormalities on testing. Thyroid function tests are useful, since hypothyroidism can produce a secondary fibromyalgia syndrome. Polymyositis produces demonstrable weakness. The diagnosis of fibromyalgia should be made hesitantly in a patient over age 50 and should never be invoked to explain fever, weight loss, or any other objective signs. Polymyalgia rheumatica produces shoulder and pelvic girdle pain, is associated with anemia and elevated ESR, and occurs after age 50. Hypophosphatemic states, such as oncogenic osteomalacia, can cause musculoskeletal pain unassociated with physical findings. In contrast to fibromyalgia, oncogenic osteomalacia usually produces pain in only a few areas and is associated with a low serum phosphate level.

► Treatment

A multidisciplinary approach is most effective. Patient education is essential. Patients can be comforted that they have a diagnosable syndrome treatable by specific though imperfect therapies and that the course is not progressive. Cognitive behavioral therapy, including programs that emphasize mindfulness meditation, is often helpful. Exercise programs are also beneficial, particularly tai chi and yoga. The following medications have shown modest efficacy: amitriptyline, fluoxetine, duloxetine, milnacipran, cyclobenzaprine, pregabalin, gabapentin, or low-dose

naltrexone. Tramadol and acetaminophen combinations have ameliorated symptoms modestly in short-term trials. Less than 50% of the patients experience a sustained improvement. NSAIDs are generally ineffective. Opioids and corticosteroids are ineffective and should not be used to treat fibromyalgia.

► Prognosis

All patients have chronic symptoms. With treatment, however, many do eventually resume increased activities. Progressive or objective findings do not develop.

- Cheng CA et al. Effectiveness of Tai Chi on fibromyalgia patients: a meta-analysis of randomized controlled trials. *Complement Ther Med.* 2019;46:1. [PMID: 31519264]
Metyas S et al. Low dose naltrexone in the treatment of fibromyalgia. *Curr Rheumatol Rev.* 2018;14:177. [PMID: 28325149]
Prabhakar A et al. The role of complementary and alternative medicine treatments in fibromyalgia: a comprehensive review. *Curr Rheumatol Rep.* 2019;21:14. [PMID: 30830504]
Wolfe F et al. Diagnosis of fibromyalgia: disagreement between fibromyalgia criteria and clinician-based fibromyalgia diagnosis in a university clinic. *Arthritis Care Res (Hoboken).* 2019;71:343. [PMID: 30724039]

THORACIC OUTLET SYNDROMES

Thoracic outlet syndromes result from compression of the neurovascular structures supplying the upper extremity. Symptoms and signs arise from intermittent or continuous pressure on elements of the brachial plexus (more than 90% of cases) or the subclavian or axillary vessels (veins or arteries) by a variety of anatomic structures of the shoulder girdle region. The neurovascular bundle can be compressed between the anterior or middle scalene muscles and a normal first thoracic rib or a cervical rib. Most commonly thoracic outlet syndromes are caused by scarred scalene neck muscle secondary to neck trauma or sagging of the shoulder girdle resulting from aging, obesity, or pendulous breasts. Faulty posture, occupation, or thoracic muscle hypertrophy from physical activity (eg, weight-lifting, baseball pitching) may be other predisposing factors.

Thoracic outlet syndromes present in most patients with some combination of four symptoms involving the upper extremity: pain, numbness, weakness, and swelling. The predominant symptoms depend on whether the compression chiefly affects neural or vascular structures. The onset of symptoms is usually gradual but can be sudden. Some patients spontaneously notice aggravation of symptoms with specific positioning of the arm. Pain radiates from the point of compression to the base of the neck, the axilla, the shoulder girdle region, arm, forearm, and hand. Paresthesias are common and distributed to the volar aspect of the fourth and fifth digits. Sensory symptoms may be aggravated at night or by prolonged use of the extremities. Weakness and muscle atrophy are the principal motor abnormalities. Vascular symptoms consist of arterial ischemia characterized by pallor of the fingers on elevation of the extremity, sensitivity to cold and, rarely, gangrene of the digits or venous obstruction marked by edema, cyanosis, and engorgement.

The symptoms of thoracic outlet syndromes can be provoked within 60 seconds over 90% of the time by having a patient elevate the arms in a “stick-em-up” position (ie, abducted 90 degrees in external rotation). Reflexes are usually not altered. Obliteration of the radial pulse with certain maneuvers of the arm or neck, once considered a highly sensitive sign of thoracic outlet obstruction, does not occur in most cases.

Chest radiography will identify patients with cervical rib (although most patients with cervical ribs are asymptomatic). MRI with the arms held in different positions is useful in identifying sites of impaired blood flow. Intrarterial or venous obstruction is confirmed by angiography. Determination of conduction velocities of the ulnar and other peripheral nerves of the upper extremity may help localize the site of their compression.

Thoracic outlet syndrome must be differentiated from osteoarthritis of the cervical spine, tumors of the superior pulmonary sulcus, cervical spinal cord, or nerve roots, and periarthritis of the shoulder.

Treatment is directed toward relief of compression of the neurovascular bundle. Greater than 95% of patients can be treated successfully with conservative therapy consisting of physical therapy and avoiding postures or activities that compress the neurovascular bundle. Operative treatment, required by less than 5% of patients, is more likely to relieve the neurologic rather than the vascular component that causes symptoms.

Jones MR et al. Thoracic outlet syndrome: a comprehensive review of pathophysiology, diagnosis, and treatment. *Pain Ther.* 2019;8:5. [PMID: 31037504]

Yin ZG et al. Outcomes of surgical management of neurogenic thoracic outlet syndrome: a systematic review and Bayesian perspective. *J Hand Surg Am.* 2019;44:416.e1. [PMID: 30122304]

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (formerly called reflex sympathetic dystrophy) is a rare disorder of the extremities characterized by autonomic and vasomotor instability. The cardinal symptoms and signs are pain localized to an arm or leg, swelling of the involved extremity, disturbances of color and temperature in the affected limb, dystrophic changes in the overlying skin and nails, and limited range of motion. Strikingly, the findings are not limited to the distribution of a single peripheral nerve. Most cases are preceded by surgery or direct physical trauma, often of a relatively minor nature, to the soft tissues, bone, or nerve. Early mobilization after injury or surgery reduces the likelihood of developing the syndrome. Any extremity can be involved, but the syndrome most commonly occurs in the hand and is associated with ipsilateral restriction of shoulder motion (“shoulder-hand” syndrome). This syndrome proceeds through phases: pain, swelling, and skin color and temperature changes develop early and, if untreated, lead to atrophy and dystrophy. The swelling in complex regional pain syndrome is diffuse (“catcher’s mitt hand”) and not restricted to joints. Pain is often burning in quality, intense, and often greatly worsened by minimal stimuli

such as light touch. The shoulder-hand variant of this disorder sometimes complicates myocardial infarction or injuries to the neck or shoulder. Complex regional pain syndrome may occur after a knee injury or after arthroscopic knee surgery. There are no systemic symptoms. In the early phases of the syndrome, bone scans are sensitive, showing diffuse increased uptake in the affected extremity; radiographs eventually reveal severe generalized osteopenia. In the posttraumatic variant, this is known as Sudeck atrophy. Symptoms and findings are bilateral in some. This syndrome should be differentiated from other cervicobrachial pain syndromes, rheumatoid arthritis, thoracic outlet obstruction, and systemic sclerosis, among others.

Early treatment offers the best prognosis for recovery. For mild cases, NSAIDs (eg, naproxen 250–500 mg twice daily orally) can be effective. For more severe cases associated with edema, prednisone, 30–60 mg/day orally for 2 weeks and then tapered over 2 weeks, can be effective. Pain management is important and facilitates physical therapy, which plays a critical role in efforts to restore function. Some patients will also benefit from antidepressant agents (eg, nortriptyline initiated at a dosage of 10 mg orally at bedtime and gradually increased to 40–75 mg at bedtime) or from anticonvulsants (eg, gabapentin 300 mg three times daily orally). Bisphosphonates, calcitonin, regional nerve blocks, and dorsal-column stimulation have also been reported to be helpful. Patients who have restricted shoulder motion may benefit from the treatment described for scapulo-humeral periarthritis. The prognosis partly depends on the stage in which the lesions are encountered and the extent and severity of associated organic disease.

Chang C et al. Complex regional pain syndrome—false hopes and miscommunications. *Autoimmun Rev.* 2019;18:270. [PMID: 30639650]

Rand SE et al. Complex regional pain syndrome: current diagnostic and treatment considerations. *Curr Sports Med Rep.* 2019;18:325. [PMID: 31503044]

RHEUMATOLOGIC MANIFESTATIONS OF CANCER

Rheumatologic syndromes may be the presenting manifestations for a variety of cancers. Dermatomyositis in adults, for example, is often associated with cancer. Hypertrophic pulmonary osteoarthropathy, which is characterized by the triad of polyarthritis, new onset of clubbing, and periosteal new bone formation, is associated with both malignant diseases (eg, lung and intrathoracic cancers) and nonmalignant ones (eg, cyanotic heart disease, cirrhosis, and lung abscess). Cancer-associated polyarthritis is rare, has both oligoarticular and polyarticular forms, and should be considered when “seronegative rheumatoid arthritis” develops abruptly in an elderly patient. Palmar fasciitis manifests as bilateral palmar swelling with finger contractures and may be the first indication of cancer, particularly ovarian carcinoma. Remitting seronegative synovitis with non-pitting edema (“RS3PE”) presents with a symmetric small-joint polyarthritis associated with non-pitting edema of the hands; it can be idiopathic or associated with malignancy. Palpable purpura due to leukocytoclastic vasculitis may be

the presenting complaint in myeloproliferative disorders. Hairy cell leukemia can be associated with medium-sized vessel vasculitis such as polyarteritis nodosa. Acute leukemia can produce joint pains that are disproportionately severe in comparison to the minimal swelling and heat that are present. Leukemic arthritis complicates approximately 5% of cases. Rheumatic manifestations of myelodysplastic syndromes include cutaneous vasculitis, lupus-like syndromes, neuropathy, and episodic intense arthritis. Erythromelalgia, a painful warmth and redness of the extremities that (unlike Raynaud) improves with cold exposure or with elevation of the extremity, is often associated with myeloproliferative diseases, particularly essential thrombocythemia.

With the widespread use of immune-checkpoint inhibitors to treat a variety of malignancies, the emergence of immune-related adverse events from these drugs is being recognized. Pneumonitis, colitis, and inflammatory arthritis are common and often can be managed with corticosteroids alone and adjustment of immunotherapy. However, the persistence of some autoimmune conditions despite cessation of cancer treatment, namely inflammatory arthritis, may require long-term immunosuppression.

Loveland JD et al. A multicenter, retrospective, case series of patients with Charcot neuroarthropathy deformities undergoing arthrodesis utilizing recombinant human platelet-derived growth factor with beta-tricalcium phosphate. *J Foot Ankle Surg.* 2020;60:74. [PMID: 33158722]

PALINDROMIC RHEUMATISM

Palindromic rheumatism is a disease of unknown cause characterized by frequent recurring attacks (at irregular intervals) of acutely inflamed joints. Periarticular pain with swelling and transient subcutaneous nodules may also occur. The attacks cease within several hours to several days. The knee and finger joints are most commonly affected, but any peripheral joint may be involved. Although hundreds of attacks may take place over a period of years, there is no permanent articular damage. Laboratory findings are usually normal. Palindromic rheumatism must be distinguished from acute gouty arthritis and an atypical acute onset of rheumatoid arthritis. In some patients, palindromic rheumatism is a prologue of rheumatoid arthritis.

Symptomatic treatment with NSAIDs is usually all that is required during the attacks. Hydroxychloroquine may be of value in preventing recurrences.

Calabrese LH et al. Rheumatic immune-related adverse events from cancer immunotherapy. *Nat Rev Rheumatol.* 2018;14:569. [PMID: 30171203]

Kostine M et al. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. *Ann Rheum Dis.* 2021;80:36. [PMID: 32327425]

NEUROGENIC ARTHROPATHY (Charcot Joint)

Neurogenic arthropathy is joint destruction resulting from loss or diminution of proprioception, pain, and temperature perception. Although initially described in the knees of patients with tabes dorsalis, it is more frequently seen in association with diabetic neuropathy (foot and ankle) or syringomyelia (shoulder). As normal muscle tone and protective reflexes are lost, secondary degenerative joint disease ensues, resulting in an enlarged, boggy, relatively painless joint with extensive cartilage erosion, osteophyte formation, and multiple loose joint bodies. Radiographs can reveal striking osteolysis that mimics osteomyelitis or dramatic destruction of the joint with subluxation, fragmentation of bone, and bony sclerosis.

Treatment is directed toward the primary disease; mechanical devices are used to assist in weight bearing and prevention of further trauma. Surgical strategies, including arthrodesis, with or without orthobiologics, can be considered if nonsurgical management fails.

Kim YK et al. Results of simple conservative treatment of midfoot Charcot arthropathy. *Clin Orthop Surg.* 2019;11:459. [PMID: 31788170]

OSTEONECROSIS (AVASCULAR NECROSIS OF BONE)

Osteonecrosis is a complication of corticosteroid use, alcoholism, trauma, SLE, pancreatitis, gout, sickle cell disease, dysbaric syndromes (eg, “the bends”), knee meniscectomy, and infiltrative diseases (eg, Gaucher disease). The most commonly affected sites are the proximal and distal femoral heads, leading to hip or knee pain. Other commonly affected sites include the ankle, shoulder, and elbow. Osteonecrosis of the jaw is associated with use of bisphosphonate therapy, usually when the bisphosphonate is used for treating metastatic cancer or plasma cell myeloma rather than osteoporosis. Initially, radiographs are often normal; MRI, CT scan, and bone scan are more sensitive techniques. Treatment involves avoidance of weight bearing on the affected joint for at least several weeks. The value of surgical core decompression is controversial. For osteonecrosis of the hip, a variety of procedures designed to preserve the femoral head have been developed for early disease, including vascularized and nonvascularized bone grafting procedures. These procedures are most effective in avoiding or forestalling the need for total hip arthroplasty in young patients who do not have advanced disease. Without a successful intervention of this nature, the natural history of avascular necrosis is usually progression of the bony infarction to cortical collapse, resulting in significant joint dysfunction. Total hip replacement is the usual outcome for all patients who are candidates for that procedure.

Kuroda Y et al. Classification of osteonecrosis of the femoral head: Who should have surgery? *Bone Joint Res.* 2019;8:451. [PMID: 31728183]

ALLERGIC & IMMUNOLOGIC DISORDERS

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IMMEDIATE HYPERSENSITIVITY

IgE antibodies occupy receptor sites on mast cells. Within minutes after exposure to the allergen, a multivalent antigen links adjacent IgE molecules, activating and degranulating mast cells. Clinical manifestations can be explained by the effects of released mediators on target end organs. Both preformed and newly generated mediators cause vasodilation and permeability changes, visceral smooth muscle contraction, mucous secretory gland stimulation, vascular permeability, and tissue inflammation. Arachidonic acid metabolites, cytokines, and other mediators (such as chemoattractants) induce a late-phase inflammatory response that appears several hours later in affected tissues when antigen exposure is continuous (eg, pollen) or chronic.

1. Anaphylaxis

► General Considerations

Anaphylaxis is the most serious and potentially life-threatening manifestation of mast cell and basophil mediator release. Anaphylaxis is defined clinically under the following circumstances: (1) an allergen exposure followed by the acute onset of illness involving skin or mucosal tissue and either respiratory compromise or hypotension (systolic blood pressure less than 90 mm Hg or 30% less than known baseline); (2) a likely allergen exposure followed by the acute onset of two or more of the following conditions: skin or mucosal tissue involvement, respiratory compromise, hypotension, and persistent gastrointestinal symptoms; or (3) a known allergen exposure followed by hypotension.

IgE-dependent anaphylaxis is usually an acute syndrome initiated by a new allergen exposure after a prior silent exposure has sensitized the patient with IgE antibodies. Thus, anaphylaxis (or systemic allergic reactions which do not meet the definition of anaphylaxis) cannot occur on first-time exposure to allergens like drugs, insect venoms, latex, and foods. In contrast, other syndromes of anaphylaxis (sometimes called “anaphylactoid”), such as reactions to radiocontrast media and most NSAID and opioid reactions, are pseudoallergic without known immunologic mechanisms and can occur with first-time exposure.

► Clinical Findings

A. Symptoms and Signs

Symptoms and signs typically occur within 30 minutes of initial exposure but may appear up to several hours later. These include (in order of frequency) (1) skin manifestations, typically urticaria but also flushing, blotchy rashes, and pruritus; (2) respiratory distress, including wheezing, stridor, bronchospasm, and airway angioedema; (3) gastrointestinal symptoms, including cramping, emesis, and

diarrhea (especially in food allergy); and (4) hypotension, often manifested as lightheadedness, dizziness, or syncope. The condition is potentially fatal, especially if untreated, and can affect both nonatopic and atopic persons.

B. Laboratory Findings

Identification of anaphylaxis is clinical as the need for treatment is urgent. Elevated serum levels of mast cell mediators, such as tryptase and histamine, may be detected shortly after a reaction providing support to the diagnosis. Referral to an allergy specialist is standard because of concern for a future reaction and need for appropriate interventions and education. Specific IgE serum or skin testing may be performed to suspected allergens. Skin testing, which is usually more sensitive, optimally occurs 4–6 weeks after a severe reaction to avoid falsely negative testing during a post-reaction “refractory” period. The positive predictive value of these tests is highly dependent on a suggestive temporal relationship to putative allergen exposure.

► Treatment

Early administration of intramuscular epinephrine at the onset of suspected anaphylaxis is the cornerstone of therapy. Supportive measures, such as oxygen, intravenous fluids and, if required, airway management are also appropriate. Adjunctive pharmacologic therapies include antihistamines, bronchodilators, and corticosteroids. Self-administered epinephrine at the earliest signs of recurrence can be life-sparing, whereas antihistamines and corticosteroids have limited value in reversing anaphylactic syndromes.

► When to Refer

Patients with new or unexplained onset of anaphylaxis should be evaluated by an allergist.

Shaker MS et al. Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145:1082. [PMID: 32001253]

Williams KW et al. Anaphylaxis and urticaria. Immunol Allergy Clin North Am. 2015;35:199. [PMID: 25459585]

2. Food Allergy

Immediate allergic reactions within 2 hours of ingestion of foods are much less common among adults than children. Most acute systemic food allergy is caused by proteins in milk, egg, wheat, soy, fish, shellfish, peanuts, and tree nuts. Milk and egg allergies in atopic children are often outgrown by adulthood. Shellfish, peanuts, and tree nuts are the most common causes of food anaphylaxis in adults. Diagnosis of food allergy relies on a combination of history, skin tests, and serum specific IgE tests. There is no role for specific IgG testing for evaluating food hypersensitivity. Because of frequent false-positive IgE tests, especially among atopic patients, oral food challenge remains the gold standard for diagnosis. However, this procedure should only be conducted by an experienced provider in a well-equipped setting. Management involves strict avoid-

ance of the culprit food and guaranteed access to self-administered epinephrine.

Other IgE-mediated food reactions include oral allergy syndrome and hypersensitivity to alpha-gal (galactose-alpha-1,3-galactose). Oral allergy syndrome, also known as pollen-associated food allergy syndrome, is the result of cross-reactivity between food and pollen proteins. Affected individuals have known seasonal pollen allergies (most commonly tree pollens) and experience itching of the oral mucosa upon ingestion of certain raw fruits and vegetables. In contrast to systemic food allergy, symptoms are limited to the oropharynx and usually do not involve other organ systems or progress to anaphylaxis.

Alpha-gal (galactose-alpha-1,3-galactose) is a carbohydrate found in red mammalian meats, including beef, pork, and lamb, but not in human tissues. Sensitization to this epitope has been linked to tick bites, so nonatopic individuals are at risk. In contrast to conventional systemic food allergy, the reaction to red meat typically occurs 4–6 hours after ingestion.

Kattan JD et al. Optimizing the diagnosis of food allergy. *Immuno Allergy Clin North Am.* 2015;35:61. [PMID: 25459577]

Platts-Mills TAE et al. Diagnosis and management of patients with the α -Gal syndrome. *J Allergy Clin Immunol Pract.* 2020;8:15. [PMID: 31568928]

Sicherer S et al. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol.* 2018;141:41. [PMID: 29157945]

3. Drug Allergy

Skin testing for immediate allergy to drugs is reliable for high molecular weight proteins (eg, cytokines, antisera, enzymes) but often not as reliable for low-molecular-weight compounds (eg, most drugs), which must bind to larger proteins (as haptens) to become immunogenic. With the exception of beta-lactam antibiotics like penicillins and some intraoperative drugs, in vivo skin testing for low-molecular-weight drugs is largely unvalidated, and interpretable only if the test is positive at a nonirritating concentration. Testing for IgE-mediated allergy to penicillin is available because the immunochemistry has been delineated and appropriate skin testing reagents are available. Skin testing with the major and minor metabolic determinants of penicillin has a very high (more than 98%) negative predictive value. Referral of individuals who relate histories of acute penicillin reactions to an allergist for skin testing is worthwhile because more than 90% have negative testing, indicating loss of allergic sensitization. Such patients may then safely receive penicillins and related antibiotics.

Mirakian R et al; Standards of Care Committee of the British Society for Allergy and Clinical Immunology. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy.* 2015;45:300. [PMID: 25623506]

Peter JG et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. *J Allergy Clin Immunol Pract.* 2017;5:547. [PMID: 28483310]

Shenoy ES et al. Evaluation and management of penicillin allergy: a review. *JAMA.* 2019;321:188. [PMID: 30644987]

4. Venom Allergy

The most common insects causing systemic allergic reactions include honeybees, vespids (yellow jackets, hornets, wasps), and fire ants. Systemic reactions often occur after several unremarkable stinging events and can develop at any age. Patients at highest risk for a severe reaction are those who have had a history of recent and severe reactions. The risk of a systemic reaction appears to decline over time since the last sting. If a systemic allergy is suspected, the patient is referred to an allergist for venom allergy testing and initiation of venom immunotherapy is recommended, if appropriate. In the interim, making self-administered epinephrine available is indicated for those with continuing exposure.

Golden DB et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol.* 2017;118:28. [PMID: 28007086]

5. Pseudoallergic Reactions

Pseudoallergic (anaphylactoid) reactions (Table 20–13) resemble immediate hypersensitivity reactions but are not mediated by allergen-IgE interaction. Examples include radiocontrast reactions, opioid reactions (direct mast cell activation), and “red man syndrome” from rapid infusion of vancomycin. In contrast to IgE-mediated reactions, these can often be prevented by prophylactic medical regimens.

A. Radiocontrast Media Reactions

Reactions to radiocontrast media are not usually IgE antibody-mediated, yet they are clinically similar to anaphylaxis and can be life-threatening. If a patient has had an anaphylactoid reaction to conventional radiocontrast media, the risk for a second reaction upon reexposure may be as high as 30%. Patients with a history of atopy are at increased risk.

Management includes use of low-osmolality contrast preparations and prophylactic administration of prednisone (50 mg orally every 6 hours beginning 13 hours before the procedure) and diphenhydramine (25–50 mg orally, intramuscularly or intravenously 60 minutes before the procedure). The use of lower-osmolality radiocontrast media in combination with the pretreatment regimen decreases the incidence of recurrent reactions to less than 1%.

B. Red Man Syndrome

Like radiocontrast media reactions, the “red man syndrome” (Table 20–13) results in anaphylactoid symptoms, especially flushing, pruritus, and erythema of the upper body. Initially described as a vancomycin-infusion reaction, it can also occur after intravenous infusion of opioids. The reaction is related to the rate of drug administration resulting in direct activation of mast cells. Management includes administration of an antihistamine such as diphenhydramine, 25–50 mg intravenously or intramuscularly, and reinitiation of the vancomycin infusion at no more than half the former rate. In patients who have previously experienced a vancomycin infusion reaction, pre-medication with an H₁-antagonist (eg, diphenhydramine)

Table 20–13. Uncommon allergic and pseudoallergic conditions.

Disease	Pathogenesis	Symptoms and Signs	Diagnostic Findings ¹	Treatment
Allergic bronchopulmonary aspergillosis	Immunologic response to pulmonary fungal colonization	Often underlying moderate to severe allergic asthma and/or cystic fibrosis, with wheezing, cough productive of thick brown sputum, fever, weight loss, fatigue	Elevated serum total IgE (> 1000 ng/mL); skin test positive to <i>Aspergillus</i>; positive <i>Aspergillus</i> precipitins, eosinophilia (off corticosteroids) (eosinophils > 1000 cells/mcL [$1.0 \times 10^9/L$]), pulmonary infiltrates, central bronchiectasis	Oral corticosteroids, antifungal (azole) agent
Hereditary angioedema	Quantitative or functional C1 esterase inhibitor deficiency, resulting in increased serum bradykinin levels	Unpredictable swelling of face, lips, tongue, hands, feet; no urticaria; gastrointestinal tract swelling causing severe abdominal pain	Decreased C1 esterase inhibitor serum level and/or function, decreased serum C4 level	Prophylactic treatment: Danazol, tranexamic acid Acute treatment: C1 esterase inhibitor product, kallikrein inhibitor, bradykinin receptor antagonist
Hypereosinophilic syndromes	Leukoproliferative disorder characterized by overproduction of eosinophils	Symptoms related to eosinophilic infiltration of organs: angioedema, urticaria, pruritic papules, chronic cough, splenomegaly, heart failure	Eosinophilia (eosinophils > 1500 cells/mcL [$1.5 \times 10^9/L$]), elevated serum vitamin B₁₂ level, elevated serum tryptase level, anemia, PDGFRA gene mutation	Corticosteroids, tyrosine kinase inhibitors
Mastocytosis	Mast cell hyperplasia	Pruritus, flushing, nausea, vomiting, diarrhea, abdominal pain, hypotension	Dense bone marrow mast cell infiltrate ($\geq 15/hpf$) on biopsy, elevated serum tryptase level (> 20 ng/mL), atypical mast cell morphology, cKIT mutation	Antihistamine, cromolyn, epinephrine, chemotherapy directed at underlying mast cell hyperplasia
“Red man syndrome” (acute infusion reaction)	Direct activation of mast cells by vancomycin, opioids	Flushing, pruritus, and erythema, especially of the upper body, during intravenous infusion of drug	Clinical history and physical examination, no role for laboratory testing	Antihistamine pretreatment 1 hour prior to subsequent vancomycin (or opioid) infusions, decreased rate of infusion
Serum sickness (and serum sickness-like syndromes)	Mediated by circulating immune complexes	Fever, pruritic urticarial or maculopapular rash, lymphadenopathy, arthralgias, arthritis, nephritis	Increased ESR, leukocytosis, possible low serum C3 and C4 levels	Self-limited illness: NSAIDs, antihistamines Severe illness: Corticosteroids, plasma exchange

¹Key diagnostic findings in bold.

cKIT, stem cell factor receptor or CD117; ESR, erythrocyte sedimentation rate; NSAID, nonsteroidal anti-inflammatory drug; PDGFRA, platelet-derived growth factor receptor alpha.

and H₂-antagonist (eg, cimetidine) is recommended 1 hour prior to the infusion. Although rare, IgE sensitization to vancomycin does occur and should be suspected in patients who have received multiple courses of the drug. Skin testing is helpful because vancomycin, as a “complete allergen,” can elicit positive skin tests. Desensitization to vancomycin is possible for patients with positive skin tests and no acceptable alternative antibiotic.

Schönmann C et al. Adverse reactions during procedures: Hypersensitivity to contrast agents and dyes. *Ann Allergy Asthma Immunol*. 2020;124:156. [PMID: 31765812]

6. Aspirin (NSAID) Exacerbated Respiratory Disease

Although hypersensitivity to aspirin and other NSAIDs is a feature of this condition, the reaction is a result of aberrant arachidonic acid metabolism, rather than a product of an IgE-activated process. The inhibition of cyclooxygenase-1 (COX-1) by these anti-inflammatory drugs results in the overproduction of cysteinyl leukotrienes and increased expression of leukotriene receptors, leading to increased airway responsiveness, bronchospasm, rhinorrhea, and nasal congestion. Reactions outside of the respiratory system can also occur, including ocular, cutaneous, and gastric symptoms.

In addition to aspirin or NSAID sensitivity, patients with aspirin exacerbated respiratory disease typically have chronic rhinosinusitis with nasal polyps and asthma, a syndrome referred to as “Samter triad” or “triad asthma.” Diagnosis is largely based on history and clinical findings. If required, a positive aspirin challenge can demonstrate the NSAID hypersensitivity, the presence of which may suggest increased responsiveness to treatments such as nasal polypectomy and aspirin desensitization and long-term aspirin use. Patients who require daily aspirin or NSAID treatment for other reasons can be desensitized to permit such treatment. Desensitization and long-term aspirin therapy have also been shown to reduce the need for nasal polypectomy and asthma therapy. Referral to an allergy specialist is appropriate for consideration of such desensitization.

Saff RR et al. Management of patients with nonaspirin-exacerbated respiratory disease aspirin hypersensitivity reactions. *Allergy Asthma Proc*. 2015;36:34. [PMID: 25562554]

Simon RA et al. Update on aspirin desensitization for chronic rhinosinusitis with polyps in aspirin-exacerbated respiratory disease (AERD). *Curr Allergy Asthma Rep*. 2015;15:508. [PMID: 25663486]

White AA et al. Aspirin—exacerbated respiratory disease. *N Engl J Med*. 2018;379:1060. [PMID: 30207919]

strong predisposing factors for atopic diatheses, eg, a strong family history of atopy or ongoing exposure to potential sources of allergen. Since the development of rhinitis precedes the presentation of asthma in over half of cases, early intervention may decrease the risk of more severe clinical illness. The type of immune response must be consistent with the nature of the disease. For example, IgE antibody causes allergic rhinitis but not allergic contact dermatitis. IgE antibodies are detected by in vivo (skin tests) or in vitro methods.

Adkinson NF Jr et al. Clinical history-driven diagnosis of allergic diseases: utilizing in vitro IgE testing. *J Allergy Clin Immunol Pract*. 2015;3:871. [PMID: 26553614]

DELAYED HYPERSENSITIVITY

According to the Gell and Coombs classification, type IV delayed hypersensitivity is mediated by activated T cells, which accumulate in areas of antigen deposition. A common example is allergic contact dermatitis, which develops when a low-molecular-weight sensitizing substance serves as a hapten for dermal proteins, becoming a complete antigen. Sensitized T cells release cytokines, activating macrophages and promoting subsequent dermal inflammation; this typically occurs 48–72 hours after contact. Another common expression of delayed hypersensitivity is drug allergy that occurs after a similar process and that often results in maculopapular or morbilliform exanthems. T-cell-mediated hypersensitivity is now understood to involve both Th1 and Th2 cells. In addition, subsequent inflammation and tissue damage occur via various effector cell types, including monocytes, eosinophils, and neutrophils.

1. Drug Exanthems

The clinical manifestation of these reactions is vast (Chapter 6), ranging from the commonly observed morbilliform rash to skin sloughing observed in Stevens-Johnson syndrome and toxic epidermal necrolysis. Given the range of cutaneous findings, the differential diagnosis is broad and includes miliaria, lichen planus, folliculitis, pityriasis rosea, tinea corporis, and mycosis fungoides. Physical examination of rash characteristics, dermatologic consultation, and biopsy findings can help narrow the differential. While a whole spectrum of drugs can result in exanthems, there are no commercially available laboratory or other diagnostic tests to reliably identify the culprit drug.

Management consists mainly of immediate cessation of suspected medications and monitoring for symptom resolution. Systemic corticosteroids may be indicated for extensive dermatitis or other organ involvement.

American College of Radiology. *ACR Manual on Contrast Media*, 2020. <https://www.acr.org/Clinical-Resources/Contrast-Manual>

Chopra AM et al. Meta-analysis of acetylsalicylic acid desensitization in patients with acute coronary syndrome. *Am J Cardiol*. 2019;124:14. [PMID: 31027657]

Phillips EJ et al. Controversies in drug allergy: testing for delayed reactions. *J Allergy Clin Immunol*. 2019;143:66. [PMID: 30573342]

ALLERGY TESTING

To maximize the positive predictive value of allergy testing, a positive test result must be correlated with the history. Patients selected for testing include those with moderate to severe disease, those who are potential candidates for allergen immunotherapy, and those with

2. Drug-Induced Hypersensitivity Syndrome (Drug Reaction With Eosinophilia & Systemic Symptoms)

► General Considerations

Potentially life-threatening, systemic drug-induced hypersensitivity reactions most commonly occur with exposure to anticonvulsants and sulfonamides, although many other classes of drugs, including other antimicrobials and antidepressants, have been implicated. The onset of symptoms typically occurs 2–6 weeks after drug initiation. As suggested by its alternative name, drug reaction with eosinophilia and systemic symptoms (DRESS), it typically includes eosinophilia and/or lymphocytosis and systemic symptoms such as fever and lymph node enlargement, along with the rash. The exact pathogenesis of DRESS is not well elucidated but may include deficient drug metabolism due to genetic mutations in specific detoxification enzymes; reactivation of herpesviruses including HHV-6, HHV-7, cytomegalovirus, and Epstein-Barr virus; and a genetic predisposition based on the presence of specific HLA haplotypes.

► HLA Haplotypes & Risk of Delayed-Onset Drug Hypersensitivity Syndromes

Activated cytotoxic CD8 T lymphocytes play a key role in the pathogenesis of serious, drug-induced adverse cutaneous reactions, such as toxic epidermal necrolysis. There are striking, medication-specific associations between inheritance of particular HLA-B alleles and risk of these hypersensitivity reactions in defined populations. Most notably, B*57:01 confers risk for reactions to abacavir; B*15:02, for carbamazepine; B*58:01, for allopurinol; and B*13:01, for dapsone. The most likely mechanism is a direct interaction between the drug and the antigen-binding cleft of the HLA-B molecule, such that many “self” antigens subsequently bound by the HLA-B molecule are perceived as “foreign,” eliciting massive CD8 T-cell activation. Current FDA recommendations call for testing for the relevant HLA-B allele prior to initiating therapy with abacavir in all patients and with carbamazepine in Asian patients. The American College of Rheumatology recommends such testing before starting allopurinol therapy in patients of Korean descent, especially those with kidney disease, and Han Chinese and individuals of Thai extraction. Pretreatment HLA testing for other drugs or in other populations may not be useful at the present time due to low prevalence of the implicated isotypes.

► Clinical Findings

A. Symptoms and Signs

Drug-induced hypersensitivity syndrome often begins with pruritus and fever, but cutaneous manifestations generally follow soon thereafter, most commonly an erythematous morbilliform rash. Although the entire skin surface can be involved, the face, trunk, and upper and lower extremities are commonly affected. The most common systemic findings involve the lymphatic (lymphadenopathy), hematologic and hepatic systems, although renal, pulmonary and cardiac involvement is also documented.

B. Laboratory Findings

Laboratory abnormalities include leukocytosis with eosinophilia (greater than $1.5 \times 10^9/L$) and atypical lymphocytosis; elevated hepatic transaminases (more than 2 times upper limits of normal) and alkaline phosphatase; and increased serum creatinine, pyuria, and proteinuria, which may indicate the development of interstitial nephritis. The most common skin biopsy findings are a dense, perivascular lymphocytic infiltrate in the papillary dermis with eosinophils and dermal edema.

► Treatment

Management consists of cessation of the causative medication and initiation of systemic corticosteroids. A dose of 1.0 mg/kg of oral prednisone is recommended as a starting dose, followed by a gradual taper occurring over 3–6 months after laboratory normalization and stabilization. Additional supportive therapies may include antipyretics for fever, topical steroids for skin lesions, or fluid and electrolyte replacement in the case of more severe exfoliative dermatitis.

Shiohara T et al. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): an update in 2019. Allergol Int. 2019;68:301. [PMID: 31000444]

PRIMARY IMMUNODEFICIENCY DISORDERS IN ADULTS

Primary immunologic deficiency diseases are estimated to affect 1 in 4000 individuals; many are genetically determined and present in childhood. Nonetheless, several important immunodeficiency disorders present in adulthood, most notably the antibody deficiency syndromes: selective IgA deficiency, common variable immunodeficiency, and specific (functional) antibody deficiency (Table 20–14). Antibody deficiency predisposes patients to recurrent infections, particularly of the respiratory tract, including refractory chronic rhinosinusitis, bronchitis, pneumonia, and bronchiectasis. Patients are most susceptible to infections with encapsulated bacteria (eg, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Neisseria meningitidis*). However, any part of the innate or adaptive immune system can be defective and results in infections with different spectra of organisms.

1. Selective IgA Deficiency

Selective IgA deficiency is the most common primary immunodeficiency disorder and is characterized by undetectable serum IgA levels (lower than 7 mg/dL) with normal levels of IgG and IgM; its prevalence is about 1 in 500 individuals (Table 20–14). Most affected individuals are asymptomatic. A minority of patients have recurrent infections such as sinusitis, otitis, and bronchitis. Selective IgA deficiency can be associated with atopic diseases and autoimmune disorders, including Graves disease, SLE, juvenile rheumatoid arthritis, type 1 diabetes mellitus, and celiac disease.

Table 20–14. Selected primary immunodeficiency syndromes.

Disease	Clinical Presentation	Diagnosis ¹	Treatment
Selective IgA deficiency	Most prevalent primary immunodeficiency; most cases asymptomatic Recurrent sinopulmonary infections; atopic disorders, rheumatoid arthritis, and SLE common; rarely, anaphylaxis to transfusion of blood or blood products	Undetectable serum IgA levels (< 7 mg/dL), normal serum IgG and IgM levels	Early use of antibiotics for bacterial infections Prophylactic antibiotics for symptomatic patients with recurrent infections
Common variable immunodeficiency	Most common symptomatic primary immunodeficiency disorder Recurrent sinopulmonary infections, parasitic (especially <i>Giardia lamblia</i>) gastrointestinal infections, autoimmune diseases, and increased risk of malignancy	Low serum IgG , low serum IgA and/or IgM; poor antibody response to immunizations ; exclusion of secondary causes of hypogammaglobulinemia	Subcutaneous or intravenous immunoglobulins Prophylactic antibiotics
Complement disorders	"Early" complement component deficiencies: autoimmune diseases "Late" complement component (C5–C8) deficiencies: recurrent meningococcal or gonococcal infections	Screen with CH50 and AH50. Obtain individual serum complement levels if abnormal	Prompt administration of antibiotics
Granulocyte disorders	Recurrent invasive skin and soft tissue infections, abscesses requiring incision and drainage Common organisms are <i>Staphylococcus aureus</i> , gram-negative bacilli, <i>Nocardia</i> , <i>Aspergillus</i>	CBC with differential to evaluate neutrophil count Dihydrorhodamine assay to evaluate neutrophil oxidative burst	Antimicrobial prophylaxis; interferon in patients with chronic granulomatous disease

¹Key diagnostic findings in bold.

CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.

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Some individuals with undetectable levels of serum IgA may have high titers of anti-IgA antibodies and are at risk for anaphylactic reactions to IgA following exposure to it through infusions of plasma (or blood transfusions). Treatment with commercial immune globulin is not indicated and may very rarely result in anaphylactic reactions.

► When to Refer

- Refer patients with anaphylaxis following infusions of plasma (or blood transfusions) to an immunologist for further evaluation of possible IgA deficiency.
- Refer patients with undetectable serum IgA and recurrent sinopulmonary infections, celiac disease, giardiasis, or a family history of immunodeficiency to an immunologist.

2. Common Variable Immunodeficiency

 ESSENTIALS OF DIAGNOSIS
<ul style="list-style-type: none"> Frequent sinopulmonary infections secondary to humoral immune deficiency. Low serum immunoglobulin levels and deficient functional antibody responses. Primary defect may be with B cells or T cells.

► General Considerations

The most common symptomatic primary immunodeficiency disorder is common variable immunodeficiency, a heterogeneous immunodeficiency disorder clinically characterized by an increased incidence of recurrent infections, autoimmune phenomena, and neoplastic diseases. The onset is generally in early adulthood but it can occur at any age. The prevalence of common variable immunodeficiency is about 1 in 25,000 in the United States. Most cases are sporadic; about 10–20% are familial.

► Clinical Findings

A. Symptoms and Signs

Increased susceptibility to infections, especially with encapsulated organisms, is the hallmark of the disease. Chronic lung disease is one of the most frequent complications of common variable immunodeficiency. Virtually all patients suffer from recurrent sinusitis; bronchitis, otitis, pharyngitis, and pneumonia are common infections. Infections may be prolonged or associated with unusual complications such as meningitis, empyema, or sepsis. Bronchiectasis occurs in at least 25% of patients with common variable immunodeficiency and is a leading cause of morbidity.

Gastrointestinal infections and dysfunction are commonly associated with common variable immunodeficiency, and a sprue-like syndrome, with diarrhea,

steatorrhea, malabsorption, protein-losing enteropathy, and hepatosplenomegaly, may develop in patients. Paradoxically, there is an increased incidence of autoimmune disease (20%), although patients may not display the usual serologic markers. Autoimmune cytopenias are most common, but autoimmune endocrinopathies, seronegative rheumatic disease, and gastrointestinal disorders are also commonly seen. Lymph nodes may be enlarged in these patients, yet biopsies show marked reduction in plasma cells. Noncaseating granulomas are frequently found in the spleen, liver, lungs, or skin. There is an increased propensity for the development of B-cell neoplasms (50- to 400-fold increased risk of lymphoma) and gastric carcinomas.

B. Laboratory Findings

Assess serum quantitative immunoglobulin levels. All patients with common variable immunodeficiency have a reduced serum IgG level, and either serum IgM or IgA or both are reduced as well. Demonstration of functional or quantitative defects in antibody production is essential and is typically performed by checking antibody response to polysaccharide (Pneumovax-23) and protein antigens (such as tetanus and diphtheria). The diagnosis is made in patients who have reduced serum immunoglobulins and poor antibody response to vaccines, after exclusion of secondary causes (eg, proteinuria, protein-losing enteropathy, drug effects such as rituximab and other immunosuppressants, antiepileptics, and hematologic malignancies).

The absolute B-cell count in the peripheral blood can be normal. A subset of these has concomitant T-cell immunodeficiency with increased numbers of activated CD8 cells, splenomegaly, and decreased delayed-type hypersensitivity.

Treatment

Patients with common variable immunodeficiency should be treated aggressively with antibiotics at the first sign of infection. Since antibody deficiency predisposes patients to high-risk pyogenic infections, antibiotic coverage should be sure to cover encapsulated bacteria. Infections with other microorganisms also can develop, including viruses, parasites, and extracellular gram-positive or gram-negative bacteria (such as *S aureus* or *P aeruginosa*). Mainstay of preventive therapy is with subcutaneous or intravenous immunoglobulin replacement therapy, with a typical monthly dose of 300–600 mg/kg. Subcutaneous injections of IgG offer the convenience of self-administration at home and lower incidence of adverse effects and can be administered every 1–4 weeks. Adjustment of the dosage or infusion interval is made primarily on the basis of clinical

responses in addition to serum IgG levels. Such therapy is essential for decreasing the incidence of potentially life-threatening infections, increasing quality of life, and reducing the progression of lung disease.

When to Refer

- Refer patients with low serum immunoglobulins and history of recurrent or unusual infections, autoimmune disease, or family history of immunodeficiency to an allergist or immunologist.
- The presence of bronchiectasis without a known underlying cause such as cystic fibrosis should raise the suspicion of a primary immunodeficiency; even when total serum immunoglobulins levels are normal, the patient can have a specific antibody deficiency that would warrant further evaluation.

3. Specific (Functional) Antibody Deficiency

Specific antibody deficiency is characterized by decreased or absent IgG antibody response to vaccines in the setting of normal or mildly decreased serum immunoglobulin levels. The clinical spectrum can range from mild to severe with features very similar to common variable immunodeficiency. Antibody deficiency should be suspected in patients with documented infections who have symptoms similar to common variable immunodeficiency but have normal serum immunoglobulin levels.

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21

Electrolyte & Acid-Base Disorders

Nayan Arora, MD

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ASSESSMENT OF THE PATIENT

The pathophysiology of all electrolyte disorders is rooted in basic principles of total body water and its distribution across fluid compartments. The optimal evaluation and treatment of fluid and electrolyte disorders requires a careful interpretation of serum and urine chemistries in conjunction with a thorough history and physical examination. While classic teaching has focused on physical examination to determine a patient's volume status, such an approach can be challenging because of limitations in accurate bedside analysis of volume status.

A. Body Water and Fluid Distribution

Total body water depends on the relative proportions of muscle and fat in the body. Total body water is typically estimated as 50% of body weight in women and 60% in men, as women, on average, have a higher proportion of fat to body weight (Table 21–1). Total body water also tends to decrease with age due to declining muscle mass. Approximately two-thirds of total body water is located in the intracellular compartment and one-third is located in the extracellular compartment. The extracellular compartment is further divided into the interstitial fluid volume (15% of body weight) and the plasma fluid volume (5% of body weight).

Changes in total body water content are best evaluated by documenting changes in body weight. Extracellular volume (ECV) may be assessed by physical examination (eg, blood pressure, pulse, jugular venous distention, edema). Quantitative assessments of ECV and intravascular volume may be invasive (ie, central venous pressure or pulmonary wedge pressure) or noninvasive (ie, inferior

vena cava diameter and right atrial pressure by echocardiography). Intracellular volume (ICV) is assessed using the serum sodium concentration.

B. Serum Electrolytes

In health, serum electrolytes are maintained within a narrow range by the kidneys (homeostasis). The serum level of an electrolyte may be normal, elevated, or decreased but may not correlate with the total body levels of that electrolyte due to shift of water or electrolytes into and out of cells.

C. Evaluation of Urine

The urine concentration of an electrolyte is helpful to determine whether the kidney is excreting or retaining the electrolyte in response to high or low serum levels. A 24-hour urine collection for daily electrolyte excretion remains the gold standard for assessment of renal electrolyte handling; however, it can be cumbersome, as well as technically challenging in certain patients. A more convenient method to determine renal electrolyte handling is the use of fractional excretion (FE) of an electrolyte X (FE_x) calculated from a spot urine sample and serum sample, using creatinine (Cr):

$$FE_x (\%) = \frac{\text{urine}_x \times \text{serum}_{Cr}}{\text{serum}_x \times \text{urine}_{Cr}} \times 100$$

A low fractional excretion indicates renal reabsorption (electrolyte retention), while a high fractional excretion indicates renal wasting (electrolyte excretion). Thus, the fractional excretion helps determine whether the kidney's response is appropriate for a specific electrolyte disorder.

D. Serum Osmolality

Total solute concentration is measured by osmolality in millimoles per kilogram. Osmolarity is measured in millimoles of solute per liter of solution. The terms are often used interchangeably in clinical medicine. Plasma osmolality is the total concentration of all the solutes contained in plasma, both electrolytes and nonelectrolytes, and normally ranges between 285 mmol/L and 295 mmol/L. Differences in osmole concentration across cell membranes

Table 21–1. Total body water (as percentage of body weight) in relation to age and sex.

Age	Male	Female
18–40	60%	50%
41–60	60–50%	50–40%
Over 60	50%	40%

lead to movement of water to the region of higher osmolality, stimulation of thirst, and secretion of antidiuretic hormone (ADH). Substances that easily permeate cell membranes (eg, urea, ethanol) are ineffective osmoles and do not cause fluid shifts across fluid compartments.

Serum osmolality (Osm) can be estimated using the following formula:

$$\text{Osm} = 2(\text{Na}^+ \text{ mEq/L}) + \frac{\text{Glucose mg/dL}}{18} + \frac{\text{BUN mg/dL}}{2.8}$$

(Note: dividing urea by 2.8 converts mg/dL to mmol/L; dividing glucose by 18 converts mg/dL to mmol/L)

Sodium is the major extracellular cation; doubling the serum sodium in the formula for estimated osmolality accounts for corresponding anions. A discrepancy between measured and estimated osmolality of greater than 10 mmol/kg suggests an osmolal gap, which is the presence of unmeasured osmoles such as ethanol, methanol, isopropanol, and ethylene glycol (see Table 38–5).

DISORDERS OF SODIUM CONCENTRATION

HYPONATREMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Must know volume status as well as serum and urine osmolality to determine etiology.
- ▶ Hyponatremia usually reflects excess water retention rather than sodium deficiency. The serum sodium concentration is not a measure of total body sodium.
- ▶ Hyponatremia in hospitalized patients commonly is caused by administration of hypotonic fluids.

General Considerations

Hyponatremia is defined as a serum sodium concentration less than 135 mEq/L (135 mmol/L) and is the most common electrolyte abnormality encountered in clinical practice. Hyponatremia represents an excess of water relative to sodium in the plasma leading to a reduction in plasma osmolality and subsequent movement of water from the extracellular fluid into the intracellular fluid. Acutely, this movement of water can result in cerebral edema, increasing the risk of seizures and even brain herniation.

Chronic hyponatremia is often asymptomatic or present with mild confusion, nausea, or falls. In these patients, cerebral adaptation has occurred as the brain cells have excreted intracellular osmoles to limit cell swelling. In this setting, over-rapid correction of chronic hyponatremia may produce profound neurologic abnormalities (osmotic demyelination syndrome).

A common misconception is that hyponatremia is secondary to a deficiency in total body sodium, when in reality it usually reflects an excess of total body water.

The basic pathophysiologic principle is the ingestion of water (oral or intravenous) in excess of the amount the kidney can excrete is commonly due to the action of ADH. A diagnostic algorithm separates the causes of hyponatremia using serum osmolality, urine sodium, and volume status (Figure 21–1).

Etiology

A. Isotonic and Hypertonic Hyponatremia

Hyponatremia is typically associated with hypoosmolality with two exceptions: pseudohyponatremia and hypertonic hyponatremia.

1. Pseudohyponatremia—This represents a laboratory artifact that rarely occurs in patients with marked hypertriglyceridemia or hypergammaglobulinemia. In these settings, there is an increase in the solid components of plasma, relative to plasma water, resulting in a lower sodium per given volume. This issue is becoming less prevalent as most laboratories are now using direct ion selective electrodes without blood dilution. Consultation with the clinical laboratory is necessary if this condition is suspected.

2. Hypertonic hyponatremia—The best clinical examples of this situation are hyperglycemia, and less commonly, mannitol infusion. Both glucose and mannitol are active osmoles, increasing the osmolality of the extracellular fluid, which pulls water from inside cells into the extracellular space. Note, this leads to a reduction in intracellular volume, and cerebral edema is not caused by hyponatremia in this setting; however, cerebral edema may occur in the treatment phase due to over-rapid correction of hyperglycemia and injudicious intravenous fluids. The increased tonicity will also stimulate thirst and vasopressin release, further contributing to water retention. To determine whether the hyponatremia can be entirely attributed to hyperglycemia, a sodium correction factor is often used. Many guidelines recommend using a decrease in the serum sodium concentration of 1.6 mEq/L (1.6 mmol/L) for every 100 mg/dL (5.5 mmol/L) rise in plasma glucose above normal.

B. Hypotonic Hyponatremia

Most cases of hyponatremia are hypotonic, highlighting sodium's role as the predominant extracellular osmole. The presence of hypotonic hyponatremia indicates that water intake exceeds the excretional capacity of the kidney. The next step is to classify hypotonic cases as ADH dependent or independent judged by the kidney's ability to excrete dilute urine.

1. ADH-independent causes—In rare circumstances, hypotonic hyponatremia can occur when the kidney's ability to excrete free water is intact (urine osmolality less than 100 mOsm/kg).

A. PSYCHOGENIC POLYDIPSIA—This condition develops where excess water intake overwhelms the kidney's capacity to excrete adequate dilute urine. Patients will have appropriately suppressed ADH, reflected by a urine osmolality less than 100 mOsm/kg. Polydipsia occurs primarily

in patients with psychiatric disorders. Psychiatric medications may also interfere with water excretion or increase thirst through anticholinergic side effects, further increasing water intake.

B. BEER POTOMANIA AND THE “TEA AND TOAST” DIET—

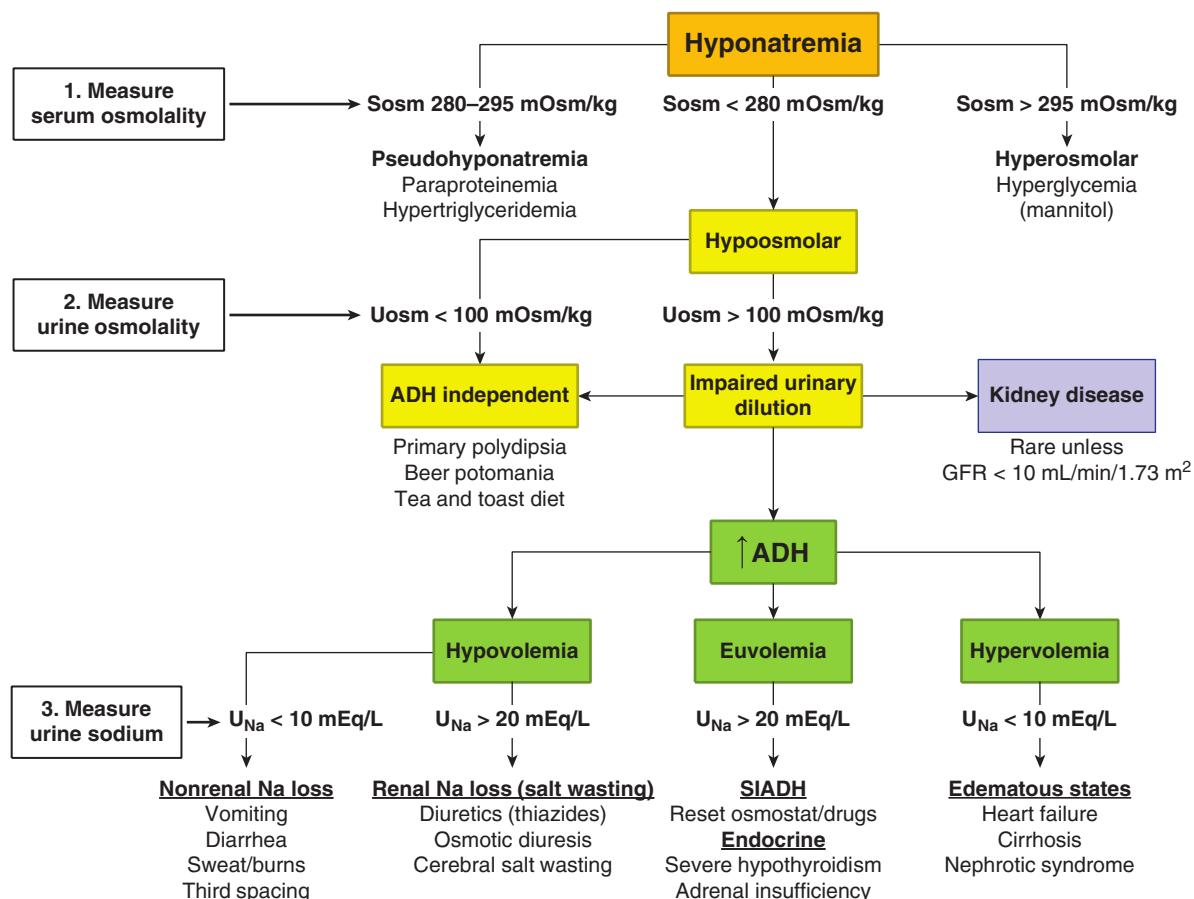
Malnourished patients who consume a low protein diet with large quantities of beer (beer potomania) or those who consume a low protein (tea and toast) diet may have a marked reduction in free water excretion due to insufficient dietary solute intake. The kidney's ability to excrete free water is dependent not only on ADH suppression, but also on solute delivery to the distal tubules. With a typical Western diet generating 1000 mOsm of solute per day, normal kidneys can dilute urine to 50 mOsm/kg, allowing a maximum urine volume of 20 L. By contrast, with a low protein diet generating 200 mOsm per day, urinary output would be limited to a maximum of 4 L per day.

c. RENAL IMPAIRMENT—Patients with advanced renal impairment (GFR less than 15 mL/min/1.73 m²), whether due to severe chronic kidney disease (CKD) or acute kidney injury, may be unable to dilute their urine (can often only achieve a minimum urine osmolality of

200–250 mOsm/L even with maximal ADH suppression) and are prone to develop water retention and hyponatremia. This can occur in the setting of normal or high plasma osmolality due to accumulation of urea. This differs from hypertonic hyponatremia because urea is an ineffective osmole and is freely permeable across cell membranes, only minimally pulling water into the plasma space.

2. ADH-dependent causes—The most common cause of hypotonic hyponatremia involves a failure to suppress ADH action. This can either be **appropriate** in the setting of hypovolemia, or a reduced effective arterial volume secondary to cirrhosis or heart failure (hypervolemia), or **inappropriate**, in the absence of hypovolemia or edematous states, which is known as the syndrome of inappropriate ADH secretion (SIADH).

A. HYPOVOLEMIC HYPONATREMIA—Hypovolemic hyponatremia occurs with renal or extrarenal volume loss (sodium and water) and subsequent hypotonic fluid replacement (Figure 21-1). The reduced blood pressure results in an increase in ADH secretion by the pituitary, limiting free water excretion. In this setting, the body sacrifices serum osmolality to preserve intravascular volume.



▲ **Figure 21-1.** A diagnostic algorithm for the causes of hyponatremia using serum osmolality, urine osmolality, and urine sodium. ADH, antidiuretic hormone; GFR, glomerular filtration rate; SIADH, syndrome of inappropriate antidiuretic hormone.

Cerebral salt wasting is a rare subset of hypovolemic hyponatremia that occurs with intracranial disease (eg, infections, cerebrovascular accidents, tumors, and neurosurgery). Clinical features include refractory hypotension, often in the setting of continuous infusion of isotonic or hypertonic saline. The pathophysiology is unclear but has been attributed to renal sodium wasting, although there is uncertainty as to whether cerebral salt wasting represents a distinct entity or SIADH with desalination of the administered saline.

B. HYPERVOLEMIC HYPONATREMIA—Hypervolemic hyponatremia commonly occurs in the edematous states of cirrhosis and heart failure, and rarely in nephrotic syndrome (Figure 21–1). In these settings, a decreased effective arterial blood volume (typically low blood pressure) occurs despite an overall increase in extracellular volume (edema) resulting in ADH secretion. In cirrhosis and heart failure, effective circulating volume is decreased due to systemic vasodilation and reduced cardiac output, respectively.

C. SIADH—In this condition, ADH is secreted in the absence of an appropriate physiologic stimuli such as a decreased effective circulating volume or hyperosmolality. The major causes of SIADH (Table 21–2) are disorders affecting the central nervous system or the lungs (such as cancer or infections) and medications. SIADH is a diagnosis of exclusion, which involves ruling out other causes of hyponatremia (eg, low effective circulating volume,

decreased solute intake, cortisol deficiency, and severe hypothyroidism). SIADH is a clinical diagnosis characterized by (1) hyponatremia; (2) decreased plasma osmolality (less than 280 mOsm/kg); (3) absence of heart, kidney, or liver disease; (4) normal thyroid and adrenal function (see Chapter 26); and (5) urine sodium usually over 20 mEq/L. Patients with SIADH may have low blood urea nitrogen (BUN) (less than 10 mg/dL [3.6 mmol/L]) and hypouricemia (less than 4 mg/dL [238 μmol/L]), which are not only dilutional but result from increased urea and uric acid clearances in response to the volume-expanded state.

D. RESET OSMOSTAT—This is a rare cause of hyponatremia in which patients regulate vasopressin release around a lower, or hypotonic, set point. Diagnosis involves documentation of dilute urine when serum sodium is lowered by administration of free water; however, this is rarely done in clinical practice. The mild hypo-osmolality of pregnancy is a form of reset osmostat.

E. ADRENAL INSUFFICIENCY AND HYPOTHYROIDISM—Cortisol normally provides a negative feedback on ADH release, and therefore cortisol deficiency can lead to uninhibited ADH and hyponatremia. Concomitant mineralocorticoid deficiency may result in hyperkalemia and metabolic acidosis. Hyponatremia due to hypothyroidism only occurs in the context of myxedema coma, which may be related to a low cardiac output state and thus decreased effective arterial blood volume.

F. NAUSEA, PAIN, AND SURGERY—Nausea and pain are potent stimulators of ADH release. Severe hyponatremia can develop after elective surgery in healthy patients due to excessive use of hypotonic fluids.

G. EXERCISE-ASSOCIATED HYPONATREMIA—Hyponatremia during or after exercise, especially endurance events such as triathlons and marathons, may be caused by a combination of excessive hypotonic fluid intake and ADH secretion (due to hypovolemia, pain, or nausea). Current guidelines suggest that endurance athletes drink water according to thirst rather than according to specified hourly rates of fluid intake. Electrolyte-containing sport drinks do not protect against hyponatremia since they are markedly hypotonic relative to serum.

H. THIAZIDE DIURETICS AND OTHER MEDICATION—Thiazides may induce hyponatremia, typically in older patients, within a few weeks of initiating therapy, and may be exacerbated by increased thirst and low solute intake. The mechanism appears to be a combination of water intake and a mild diuretic-induced volume contraction leading to ADH secretion. Loop diuretics do not cause hyponatremia as frequently due to impairment of the medullary concentration gradient, limiting the ability of ADH to promote water retention.

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase ADH by inhibiting prostaglandin formation. Selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine, and citalopram) can also cause hyponatremia, especially in geriatric patients. Enhanced secretion or action of ADH may result from increased serotonergic tone.

Table 21–2. Common causes of syndrome of inappropriate ADH secretion (SIADH).

Central nervous system disorders
Stroke
Hemorrhage
Infection
Trauma
Inflammatory and demyelinating diseases
Pulmonary lesions
Infections (viral, bacterial, fungal)
Malignancies
Many but particularly small cell carcinoma of the lung
Drugs (this is only a partial list as many have been implicated)
Antidepressants: SSRIs, tricyclics, monoamine oxidase inhibitors
Antineoplastics: cyclophosphamide, ifosfamide, methotrexate
Anticonvulsants: carbamazepine, sodium valproate, lamotrigine
Neuroleptics: haloperidol, fluphenazine, trifluoperazine thioridazine, thiothixene
NSAIDs
Methylenedioxymethamphetamine (MDMA; Ecstasy)
Amiodarone
Ciprofloxacin
Opioids
Others
HIV
Pain, postoperative, stress
Hereditary
Idiopathic

NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Use of 3,4-methylenedioxymethamphetamine (MDMA, also known as Ecstasy) can lead to hyponatremia and severe neurologic symptoms, including seizures, cerebral edema, and brainstem herniation. MDMA and its metabolites increase ADH release from the hypothalamus. Polydipsia may contribute to hyponatremia since MDMA users typically increase fluid intake to prevent hyperthermia.

Clinical Findings

A. Symptoms and Signs

Whether hyponatremia is symptomatic depends on both its severity and acuity. **Chronic hyponatremia**, defined as lasting longer than 48 hours, is often diagnosed on routine electrolyte measurements; patients are often asymptomatic as the brain has adapted to the surrounding hypotonicity. Subtle abnormalities, such as mild concentration and cognitive deficits, as well as gait disturbances that can lead to falls, may be present. **Acute hyponatremia** (defined as lasting less than 48 hours) can result in marked neurologic symptoms, even with relatively modest hyponatremia, due to acute brain cell swelling and subsequent rise in intracranial pressure. Early symptoms include headache and decrease in attentiveness, which can lead to lethargy, disorientation, and nausea. The most serious symptoms include marked confusion and decreased levels of consciousness, vomiting, seizures, coma, brainstem herniation, and death.

Clinical evaluation starts with a history of medications, changes in fluid intake (polydipsia, anorexia, intravenous fluid rates and composition), and fluid output (nausea and vomiting, diarrhea, ostomy output, polyuria, oliguria, insensible losses). The physical examination should attempt to categorize volume status (see Body Water and Fluid Distribution, above). The next determination is why ADH is being released and conditions in which release may be halted abruptly, which can impact the approach to therapy.

B. Laboratory Findings

The initial laboratory assessment should include serum and urine electrolytes and serum and urine osmolality. In clinical practice ADH levels are not measured; urine osmolality is used as a surrogate for ADH activity. Urine osmolality should be checked not only at the time of diagnosis but may also be useful if checked serially during therapy. Bedside assessment of volume status is often insensitive; therefore, a urine sodium may help differentiate between hypovolemia and euolemia, particularly in nonedematous patients (Figure 21–1). The etiology of most cases of hyponatremia will be apparent by appropriate interpretation of the above laboratory values, in addition to patient history and assessment of volume status. Additional testing, such as thyroid and adrenal function tests, may be warranted in the appropriate context.

Treatment

The initial treatment of hyponatremia is contingent on two primary factors, the acuity of onset and the severity of

symptoms. In patients with documented acute hyponatremia, ie, onset within 48 hours, sodium can be corrected at the rate at which it fell. In general, most cases are chronic and therefore need to be corrected more slowly to minimize risk of osmotic demyelination.

Pseudohyponatremia from hypertriglyceridemia or hyperproteinemia requires no therapy except confirmation with the clinical laboratory. Translational hyponatremia from glucose or mannitol can be managed with glucose correction or mannitol discontinuation (if possible). Patients with hypovolemic hyponatremia require fluid resuscitation. Data from 2018 suggest that balanced crystalloid solutions (lactated Ringer solution) may be a superior choice for resuscitation over normal saline, particularly in ICU patients. The correction of the volume depletion will remove the stimulus for ADH and permit renal excretion of a dilute urine. Great care must be taken because the rapid renal excretion of the excess water may correct the serum sodium level too quickly.

A. Symptomatic Hyponatremia

If a patient has hyponatremia and severe symptoms (eg, seizures, confusion), then emergent treatment with hypertonic saline should commence regardless of etiology. A relatively small increase in serum sodium of 4–5 mEq/L is generally sufficient to promptly reverse severe neurologic symptoms and decrease intracranial pressure. This can be accomplished most effectively by using boluses of 100 mL of 3% NaCl over 10 minutes, which can be repeated twice if needed. Each bolus might be predicted to raise the serum sodium by 1–2 mEq/L. In patients with less severe symptoms, an intravenous infusion of 3% NaCl (0.5–2 mL/kg/h) may be used.

It cannot be overstated that there is no substitute for frequent laboratory monitoring during therapy for hyponatremia, particularly severe cases, which should occur every 1–2 hours.

B. Osmotic Demyelination and Correction Rate

Iatrogenic osmotic demyelination syndrome is the result of overly rapid correction of serum sodium in patients with chronic hyponatremia. Previously called central pontine myelinolysis, osmotic demyelination syndrome may also occur outside the brainstem. Demyelination generally occurs 2–6 days after inappropriate sodium correction and presents with profound neurologic deficits that are often irreversible. Risk factors for osmotic demyelination syndrome include the severity of hyponatremia (majority less than 120 mEq/L), alcohol use disorder (alcoholism), liver disease, malnutrition, and concurrent hypokalemia.

The optimal correction rate for hyponatremia is debated, though consensus guidelines suggest a correction not to exceed 8 mEq/L in a 24-hour period. It should be emphasized that this represents a limit and not a goal. In fact, in patients who are deemed high risk for osmotic demyelination syndrome, based on criteria detailed above, a **goal of 4–6 mEq/L/day** is appropriate. If rapid discontinuation of the effects of vasopressin are

anticipated, particularly in patients who are at high risk for osmotic demyelination syndrome, prophylactic use of intravenous desmopressin acetate (DDAVP) to prevent a water diuresis should be considered. In the event of overcorrection, free water, with or without DDAVP, should be infused to re-lower the serum sodium to an acceptable level.

C. Chronic Hyponatremia

In most patients with chronic hyponatremia, fluid restriction is a cornerstone of therapy, although if the urine remains concentrated (greater than 300 mOsm/kg), it can be difficult to adhere to a strict water restriction. Other measures to increase free water excretion should be considered. Options include loop diuretics, with or without salt tablets, which impair the medullary concentration gradient limiting renal concentration, vasopressin receptor antagonists (vaptans), and oral urea.

Vaptans impair ADH action by inhibiting the vasopressin type 2 (V_2)-receptors in the collecting duct, thereby inducing a water diuresis. While a logical target for therapy in refractory hyponatremia, these agents have not been shown to improve hard outcomes and are associated with risks of liver toxicity and sodium overcorrection. If these agents are used, they should generally be avoided in patients with cirrhosis, duration should be limited to 30 days, and fluid restriction should concurrently be lifted in order to reduce the risk of excessive serum sodium correction. An alternative option is the use of oral urea to induce an osmotic diuresis, which enhances free water clearance. The disadvantage of palatability has been addressed by combining urea with sodium bicarbonate, citric acid, and sucrose.

► When to Refer

- Nephrology consultation should be considered in patients with hyponatremia of uncertain cause or in refractory, or complicated cases.
- Aggressive therapies with hypertonic saline, V_2 -antagonists, or dialysis mandate specialist consultation.
- Consultation may be necessary with severe liver or heart disease.

► When to Admit

Hospital admission is necessary for severe or symptomatic patients or those requiring aggressive therapies (such as hypertonic saline, initiating vaptans) for close monitoring and frequent laboratory testing.

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HYPERNATREMIA



ESSENTIALS OF DIAGNOSIS

- Increased thirst and water intake are the main defense against hypernatremia.
- Urine osmolality helps differentiate renal from nonrenal water loss.

► General Considerations

Hypernatremia is defined as a sodium concentration greater than 145 mEq/L. All patients with hypernatremia have hyperosmolality, unlike hyponatremic patients who can have a low, normal, or high serum osmolality. Hypernatremia develops when there is a relative loss of water that is inadequately compensated for by water ingestion. Rarely, excess sodium intake contributes to hypernatremia when it is associated with an increase in extracellular volume.

The primary responses to hypernatremia are stimulation of thirst (to increase water intake) and increased secretion of ADH (to minimize water loss in the urine). Cells in the hypothalamus are able to sense minimal changes in serum osmolarity, triggering the thirst mechanism and subsequent intake of water. It is nearly impossible to develop hypernatremia in the context of an intact thirst mechanism with appropriate access to water.

► Clinical Findings

A. Symptoms and Signs

When the patient is dehydrated, orthostatic hypotension and oliguria are typical findings. Because water shifts from the cells to the intravascular space to protect volume status, symptoms may be delayed. Lethargy, irritability, and weakness are early signs. Hyperthermia, delirium, seizures, and coma may be seen with severe hypernatremia (ie, sodium greater than 160 mEq/L). Symptoms in older adults may not be specific.

B. Laboratory Findings

The first steps in evaluating patients with hypernatremia are assessing the urine volume, osmolality, and the osmole excretion rate. The latter can be calculated by multiplying the urine osmolality with urine volume. The copeptin test is discussed below.

C. Etiology

The initial step is to determine whether the patient with hypernatremia is oliguric, ie, urine flow less than 0.5 mL/min, or nonoliguric. Patients who are nonoliguric can be further subdivided by measurement of a urine osmolality.

1. The oliguric patient (urine flow less than 0.5 mL/min)—

This is found in several scenarios.

A. REDUCED WATER INTAKE—Hypernatremia will develop in patients with reduced water intake secondary to the inability to communicate and/or limited access to water.

B. NONRENAL WATER LOSSES—Nonrenal sites of water loss include sweat, gastrointestinal (GI) tract, and the respiratory tract. This is most commonly seen in patients with diarrhea or in febrile patients on a ventilator.

C. SHIFT OF WATER INTO CELLS—Rarely, hypernatremia may manifest from a shift of water into cells due to the intracellular gain of an effective osmole. This may be seen with seizures or rhabdomyolysis.

2. The nonoliguric patient (urine flow greater than 0.5 mL/min)—

A. URINE OSMOLALITY LESS THAN 250 MOSM/KG—Hypernatremia in the setting of dilute urine is characteristic of diabetes insipidus (DI) or release of a vasopressinase. Central DI results from inadequate ADH release from the pituitary (stroke, tumor, infiltration). In nephrogenic DI, ADH levels are normal or even elevated, but the kidneys are less sensitive to the effects. Common causes include lithium therapy, post-relief of urinary obstruction, chronic interstitial nephritis, hypercalcemia, and hypokalemia. Central and nephrogenic DI can be distinguished by the response to exogenous DDAVP administration while hypernatremic. An innovative test to assist in the differentiation of patients with hypotonic polyuria is the measurement of **coopeptin**, a C-terminal peptide synthesized with vasopressin, which mirrors its concentration over a wide range of plasma osmolalities. Elevated levels of coopeptin in the setting of hypernatremia suggest the presence of vasopressin and therefore exclude a diagnosis of central DI. Vasopressin is unstable in isolated plasma, and levels are not helpful.

B. URINE OSMOLALITY GREATER THAN 300 MOSM/KG—Patients with an elevated urine osmolality and a high urine volume have an osmotic diuresis. Both glucose and urea in the urine can promote polyuria associated with an increased free water excretion.

Treatment

Treatment of hypernatremia includes both correcting the cause of the fluid loss, and replacing the water electrolyte deficit.

A. Choice of Fluid for Replacement

In general, the treatment of patients with hypernatremia involves inducing a positive water balance by the administration of hypotonic fluids. This can be accomplished either through the GI tract with oral intake or boluses via a feeding tube or intravenously (or a combination of both). Because it can be difficult to correct large water deficits via the GI tract alone, the most common strategy is infusion of 5% dextrose in water (distilled water is contraindicated due to the development of hemolysis). Although there appears to be little risk in the rapid correction of hypernatremia, caution should be exercised when infusing large amount of 5% dextrose in water due to the risk of hyperglycemia and subsequent development of an osmotic diuresis, which can aggravate hypernatremia.

In patients who are concurrently volume depleted, priority should be to restore euolemia via the administration of isotonic fluids.

B. Calculation of Water Deficit

Fluid replacement should include correcting the free water deficit and adding maintenance fluid to replace ongoing and anticipated fluid losses.

1. Chronic hypernatremia—The water deficit is the amount of water calculated to restore the sodium concentration to normal (140 mEq/L). Total body water (TBW) (Table 21-1) correlates with muscle mass and therefore decreases with advancing age, cachexia, and dehydration and, on average, is lower in women than in men. Current TBW equals 40–60% current body weight.

$$\text{Water deficit (L)} = \text{Current TBW} \times \frac{S_{\text{Na}} - 140}{140}$$

It should be emphasized that the water deficit represents a static period in time and a critical mistake that is often made when considering the volume of water needed to restore sodium balance is failure to incorporate ongoing water loss via urinary output and insensible losses. Insensible losses can be estimated as 500–1000 mL daily; however, they can vary significantly. The proportion of urine volume that is free water can be estimated by calculating the electrolyte free water (EFW) clearance via the equation below.

$$C_{\text{EFW}} (\text{L}) = \text{Urine volume} \times \left(1 - \frac{U_{\text{Na}} + U_{\text{K}}}{S_{\text{Na}}} \right)$$

2. Rate of sodium correction—Although it would be appealing to apply similar principles for patients with hyponatremia to patients with hypernatremia, this practice is not supported by the literature. Adverse neurologic symptoms from overly rapid correction of hypernatremia have only been described in children. A slow rate of correction is usually recommended on the basis of osmotic brain adaptation that occurs with chronic hypernatremia and corresponding theoretical risk of cerebral edema if hypernatremia is corrected too quickly. However, a relatively large retrospective study found no evidence of morbidity or mortality with rapid correction of hypernatremia in critically ill patients with admission or hospital-acquired hypernatremia. Common clinical practice is to limit correction of chronic hypernatremia to below 12 mEq/L in 24 hours given the absence of data to suggest slow correction rates are harmful. However, in the event that this rate is inadvertently exceeded, the serum sodium should not be raised. In patients with acute hypernatremia, the serum sodium should be corrected to normal within 24 hours.

3. Treatment of the underlying cause—The underlying cause of the hypernatremia should be identified and addressed. For patients who have central DI, vasopressin deficiency should be replaced by administration of DDAVP.

When to Refer

Patients with refractory or unexplained hypernatremia should be referred for nephrology consultation.

► When to Admit

- Patients with symptomatic hypernatremia require hospitalization for evaluation and treatment.
- Significant comorbidities or concomitant acute illnesses, especially if contributing to hypernatremia, may necessitate hospitalization.

Chauhan K et al. Rate of correction of hypernatremia and health outcomes in critically ill patients. *Clin J Am Soc Nephrol*. 2019;14:656. [PMID: 30948456]

Fenske W et al. A copeptin-based approach in the diagnosis of diabetes insipidus. *N Engl J Med*. 2018;379:428. [PMID: 30067922]

Seay NW et al. Diagnosis and management of disorders of body tonicity-hyponatremia and hypernatremia: Core Curriculum 2020. *Am J Kidney Dis*. 2020;75:272. [PMID: 31606238]

DISORDERS OF POTASSIUM CONCENTRATION

HYPOKALEMIA



ESSENTIALS OF DIAGNOSIS

- Serum potassium < 3.5 mEq/L (3.5 mmol/L).
- Severe hypokalemia may induce arrhythmias and rhabdomyolysis.
- Assessment of urine potassium excretion (urine potassium to creatinine ratio) can distinguish renal from nonrenal loss of potassium.

► General Considerations

Hypokalemia can result from insufficient dietary potassium intake, intracellular shifting of potassium from the extracellular space, or potassium loss (renal or extra-renal) (Table 21–3). A low dietary potassium intake is usually not sufficient as the kidneys can lower urine potassium excretion to very low levels (less than 15 mEq/L). Shift of potassium into cells is increased by insulin and beta-adrenergic stimulation. Excess potassium excretion by the kidneys is usually due to increased aldosterone action in the setting of preserved delivery of sodium to the distal nephron. Magnesium is an important regulator of potassium handling and low levels lead to persistent renal excretion of potassium such that hypokalemia is often refractory to treatment until the magnesium deficiency is corrected. Loop diuretics (eg, furosemide) cause substantial renal potassium and magnesium losses.

► Clinical Findings

A. Symptoms and Signs

Hypokalemia is usually asymptomatic but when severe may lead to muscle weakness and cardiac arrhythmias. Involvement of GI smooth muscle may result in

Table 21–3. Causes of hypokalemia.

Decreased potassium intake

Potassium shift into the cell

Alkalosis

Beta-adrenergic agonists

Insulin release (postprandial, exogenous, insulinoma)

Hypokalemic periodic paralysis

Renal potassium loss with metabolic acidosis

Proximal and distal RTAs

Toluene inhalation (glue sniffing)

Renal potassium loss with metabolic alkalosis

Normal/low blood pressure

Bartter syndrome

Gitelman syndrome

Magnesium deficiency

Vomiting

Loop/thiazide diuretics

High blood pressure

Elevated renin and aldosterone

Malignant hypertension

Renin-producing tumor

Renal artery stenosis

Depressed renin and elevated aldosterone

Adrenal adenoma

Glucocorticoid remediable aldosteronism

Adrenal hyperplasia

Depressed renin and aldosterone

Cushing syndrome

Black licorice

Apparent mineralocorticoid excess

Liddle syndrome

Increased gastrointestinal losses

Diarrhea

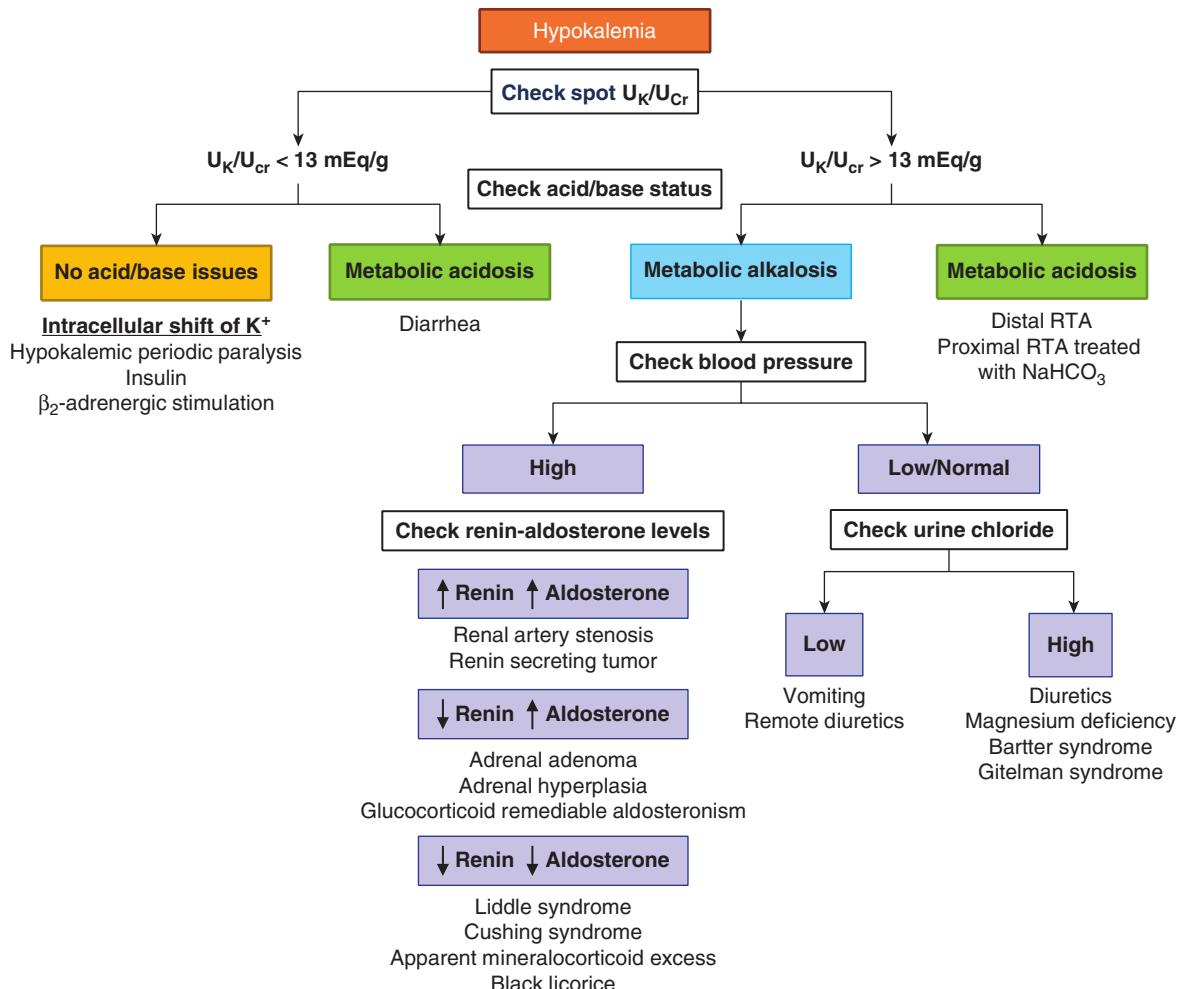
Laxative abuse

RTA, renal tubular acidosis.

constipation or ileus. Rhabdomyolysis with associated acute kidney injury can be seen with serum potassium less than 2.5 mEq/L. Hypokalemia may additionally present as polyuria and polydipsia due to diminished concentrating ability of the kidney (nephrogenic DI) and chronic hypokalemia can lead to kidney disease (tubulointerstitial nephritis).

B. Laboratory Findings

Transient hypokalemia is generally secondary to intracellular shift, while sustained hypokalemia is secondary to potassium wasting or, rarely, inadequate intake. Assessment of renal potassium excretion can help distinguish renal from nonrenal causes of hypokalemia. A 24-hour urine collection is the most accurate method for assessing renal handling of potassium, with a level less than 25 mEq/day compatible with appropriate renal potassium retention, and higher values corresponding to renal potassium wasting. A more immediate assessment can be made by measuring a urine potassium to creatinine ratio (U_K/U_{Cr}) on a spot urine sample (Figure 21–2). In the setting of hypokalemia, a U_K/U_{Cr} ratio less than 13 mEq/g (or 1.5 mEq/mmol) is suggestive of a nonrenal etiology, most commonly GI losses, intracellular potassium shifts, or



▲ **Figure 21–2.** Differentiating renal from nonrenal causes of hypokalemia using a spot urine potassium and a spot urine creatinine. NaHCO_3 , sodium bicarbonate; RTA, renal tubular acidosis; U_K/U_{Cr} , urine potassium to creatinine ratio.

inadequate dietary intake, whereas higher values imply renal potassium wasting.

C. Electrocardiogram

Hypokalemia leads to a characteristic progression of electrocardiogram (ECG) changes, initially T wave flattening, subsequently ST depressions and T wave inversions, ultimately leading to U waves as the hypokalemia becomes more severe. There is significant interpatient variability in the degree of hypokalemia and corresponding ECG findings; therefore, typical ECG patterns may not be observed in all patients.

► Etiology

1. Inadequate dietary intake—While the kidney can excrete urine that is virtually free of sodium, there continues to be a small amount of potassium excretion even in the setting of diets completely devoid of potassium. With extreme potassium free diets, such as anorexia nervosa and

alcohol use disorder, the hypokalemia is worsened by concurrent magnesium depletion.

2. Intracellular shift—The most important determinants of intracellular potassium shifts are postprandial insulin and catecholamine release. These physiologic conditions can be exacerbated by beta-adrenergic-agonist administration, as well as high adrenergic states, which can be seen in situations such as alcohol withdrawal and myocardial infarctions. Rare causes include insulinomas and hypokalemic periodic paralysis.

3. GI losses—The most common cause of nonrenal potassium wasting is GI loss, both diarrhea and vomiting. Diarrhea may have a high potassium and bicarbonate content resulting in hypokalemia with a concurrent nongap (hyperchloremic) metabolic acidosis. Vomiting leads to hypokalemia with a metabolic alkalosis with most of the potassium loss due to renal wasting (secondary to hypovolemia-induced hyperaldosteronism).

4. Renal wasting—Renal potassium wasting occurs in states where increased distal sodium delivery is coupled to increased aldosterone activity. This most commonly occurs with diuretic use. Rarely, renal tubulopathies (Bartter syndrome or Gitelman syndrome) or renal tubular acidosis (RTA) may present with hypokalemia.

Primary hyperaldosteronism (Conn syndrome) is due to excess aldosterone production by the adrenal glands, which causes extracellular volume expansion resulting in hypertension associated with hypokalemia and a metabolic alkalosis. Other rare forms of increased mineralocorticoid activity may be identified by measuring plasma renin activity and serum aldosterone levels.

Treatment

Any underlying conditions should be treated and causative drugs discontinued. Magnesium deficiency should be corrected, particularly in refractory hypokalemia. Oral potassium supplementation is the safest treatment for mild to moderate deficiency, although potassium supplements may cause GI upset. With mild to moderate diuretic doses, 20 mEq/day of oral potassium is generally sufficient to prevent hypokalemia, whereas with established hypokalemia, 40–100 mEq/day over a period of days to weeks may be needed to treat hypokalemia and fully replete potassium stores.

Intravenous potassium is reserved for severe hypokalemia (less than 3.0 mEq/L) and requires careful monitoring due to the risk of transient hyperkalemia. Potassium chloride may be given through a peripheral intravenous line at rates up to 10–15 mEq/h diluted in 0.5% or 0.9% normal saline, but higher rates (up to 20 mEq/h) require central access due to the risk of peripheral vein irritation. In the event of concurrent metabolic acidosis, potassium repletion should take precedence over alkali administration as correction of the acidosis will result in intracellular shift of potassium, further decreasing extracellular potassium concentration. Similarly, potassium should be given in a saline, rather than dextrose, solution since dextrose would stimulate insulin release and, hence, intracellular shift.

When to Refer

Patients with unexplained hypokalemia, refractory or persistent hypokalemia, or suggestive alternative diagnoses (eg, aldosteronism or hypokalemic periodic paralysis) should be referred for nephrology consultation.

When to Admit

Patients with symptomatic or severe hypokalemia (less than 2.5 mEq/L), especially with cardiac manifestations, require cardiac monitoring, potassium supplementation, and frequent laboratory testing.

Gumz ML et al. An integrated view of potassium homeostasis. *N Engl J Med*. 2015;373:60. [PMID: 26132942]

Palmer BF et al. Physiology and pathophysiology of potassium homeostasis: Core Curriculum 2019. *Am J Kidney Dis*. 2019; 74:682. [PMID: 31227226]

HYPERKALEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Serum potassium > 5.2 mEq/L (5.2 mmol/L).
- ▶ Check medications carefully. Hyperkalemia may develop from angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics, most commonly in patients with kidney dysfunction.
- ▶ The ECG may be normal despite life-threatening hyperkalemia.
- ▶ Rule out pseudohyperkalemia and extracellular potassium shift from cells.

General Considerations

Hyperkalemia is a rare occurrence in normal individuals due to adaptive mechanisms designed to prevent accumulation of potassium in the extracellular fluid, mainly via rapid urinary excretion. **Persistent hyperkalemia** generally requires an impairment in renal potassium excretion due to impaired secretion of or hyporesponsiveness to aldosterone, impaired delivery of sodium and water to the distal nephron, or kidney disease (acute or chronic) (Table 21-4).

Table 21-4. Causes of hyperkalemia.

Pseudohyperkalemia

Marked thrombocytosis or leukocytosis with release of intracellular K⁺
Repeated fist clenching during phlebotomy, tourniquet application, use of small-bore needles during lab draw

Extracellular shift of K⁺

Metabolic acidosis
Insulin deficiency
Hyperglycemia
Alpha-adrenergic stimulation
Tissue injury (rhabdomyolysis, hemolysis, tumor lysis)
Hyperkalemic periodic paralysis
Drugs (digoxin overdose, succinylcholine)

Kidney disease, acute and chronic

Renal secretory defects (may or may not have reduced kidney function): interstitial nephritis, systemic lupus erythematosus, sickle cell disease, amyloidosis, obstructive nephropathy, kidney transplant

Hypoaldosteronism

Addison disease
Type IV renal tubular acidosis
Heparin
Ketoconazole

Drugs that inhibit potassium excretion

Drugs that inhibit potassium excretion: spironolactone, eplerenone, dospirenone, NSAIDs, ACE inhibitors, angiotensin II receptor blockers, triamterene, amiloride, trimethoprim, pentamidine, cyclosporine, tacrolimus

Excessive intake of K⁺

Especially in patients with diminished kidney excretion

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

Transient hyperkalemia suggests shift of potassium from inside cells into the extracellular fluid, which can occur in the context of tissue damage (rhabdomyolysis, tumor lysis, massive hemolysis, and trauma) or metabolic acidosis. Finally, pseudohyperkalemia is a laboratory artifact in which there is an elevation in serum potassium in the absence of true electrolyte imbalance as a result of tourniquet application or fist clenching during blood draw, or improper transport or processing of venous samples in patients with marked thrombocytosis or leukocytosis.

Clinical Findings

A. Symptoms and Signs

The symptoms of hyperkalemia are a consequence of impaired neuromuscular transmission. The most serious manifestations are cardiac conduction abnormalities and neuromuscular manifestations, such as muscle weakness, which may be profound. This generally occurs with potassium concentrations above 7 mEq/L, though it can vary depending on the acuity in development of hyperkalemia. Hyperkalemic period paralysis is a rare genetic disorder characterized by episodes of painless muscle weakness precipitated by potassium ingestion, rest after heavy exercise, and cold exposure. Hyperkalemia additionally impairs urinary ammonium excretion and may lead to metabolic acidosis.

B. Electrocardiogram

Electrocardiography is an unreliable method for detecting hyperkalemia; clinical studies show poor correlation between serum potassium and cardiac manifestations. The rapidity in development of hyperkalemia may correlate with the development of ECG changes. Typical sequential changes on the electrocardiogram are peaking of the T waves, ST-segment depression, and widening of the PR and QRS intervals. As the QRS continues to widen, sine waves may develop, which are concerning for imminent ventricular fibrillation and ultimately asystole.

Etiology

1. Increased potassium release from cells—

A. PSEUDOHYPERKALEMIA—This condition arises during specimen collection due to fist clenching, application of tourniquets, or using small bore needles. The presence of hemolysis in the processed sample can suggest these etiologies. A more striking example occurs in patients with marked thrombocytosis (greater than 500,000/mcL [$500 \times 10^9/\text{L}$]) or leukocytosis (greater than 100,000/mcL [$100 \times 10^9/\text{L}$]), particularly leukemic cells. Centrifugation or transport via a pneumatic tube system causes significant in vitro cell destruction due to cell fragility. If this condition is suspected a noncentrifuged, a whole blood sample that is walked to the laboratory is required for confirmation.

B. TISSUE BREAKDOWN—Tissue damage results in release of intracellular potassium to the extracellular space.

Common clinical examples include tumor lysis syndrome, crush injuries and severe hemolysis. Hyperkalemia is more common when concurrent renal impairment is present.

C. HYPERGLYCEMIA—Patients with uncontrolled diabetes may have hyperkalemia, even in the setting of a low total body potassium, due to a combination of insulin deficiency and hyperosmolarity from hyperglycemia.

D. METABOLIC ACIDOSIS—Acidosis results in potassium shifting out of the intracellular fluid due to buffering of hydrogen ions into cells. Serum potassium concentration rises approximately 0.7 mEq/L for every decrease of 0.1 pH unit. This effect is not seen with organic acidosis, such as lactic acidosis or ketoacidosis.

2. Impaired renal excretion—

A. ACUTE KIDNEY INJURY—A rapid reduction in kidney function leads to poor renal excretion of potassium and does not allow sufficient time for nonrenal adaptive mechanisms to take effect. Hyperkalemia occurs more commonly in oliguric patients.

B. CHRONIC KIDNEY DISEASE—The ability to maintain normal serum potassium is generally preserved until GFR declines to less than 20–30 mL/min/1.73 m². This is primarily due to adaptive mechanisms, particularly increases in potassium excretion by remaining functioning nephrons and by increased GI tract potassium excretion. Hyperkalemia in patients with more modest decreases in GFR are often due to medications that disrupt the renin-angiotensin-aldosterone system, which are commonly used in these patients.

C. LOW EFFECTIVE CIRCULATING VOLUME—Volume depletion as well as the edematous states of cirrhosis and heart failure can cause hyperkalemia due to a decrease in distal delivery of sodium and water, which impairs potassium excretion.

D. REDUCED ALDOSTERONE ACTION—Mineralocorticoid deficiency from Addison disease may cause hyperkalemia due to a decreased renal excretion of potassium. Mineralocorticoid resistance due to genetic disorders, interstitial kidney disease, or urinary tract obstruction also leads to hyperkalemia.

3. Medications—A number of medications can be implicated in the development of hyperkalemia and a careful review of a patient's medication list is imperative. Common medications include ACE inhibitors, angiotensin receptor blockers (ARBs), and NSAIDs, which reduce aldosterone release. Concomitant use of aldosterone antagonists (spironolactone or eplerenone) or medications that directly block the sodium channels of the principal cells (amiloride, triamterene, or trimethoprim) further increase risk of hyperkalemia. Beta-blockers can cause mild hyperkalemia by interfering with potassium uptake by cells, a phenomenon more commonly observed with nonselective beta-blockers. Heparin inhibits aldosterone production in the adrenal glands. Calcineurin inhibitors, such as cyclosporine and tacrolimus, can induce hyperkalemia, partly stimulating the sodium chloride co-transporter in the

distal nephron impairing distal sodium delivery. These medications should be used cautiously in patients with renal impairment, and laboratory monitoring is indicated within 1–2 weeks of drug initiation or dosage increase.

► Treatment

The diagnosis should be confirmed by repeat laboratory testing to rule out spurious hyperkalemia, especially in the absence of medications that cause hyperkalemia or in patients without kidney disease. The initial treatment is determined by the presence of signs and symptoms as well as the severity in plasma potassium elevation. In all patients, exogenous sources of potassium should be eliminated, medications that can impair potassium excretion discontinued, volume depletion corrected, and metabolic acidosis improved.

In emergency situations (cardiac toxicity, muscle weakness, or potassium greater than 6.5 mEq/L), initial therapy should be intravenous calcium gluconate to stabilize the myocardium in order to protect against arrhythmias, followed by therapies to shift potassium into cells. Insulin and beta-agonists shift potassium intracellularly within 10–15 minutes of administration but have a short duration of action (1–2 hours) (Table 21–5). Sodium bicarbonate may help shift potassium into cells in patients with a concurrent metabolic acidosis. Once the patient is stabilized, therapies are focused on potassium excretion.

Potassium excretion may be enhanced with the use of loop diuretics. Patiromer and sodium zirconium cyclosilicate are potassium-binding drugs that may be used to treat chronic hyperkalemia. Studies have demonstrated that these drugs are well tolerated and effective in patients with hyperkalemia who have either chronic kidney disease or heart failure and take at least one medication that inhibits the renin-angiotensin-aldosterone system. Neither drug has been studied in acute hyperkalemia. Sodium polystyrene (Kayexalate) has been used for decades although its efficacy and safety have been questioned. It may not increase potassium excretion greater than laxatives alone and has been associated with colonic necrosis, both with and without sorbitol coadministration; sodium polystyrene is contraindicated in patients with risk factors for colonic necrosis, such as bowel obstruction, ileus, and postoperative state. Hemodialysis may be necessary to remove potassium in patients with acute or chronic kidney injury, particularly in patients who are oliguric.

► When to Refer

- Patients with hyperkalemia from kidney disease and reduced renal potassium excretion should see a nephrologist.
- Transplant patients may need adjustment of their immunosuppression regimen by transplant specialists.

► When to Admit

Patients with severe hyperkalemia (greater than 6 mEq/L), any degree of hyperkalemia associated with ECG changes, or

concomitant illness that may worsen hyperkalemia (eg, tumor lysis, rhabdomyolysis, metabolic acidosis) should be sent to the emergency department for immediate treatment.

Kovesdy CP. Updates in hyperkalemia: outcomes and therapeutic strategies. *Rev Endocr Metab Disord*. 2017;18:41. [PMID: 27600582]

Kovesdy CP et al. Potassium homeostasis in health and disease: a scientific workshop cosponsored by the National Kidney Foundation and the American Society of Hypertension. *J Am Soc Hypertens*. 2017;11:783. [PMID: 29030153]

DISORDERS OF CALCIUM CONCENTRATION

The normal total plasma (or serum) calcium concentration is 8.5–10.5 mg/dL (2.1–2.6 mmol/L). Ionized calcium (normal: 4.6–5.3 mg/dL [1.16–1.31 mmol/L]) is the physiologically active portion and is necessary for muscle contraction and nerve function. In most situations, measuring total calcium concentration is sufficient since changes mirror that seen in ionized calcium concentration; exceptions include patients with hypoalbuminemia and certain acid-base disorders.

HYPOCALCEMIA

ESSENTIALS OF DIAGNOSIS

- Usually asymptomatic but can cause cramps or tetany if severe.
- Decreased serum parathyroid hormone (PTH), vitamin D, or magnesium levels.
- Despite a low total serum calcium, calcium metabolism is likely normal if ionized calcium level is normal.

► General Considerations

The most common cause of low total serum calcium is hypoalbuminemia. When serum albumin concentration is lower than 4 g/dL (40 g/L), serum Ca^{2+} concentration is reduced by 0.8–1 mg/dL (0.20–0.25 mmol/L) for every 1 g/dL (10 g/L) of albumin. True hypocalcemia (decreased ionized calcium) implies insufficient action of PTH or active vitamin D. Important causes of hypocalcemia are listed in Table 21–6.

The most common cause of hypocalcemia is advanced CKD, in which decreased production of calcitriol and hyperphosphatemia both play a role (see Chapter 22). Rarely, primary hypoparathyroidism due to mutations of the calcium-sensing receptor inappropriately suppressing PTH release leads to hypocalcemia (see Chapter 26). Magnesium depletion reduces both PTH release and tissue responsiveness to PTH, causing hypocalcemia. Hypocalcemia in pancreatitis is a marker of severe disease. Elderly hospitalized patients with hypocalcemia and

Table 21–5. Treatment of hyperkalemia.

Treatment of Hyperkalemia					
Emergent/Stabilizing Therapy					
Modality	Mechanism of Action	Onset	Duration	Prescription	K ⁺ Removed From Body
Calcium	Antagonizes cardiac conduction abnormalities	0–5 minutes	1 hour	Intravenous: calcium gluconate 10%, 5–30 mL or calcium chloride 5%, 5–30 mL	None
Bicarbonate	Distributes K ⁺ into cells	15–30 minutes	1–2 hours	Intravenous: NaHCO ₃ , 50–100 mEq Note: Sodium bicarbonate may not be effective in end-stage kidney disease patients; dialysis is more expedient and effective. Some patients may not tolerate the additional sodium load of bicarbonate therapy.	None
Insulin	Distributes K ⁺ into cells	15–60 minutes	4–6 hours	Intravenous: regular insulin, 5–10 units, plus glucose 50%, 25 g	None
Albuterol	Distributes K ⁺ into cells	15–30 minutes	2–4 hours	Nebulized albuterol, 10–20 mg in 4 mL normal saline, inhaled over 10 minutes Note: Much higher doses are necessary for hyperkalemia therapy (10–20 mg) than for airway disease (2.5 mg).	None
Nonemergent/Excretory Therapy					
Modality	Mechanism of Action	Onset of Action		Prescription	K ⁺ Removed From Body
Loop diuretic	Renal K ⁺ excretion	0.5–2 hours		Intravenous: furosemide, 40–160 mg	Variable
Patromer	Ca ²⁺ -K ⁺ cation exchange resin	~7 hours		Oral: 4.2–16.8 g once or twice daily	Mean 0.75 mEq/L
Sodium zirconium cyclosilicate	Selective potassium cation trapping agent	1 hour		Oral: 10 g up to three times daily	0.7 mEq/L per 10g dose
Sodium polystyrene sulfonate (eg, Kayexalate)	Ion-exchange resin binds K ⁺	1–3 hours		Oral: 15–60 g in 20% sorbitol (60–240 mL) Rectal: 30–60 g in 20% sorbitol Note: Resins with sorbitol may cause bowel necrosis and intestinal perforation, especially in patients with abnormal bowel function.	0.5–1 mEq/g resin
Hemodialysis ¹	Extracorporeal K ⁺ removal	1–8 hours		Note: A fast and effective therapy for hyperkalemia, hemodialysis can be delayed by vascular access placement and equipment and/or staff availability. Serum K can be rapidly corrected within minutes, but post-dialysis rebound can occur.	25–50 mEq/h
Peritoneal dialysis	Peritoneal K ⁺ removal	1–4 hours		Frequent exchanges	50–70 mEq/24h

¹Can be both acute immediate and urgent treatment of hyperkalemia.Modified and reproduced, with permission, from Cogan MG. *Fluid and Electrolytes: Physiology and Pathophysiology*. McGraw-Hill, 1991.

Table 21–6. Causes of hypocalcemia.

Decreased intake or absorption
Malabsorption
Small bowel bypass, short bowel
Vitamin D deficit (decreased absorption, decreased production of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D)
Increased loss
Alcohol use disorder
Chronic kidney disease
Diuretic therapy
Endocrine disease
Hypoparathyroidism (genetic, acquired; including hypomagnesemia and hypermagnesemia)
Post-parathyroideectomy (hungry bone syndrome)
Pseudohypoparathyroidism
Calcitonin secretion with medullary carcinoma of the thyroid
Familial hypocalcemia
Associated diseases
Pancreatitis
Rhabdomyolysis
Septic shock
Physiologic causes
Decreased serum albumin ¹
Decreased end-organ response to vitamin D
Hyperphosphatemia
Aminoglycoside antibiotics, plicamycin, loop diuretics, foscarnet

¹Ionized calcium concentration is normal.

hypophosphatemia, with or without an elevated PTH level, are likely vitamin D deficient.

► Clinical Findings

A. Symptoms and Signs

The hallmark sign of severe hypocalcemia (ionized calcium below 1 mmol/L) is tetany from increased neuromuscular irritability. Laryngospasm with stridor can obstruct the airway. Convulsions, perioral and peripheral paresthesias, and abdominal pain can develop. Less pronounced symptoms include fatigue, anxiety, and depression. Classic physical findings include Chvostek sign (contraction of the facial muscle in response to tapping the facial nerve) and Trousseau sign (carpal spasm occurring with occlusion of the brachial artery by a blood pressure cuff). QT prolongation predisposes to ventricular arrhythmias, though serious dysrhythmias are rare.

B. Laboratory Findings

Serum calcium concentration is low (less than 8.5 mg/dL [2.1 mmol/L]). In true hypocalcemia, the ionized serum calcium concentration is also low (less than 4.6 mg/dL [1.15 mmol/L]). Serum phosphate is usually elevated in hypoparathyroidism or in advanced CKD, whereas it is suppressed in vitamin D deficiency.

Serum magnesium concentration is commonly low. In respiratory alkalosis, total serum calcium is normal but ionized calcium is low. The ECG shows a prolonged QT interval.

► Treatment¹

A. Severe, Symptomatic Hypocalcemia

In the presence of tetany, arrhythmias, or seizures, intravenous calcium gluconate is indicated.¹ Because of the short duration of action, continuous calcium infusion is usually required. Ten to 15 milligrams of calcium per kilogram body weight, or six to eight 10-mL vials of 10% calcium gluconate (558–744 mg of calcium), are added to 1 L of D₅W and infused over 4–6 hours. By monitoring the serum calcium frequently (every 4–6 hours), the infusion rate is adjusted to maintain the serum calcium at 7–8.5 mg/dL.

B. Asymptomatic Hypocalcemia

Oral calcium (1–2 g of elemental calcium) and vitamin D preparations, including active vitamin D sterols, are used. Calcium carbonate is well tolerated and less expensive than many other calcium tablets. A check of urinary calcium excretion is recommended after the initiation of therapy because chronic hypercalciuria (urine calcium excretion greater than 300 mg or 7.5 mmol per day) or urine calcium:creatinine ratio greater than 0.3 may impair kidney function in these patients. The low serum calcium associated with hypoalbuminemia does not require replacement therapy. If serum magnesium is low, therapy must include magnesium replacement, which by itself often corrects hypocalcemia.

► When to Refer

Patients with complicated hypocalcemia from hypoparathyroidism, familial hypocalcemia, or CKD require referral to an endocrinologist or nephrologist.

► When to Admit

Patients with tetany, arrhythmias, seizures, or other symptoms of hypocalcemia require immediate therapy.

Aberegg SK. Ionized calcium in the ICU: should it be measured and corrected? Chest. 2016;149:846. [PMID: 26836894]
Schafer AL et al. Hypocalcemia: diagnosis and treatment. In: Feingold KR et al, editors. Endotext. 2016. [PMID: 25905251]

HYPERCALCEMIA



ESSENTIALS OF DIAGNOSIS

- Most common causes: primary hyperparathyroidism and malignancy-associated hypercalcemia.
- Asymptomatic, mild hypercalcemia (> 10.5 mg/dL [2.6 mmol/L]) is usually due to primary hyperparathyroidism.
- Symptomatic, severe hypercalcemia (> 13 mg/dL [3.2 mmol/L]) is usually due to hypercalcemia of malignancy.

¹See also Chapter 26 for discussion of the treatment of hypoparathyroidism.

Table 21–7. Causes of hypercalcemia.

Increased intake or absorption
Milk-alkali syndrome
Vitamin D or vitamin A excess
Endocrine disorders
Primary hyperparathyroidism
Secondary or tertiary hyperparathyroidism (usually associated with hypocalcemia)
Acromegaly
Adrenal insufficiency
Pheochromocytoma
Thyrototoxicosis
Neoplastic diseases
Tumors producing PTH-related proteins (ovary, kidney, lung)
Plasma cell myeloma (elaboration of osteoclast-activating factor)
Lymphoma (occasionally from production of calcitriol)
Miscellaneous causes
Thiazide diuretics
Granulomatous diseases (production of calcitriol)
Paget disease of bone
Hypophosphatasia
Immobilization
Familial hypocalciuric hypercalcemia
Complications of kidney transplantation
Lithium intake

PTH, parathyroid hormone.

Hypercalcemia may affect GI, kidney, and neurologic function. Mild hypercalcemia (below 12 mg/dL) is often asymptomatic. Moderate hypercalcemia (12–14 mg/dL) may be tolerated if it is longstanding yet tends to be symptomatic if acute. Severe hypercalcemia (above 14 mg/dL) is frequently symptomatic. Common symptoms include anxiety, lethargy, constipation, anorexia, and cognitive changes, which can progress to lethargy and stupor in severe cases. Pancreatitis from calcium deposition in the pancreatic duct is a rare complication. Polyuria and dehydration may occur from impaired renal concentrating ability. Other symptoms include renal colic and hematuria from nephrolithiasis. Acute hypercalcemia can shorten the QT interval, though clinically relevant arrhythmias are rare.

B. Laboratory Findings

The serum ionized calcium exceeds 1.32 mmol/L (correct for serum albumin if ionized calcium is unavailable [see Hypocalcemia, above]). Check serum PTH to determine if hypercalcemia is PTH-mediated or non-PTH mediated.

PTH should be completely suppressed in the presence of hypercalcemia if kidney function is normal. Therefore, “normal” levels of PTH with hypercalcemia do not rule out hyperparathyroidism. Asymptomatic patients with mild hypercalcemia and PTH in the normal or slightly elevated range should have a 24-hour urine calcium or spot urine calcium to creatinine ratio checked for familial hypocalciuric hypercalcemia. If PTH is appropriately suppressed (typically below 20 pg/mL) PTHrP and vitamin D and its metabolites should be measured. Causes of a suppressed PTH and PTHrP with low or normal 25-OH and 1,25-OH vitamin D₃ levels include plasma cell myeloma, vitamin A intoxication, thyrotoxicosis, and immobilization. Hypocalciuria (below 100 mg/day) occurs in familial hypocalciuric hypercalcemia, thiazide diuretic use, and milk-alkali syndrome. Hypophosphatemia is more common with primary hyperparathyroidism and humoral hypercalcemia of malignancy (elevated PTHrP). In patients with an elevated 1,25-OH vitamin D₃, a chest radiograph may assess for the presence of granulomatous disease.

C. Treatment

Until the primary cause can be identified and treated, therapy is initiated to promote immediate reduction in serum calcium. Asymptomatic patients with mild hypercalcemia (below 12 mg/dL) do not require immediate therapy; patients should be cautioned to avoid measures that exacerbate hypercalcemia, such as volume depletion and thiazide diuretics. Patients with symptomatic hypercalcemia, a sudden rise in serum calcium above 12 mg/dL and those with severe hypercalcemia (above 14 mg/dL) should receive immediate therapy. Begin treatment with 0.9% normal saline, 200–300 mL/h, until euolemia is achieved (lactated Ringer is generally avoided because it contains a small amount of calcium). Loop diuretics to enhance renal calcium excretion should generally be avoided due to possible complications, such as nephrolithiasis. These agents were used more commonly in the era of more aggressive volume administration, ie, beyond that needed to achieve

► General Considerations

Important causes of hypercalcemia are listed in Table 21–7. Primary hyperparathyroidism and malignancy account for 90% of cases. Primary hyperparathyroidism is the most common cause of hypercalcemia (usually mild) in ambulatory patients. Hypercalcemia above 14 mg/dL is most often associated with malignancy and is rare with primary hyperparathyroidism. Tumor production of PTH-related proteins (PTHrP) is the most common paraneoplastic endocrine syndrome, accounting for most cases of hypercalcemia in inpatients. The neoplasm is clinically apparent in nearly all cases when the hypercalcemia is detected, and the prognosis is poor. Granulomatous diseases, such as sarcoidosis and tuberculosis, cause hypercalcemia via overproduction of active vitamin D (1,25 dihydroxyvitamin D₃). Patients with mild hypercalcemia and normal to slightly elevated PTH levels should be assessed for familial hypocalciuric hypercalcemia.

Milk-alkali syndrome has had a resurgence due to calcium ingestion for prevention of osteoporosis and treatment of dyspepsia. Heavy calcium carbonate intake causes hypercalcemic acute kidney injury, likely from renal vasoconstriction. The decreased GFR impairs bicarbonate excretion, while hypercalcemia stimulates proton secretion and bicarbonate reabsorption. Metabolic alkalosis decreases calcium excretion, maintaining hypercalcemia.

► Clinical Findings

A. Symptoms and Signs

The history and physical examination should focus on the duration of hypercalcemia and evidence for a neoplasm.

euvolemia, and prior to the wide availability of more effective medications, such as bisphosphonates and calcitonin. Loop diuretics may be carefully used in the context of preventing or managing volume overload, particularly in patients with heart failure or kidney dysfunction.

Calcitonin, 4–8 international units/kg intramuscularly or subcutaneously every 6–12 hours, enhances renal excretion of calcium and decreases bone resorption by interfering with osteoclast activity. Calcitonin efficacy is limited to 48 hours because of tachyphylaxis.

Bisphosphonates are the treatment of choice for hypercalcemia secondary to excessive bone resorption. Denosumab, a monoclonal antibody against RANKL, inhibits osteoclasts, reducing bone resorption and serum calcium levels; this medication is an option when hypercalcemia is refractory to bisphosphonate therapy or when bisphosphonates are contraindicated (ie, severe renal impairment). The calcimimetic agent cinacalcet suppresses PTH secretion and decreases serum calcium concentration; it has been recommended for use in patients with symptomatic or severe primary hyperparathyroidism who are unable to undergo parathyroidectomy and patients with inoperable parathyroid carcinoma. (See Chapters 26 and 39.) Hemodialysis using a low calcium dialysate is an effective therapy for hypercalcemia refractory to the above therapies. Hypercalcemia in granulomatous disease is from overproduction of calcitriol; prednisone inhibits calcitriol synthesis and reduces serum calcium levels within 2–5 days.

Typically, if dialysis patients do not receive proper supplementation of calcium and active vitamin D, hypocalcemia and hyperphosphatemia develop. Conversely, hypercalcemia can develop in severe tertiary hyperparathyroidism with high PTH levels, or from excess vitamin D supplementation. Hypercalcemia in dialysis patients usually occurs when there is hyperphosphatemia; metastatic calcification may occur.

► When to Refer

- Patients may require referral to an oncologist or endocrinologist depending on the cause of hypercalcemia.
- Patients with granulomatous diseases (eg, tuberculosis and other chronic infections, granulomatosis with polyangiitis, sarcoidosis) may require assistance from infectious disease specialists, rheumatologists, or pulmonologists.

► When to Admit

- Patients with symptomatic or severe hypercalcemia require immediate treatment.
- Unexplained hypercalcemia with associated conditions, such as acute kidney injury or suspected malignancy, may require urgent treatment and expedited evaluation.

Bazari H et al. Case records of the Massachusetts General Hospital. Case 24-2016. A 66-year-old man with malaise, weakness, and hypercalcemia. *N Engl J Med.* 2016;375:567. [PMID: 27509105]

Carrick AI et al. Rapid fire: hypercalcemia. *Emerg Med Clin North Am.* 2018;36:549. [PMID: 30037441]

Tebben PJ et al. Vitamin D-mediated hypercalcemia: mechanisms, diagnosis, and treatment. *Endocr Rev.* 2016;37:521. [PMID: 27588937]

Villalba-Ferrer F et al. Hypercalcemic crisis due to primary hyperparathyroidism resistant to medical treatment. *Cir Cir.* 2020;88:13. [PMID: 33284269]

Zaggag J et al. Hypercalcemia and cancer: differential diagnosis and treatment. *CA Cancer J Clin.* 2018;68:377. [PMID: 30240520]

DISORDERS OF PHOSPHORUS CONCENTRATION

Plasma phosphorus is mainly inorganic phosphate and represents a small fraction (less than 0.2%) of total body phosphate. Important determinants of plasma inorganic phosphate are renal excretion, intestinal absorption, and shift between the intracellular and extracellular spaces. The kidney is the most important regulator of the serum phosphate level. PTH decreases reabsorption of phosphate in the proximal tubule while 1,25-dihydroxyvitamin D increases reabsorption. Renal proximal tubular reabsorption of phosphate is decreased by hypertension, corticosteroids, metabolic acidosis, and proximal tubular dysfunction (as in Fanconi syndrome). Fibroblast growth factor 23 (FGF23) is a potent phosphaturic hormone. Intestinal absorption of phosphate is facilitated by active vitamin D. Cellular phosphate uptake is stimulated by various factors and conditions, including alkalemia, insulin, epinephrine, refeeding syndrome, hungry bone syndrome, and accelerated cell proliferation.

Phosphorus metabolism and homeostasis are intimately related to calcium metabolism.

HYPOPHOSPHATEMIA



ESSENTIALS OF DIAGNOSIS

- Severe hypophosphatemia may cause tissue hypoxia and rhabdomyolysis.
- Renal loss of phosphate can be diagnosed by calculating the fractional excretion of phosphate (FePO_4).
- PTH and FGF23 are the major factors that increase urine phosphate.

► General Considerations

The etiology of hypophosphatemia can be categorized as decreased intestinal absorption, increased urinary excretion, or transcellular shift (Table 21–8). Hypophosphatemia may occur in the presence of normal phosphate stores. Serum phosphate levels decrease transiently after food intake, which stimulates endogenous insulin release. In patients with depleted phosphate stores, such as alcoholic or malnourished patients, carbohydrate intake can induce severe hypophosphatemia (refeeding syndrome). Acute respiratory alkalosis can lower serum phosphate

Table 21–8. Causes of hypophosphatemia.

Decreased intestinal absorption
Starvation
Parenteral alimentation with inadequate phosphate content
Malabsorption syndrome, small bowel bypass
Absorption blocked by oral antacids with aluminum or magnesium
Vitamin D-deficient and vitamin D-resistant osteomalacia
Increased urinary excretion
Phosphaturic drugs: theophylline, diuretics, bronchodilators, corticosteroids
Hyperparathyroidism (primary or secondary)
Hyperthyroidism
Renal tubular defects with excessive phosphaturia (congenital, Fanconi syndrome induced by monoclonal gammopathy, heavy metal poisoning), alcohol use disorder
Hypokalemic nephropathy
Inadequately controlled diabetes mellitus
Hypophosphatemic rickets
Phosphatonins of oncogenic osteomalacia (eg, FGF23 production)
Transcellular shift of phosphorus
Administration of glucose
Anabolic steroids, estrogen, oral contraceptives, beta-adrenergic agonists, xanthine derivatives
Hungry bone syndrome
Acute respiratory alkalosis
Salicylate poisoning
Other
Electrolyte abnormalities
Hypercalcemia
Hypomagnesemia
Metabolic alkalosis
Abnormal losses followed by inadequate repletion
Diabetes mellitus with acidosis, particularly during aggressive therapy
Recovery from starvation or prolonged catabolic state
Chronic alcohol use disorder, particularly during restoration of nutrition; associated with hypomagnesemia
Recovery from severe burns

FGF23, fibroblast growth factor 23.

concentrations by stimulating glycolysis. Several drugs can impair intestinal absorption of phosphate, particularly calcium-, magnesium-, and aluminum-containing antacids. Elevated PTH causes hypophosphatemia by inhibiting reabsorption in the kidney. Vitamin D deficiency decreases intestinal phosphate and calcium absorption with the resultant hypocalcemia stimulating PTH release, increasing urinary phosphate excretion. Generalized dysfunction in the proximal tubule, Fanconi syndrome, is characterized by hypophosphatemia, metabolic acidosis, glucosuria, and aminoaciduria. Mutations in FGF-23 are associated with urinary phosphorous wasting with rickets or osteomalacia.

► Clinical Findings

A. Symptoms and Signs

Phosphorous is a key ingredient component of adenosine triphosphate (ATP), and clinical manifestations are related to ATP deficiency. Symptoms are rare until blood

phosphate levels fall below 1.0 mg/dL and are more prominent with acute declines. Symptoms include weakness, paresthesias, and encephalopathy (irritability, confusion, dysarthria, seizures, and coma). Respiratory failure or failure to wean from mechanical ventilation may occur because of diaphragmatic weakness. Decreased myocardial contractility is uncommon but a serious manifestation. Chronic severe depletion may cause anorexia, pain in muscles and bones, and fractures.

B. Laboratory Findings

While the etiology of hypophosphatemia is often determined from the patient's history and review of medications, urinary phosphate excretion can distinguish between renal and nonrenal causes. Phosphate excretion can be determined by a 24-hour urine collection or by calculation of the FEPO_4 . The normal renal response to hypophosphatemia is to decrease urinary phosphate excretion to less than 100 mg/day and FEPO_4 less than 5%. Renal wasting of phosphate (or increased FEPO_4) occurs most commonly with hyperparathyroidism and Fanconi syndrome (Table 21–8). The clinical usefulness of serum FGF23 levels is undetermined except in uncommon diseases.

Other clinical features may be suggestive of hypophosphatemia, such as hemolytic anemia and rhabdomyolysis. Fanconi syndrome may present with any combination of uricosuria, aminoaciduria, normoglycemic glucosuria, normal anion gap metabolic acidosis, and phosphaturia. In chronic hypophosphatemia, radiographs and bone biopsies show changes resembling osteomalacia.

► Treatment

Hypophosphatemia can be prevented by including phosphate in repletion and maintenance fluids. Moderate hypophosphatemia (greater than 1 mg/dL) and asymptomatic patients should be treated with oral phosphate. A typical dose is 40–80 mmol, divided into three or four doses over 24 hours. Patients with severe hypophosphatemia (below 1 mg/dL), symptomatic patients, and those who cannot tolerate oral therapy should be treated with intravenous replacement. Hypocalcemia, hypotension, hyperphosphatemia, and ECG abnormalities can be seen with intravenous therapy, which can be avoided by providing moderate doses. A typical dose is 15 mmol over 2 hours; the rate should be decreased if hypotension occurs and monitoring of plasma phosphate and calcium every 6 hours is necessary. Magnesium deficiency often coexists and should be treated.

Contraindications to phosphate replacement include hypoparathyroidism, advanced CKD, tissue damage and necrosis, and hypercalcemia. When an associated hyperglycemia is treated, phosphate accompanies glucose into cells, and hypophosphatemia may ensue.

► When to Refer

- Patients with refractory hypophosphatemia with increased urinary phosphate excretion may require

evaluation by an endocrinologist (eg, for **hyperparathyroidism** and **vitamin D disorders**) or a nephrologist (eg, for renal tubular defects).

- Patients with decreased GI absorption may require referral to a gastroenterologist.

► When to Admit

Patients with severe or refractory hypophosphatemia will require intravenous phosphate.

García Martín A et al. Phosphate disorders and clinical management of hypophosphatemia and hyperphosphatemia. *Endocrinol Diabetes Nutr*. 2020;67:205. [PMID: 31501071]

HYPERPHOSPHATEMIA



ESSENTIALS OF DIAGNOSIS

- Advanced CKD is the most common cause.
- Hyperphosphatemia in the presence of hypercalcemia imposes a high risk of metastatic calcification.

► General Considerations

The two most common etiologies of hyperphosphatemia are decreased kidney clearance from CKD and transcellular shift. Increased dietary intake of phosphates in the setting of advanced CKD can cause hyperphosphatemia. Phosphate containing laxatives taken as preparation for a GI procedure routinely cause transient hyperphosphatemia, unless the patient has impaired kidney function. Rapid cell breakdown from tumor lysis syndrome, rhabdomyolysis, and massive hemolysis releases intracellular phosphate. Hyperphosphatemia from insulin deficiency can occur in diabetic ketoacidosis (DKA). These patients, however, are typically phosphate depleted and are at risk for developing hypophosphatemia with insulin therapy. Other causes are listed in Table 21–9.

► Clinical Findings

A. Symptoms and Signs

Acute hyperphosphatemia is generally asymptomatic, and symptoms are generally associated with concurrent hypocalcemia.

B. Laboratory Findings

In addition to elevated phosphate, blood chemistry abnormalities are those of the underlying disease.

► Treatment

Treatment is directed at the underlying cause. Acute hyperphosphatemia with *symptomatic* hypocalcemia and ECG changes (QTc prolongation) can be life-threatening. Intravenous calcium can be given in this situation, though it

Table 21–9. Causes of hyperphosphatemia.

Massive load of phosphate into the extracellular fluid

Exogenous sources
Hypervitaminosis D
Laxatives or enemas containing phosphate
Intravenous phosphate supplement
Endogenous sources
Rhabdomyolysis (especially if chronic kidney disease coexists)
Tumor lysis by chemotherapy, particularly lymphoproliferative diseases
Metabolic acidosis (lactic acidosis, ketoacidosis)
Respiratory acidosis (phosphate incorporation into cells is disturbed)

Decreased excretion into urine

Chronic kidney disease
Acute kidney injury
Hypoparathyroidism
Pseudohypoparathyroidism
Acromegaly

Pseudohyperphosphatemia

Plasma cell myeloma
Hyperbilirubinemia
Hypertriglyceridemia
Hemolysis in vitro

should be avoided in asymptomatic patients due to the risk of vascular calcification. Hemodialysis may be necessary in patients with impaired kidney function. In chronic hyperphosphatemia, dietary phosphate intake should be decreased and absorption reduced with oral phosphate binders, such as calcium acetate, calcium carbonate, sevelamer, or ferric citrate.

► When to Admit

Patients with acute severe hyperphosphatemia require hospitalization for emergent therapy, possibly including dialysis. Concomitant illnesses, such as acute kidney injury or cell lysis, may necessitate admission.

Criscuolo M et al. Tumor lysis syndrome: review of pathogenesis, risk factors, and management of a medical emergency. *Expert Rev Hematol*. 2016;9:197. [PMID: 26629730]

Palmer SC et al. Phosphate-binding agents in adults with CKD: a network meta-analysis of randomized trials. *Am J Kidney Dis*. 2016;68:691. [PMID: 27461851]

DISORDERS OF MAGNESIUM CONCENTRATION

Normal plasma magnesium concentration is 1.7–2.1 mg/dL (0.7–0.85 mmol/L). Similar to calcium, only the ionized form is metabolically active. The primary source of magnesium excretion is via the kidney. Magnesium's physiologic effects on the nervous system resemble those of calcium.

Altered magnesium concentration usually provokes an associated alteration of Ca^{2+} . Both hypomagnesemia and hypermagnesemia can decrease PTH secretion or action. Severe hypermagnesemia (greater than 5 mg/dL

[2.1 mmol/L]) suppresses PTH secretion with consequent hypocalcemia; this disorder is typically seen only in patients receiving magnesium therapy for preeclampsia. Severe hypomagnesemia causes PTH resistance in end organs and eventually decreased PTH secretion in severe cases.

HYPOMAGNESEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Serum concentration of magnesium may be normal even in the presence of magnesium depletion. Check urinary magnesium excretion if renal magnesium wasting is suspected.
- ▶ Causes neurologic symptoms and arrhythmias.
- ▶ Associated with hypocalcemia.

General Considerations

Causes of hypomagnesemia are listed in Table 21–10. Hypomagnesemia and hypokalemia share many etiologies, including diarrhea, alcohol use disorder, and diuretic use. Renal potassium wasting also occurs from hypomagnesemia and is refractory to potassium replacement until magnesium is repleted. Hypomagnesemia also suppresses PTH release and causes end-organ resistance to PTH and low 1,25-dihydroxyvitamin D levels. The resultant hypocalcemia is refractory to calcium replacement until the magnesium is normalized. Normomagnesemia does not exclude magnesium depletion because only 1% of total body magnesium is in the extracellular fluid; magnesium repletion should be considered in patients with risk factors for

Table 21–10. Causes of hypomagnesemia.

Diminished absorption or intake

- Malabsorption, chronic diarrhea, laxative abuse
- Proton pump inhibitors
- Prolonged gastrointestinal suction
- Small bowel bypass
- Malnutrition
- Alcohol use disorder
- Total parenteral alimentation with inadequate Mg²⁺ content

Increased renal loss

- Diuretic therapy (loop diuretics, thiazide diuretics)
- Hyperaldosteronism, Gitelman syndrome
- Hyperparathyroidism, hyperthyroidism
- Hypercalcemia
- Volume expansion
- Tubulointerstitial diseases
- Transplant kidney
- Drugs (aminoglycoside, cetuximab, cisplatin, amphotericin B, pentamidine)

Others

- Diabetes mellitus
- Post-parathyroidectomy (hungry bone syndrome)
- Respiratory alkalosis
- Pregnancy

hypomagnesemia and refractory hypokalemia or hypocalcemia. There is an FDA warning about hypomagnesemia for patients taking proton pump inhibitors. The presumed mechanism is decreased intestinal magnesium absorption, but it is not clear why this complication develops in only a small fraction of patients taking these medications. The potassium binder patiromer can cause hypomagnesemia by binding magnesium in the colon.

Clinical Findings

A. Symptoms and Signs

Because hypomagnesemia causes hypokalemia and hypocalcemia, it is difficult to determine whether symptoms are from hypomagnesemia or from potassium and calcium depletion. Marked neuromuscular and central nervous system hyperirritability may produce tremors, cramps, Troussseau and Chvostek signs, confusion, disorientation, and coma. Weakness is common. Cardiovascular manifestations include hypertension, tachycardia, and ventricular arrhythmias, including torsades de pointes.

B. Laboratory Findings

Urinary excretion of magnesium exceeding 10–30 mg/day or a fractional excretion greater than 3% indicates renal magnesium wasting. Hypocalcemia and hypokalemia are often present. The ECG may show widening of the QRS complex, peaked T waves with ultimate diminution, and a prolonged PR interval. PTH secretion is often suppressed (see Hypocalcemia).

Treatment

Magnesium oxide, 250–500 mg orally once or twice daily, is useful for treating chronic hypomagnesemia. Symptomatic hypomagnesemia requires intravenous magnesium sulfate 1–2 g over 5–60 minutes mixed in either dextrose 5% or 0.9% normal saline. Torsades de pointes in the setting of hypomagnesemia can be treated with 1–2 g of magnesium sulfate in 10 mL of dextrose 5% solution pushed intravenously over 15 minutes. Severe, non-life-threatening deficiency can be treated at a rate to 1–2 g/h over 3–6 hours. Intravenous magnesium inhibits renal reabsorption and patients will demonstrate increased renal wasting during therapy. Serum levels must be monitored daily and dosage adjusted to keep the concentration from rising above 3 mg/dL (1.23 mmol/L). Tendon reflexes may be checked for hyporeflexia of hypermagnesemia. K⁺ and Ca²⁺ replacement may be required, but patients with hypokalemia and hypocalcemia of hypomagnesemia do not recover without magnesium supplementation.

Patients with normal kidney function can excrete excess magnesium; hypermagnesemia should not develop with replacement dosages. In patients with CKD, magnesium replacement should be done cautiously to avoid hypermagnesemia. Reduced doses (50–75% dose reduction) and more frequent monitoring (at least twice daily) are indicated.

Gommers LM et al. Hypomagnesemia in type 2 diabetes: a vicious circle? Diabetes. 2016;65:3. [PMID: 26696633]

HYPERMAGNESEMIA



ESSENTIALS OF DIAGNOSIS

- Often associated with advanced CKD and chronic intake of magnesium-containing drugs.

► General Considerations

Hypermagnesemia is almost always the result of advanced CKD and impaired magnesium excretion. Antacids and laxatives are underrecognized sources of magnesium. Pregnant patients may have severe hypermagnesemia from intravenous magnesium for preeclampsia and eclampsia. Magnesium replacement should be done cautiously in patients with CKD; dose reductions up to 75% may be necessary to avoid hypermagnesemia.

► Clinical Findings

A. Symptoms and Signs

Muscle weakness, decreased deep tendon reflexes, mental obtundation, and confusion are characteristic manifestations. Weakness, flaccid paralysis, ileus, and hypotension are noted. Serious findings include respiratory muscle paralysis, complete heart block, and cardiac arrest.

B. Laboratory Findings and Electrocardiogram

Serum Mg^{2+} is elevated. In the common setting of CKD, BUN, creatinine, potassium, phosphate, and uric acid may all be elevated. Serum Ca^{2+} is often low. The ECG may show increased PR interval, broadened QRS complexes, and QT prolongation.

► Treatment

Exogenous sources of magnesium should be discontinued. Calcium antagonizes Mg^{2+} and may be given intravenously as calcium chloride, 500 mg or more at a rate of 100 mg (4.1 mmol) per minute. Hemodialysis may be necessary to remove magnesium, particularly with severe kidney disease.

Long-term use of magnesium hydroxide and magnesium sulfate should be avoided in patients with advanced stages of CKD.

Broman M et al. Analysis of hypo- and hypermagnesemia in an intensive care unit cohort. *Acta Anaesthesiol Scand*. 2018;62:648. [PMID: 29341068]

ACID-BASE DISORDERS

To best evaluate acid-base status, a blood gas and chemistry panel are required. Venous blood pH, typically 0.03–0.04 units lower than arterial blood pH, closely approximates arterial blood pH. An arterial blood gas should be obtained if more accurate assessment of

blood pH and Pco_2 is required. Bicarbonate (HCO_3^-) is calculated from the Henderson-Hasselbalch equation below; therefore, the bicarbonate value in the electrolyte panel is typically used.

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times PCO_2}$$

Primary acid-base disorders are secondary to changes in either serum bicarbonate or Pco_2 . The first step is to look at the pH of a blood gas (venous or arterial). If changes in pH are secondary to changes in HCO_3^- , a metabolic disorder is present. If changes in pH are secondary to changes in Pco_2 , a respiratory disorder is present. If the pH is < 7.40, the primary process is acidosis, either respiratory (Pco_2 greater than 40 mm Hg) or metabolic (HCO_3^- less than 24 mEq/L). If the pH is > 7.40, the primary process is alkalosis, either respiratory (Pco_2 less than 40 mm Hg) or metabolic (HCO_3^- greater than 24 mEq/L). Normally, the kidneys compensate for respiratory acid-base disorders and the lungs compensate for metabolic disorders in order to maintain pH in a narrow physiologic range. For example, with metabolic acidosis (low pH, low HCO_3^-), alveolar ventilation increases (Pco_2 decreases), returning pH close to the normal range. Similarly, with respiratory acidosis (low pH, high Pco_2), the kidneys excrete H^+ (HCO_3^- increase) to return the pH close to normal range. Such compensation can only bring the pH toward normal, though it can never completely correct it. In order to normalize pH, the primary disorder must be corrected.

One respiratory or metabolic disorder with its appropriate compensatory response is a simple acid-base disorder. A mixed acid-base disorder is when multiple simple disorders are present simultaneously. Diagnosing an acid-base disorder requires a systematic approach (see box Step-by-Step Analysis of Acid-Base Status). Once the primary disorder has been identified, the clinician should assess whether the compensatory response is appropriate (Table 21–11). An inadequate or an exaggerated response indicates the presence of another primary acid-base disturbance.

STEP-BY-STEP ANALYSIS OF ACID-BASE STATUS

Step 1: Look at the pH on a blood gas to determine the primary disorder, either acidemia or alkalemia.

Step 2: Look at the serum HCO_3^- value to determine if the primary disorder is metabolic.

Step 3: Calculate the anion gap (see Table 21–12).

Step 4: Calculate the delta gap.

Step 5: Evaluate magnitude of compensation (see Table 21–11).

Step 6: Examine the patient to determine whether the clinical signs are compatible with the acid-base analysis.

Table 21–11. Primary acid-base disorders and expected compensation.

Disorder	Primary Defect	Compensatory Response	Magnitude of Compensation
Respiratory acidosis			
Acute	↑ PCO_2	↑ HCO_3^-	↑ HCO_3^- 1 mEq/L per 10 mm Hg ↑ PCO_2
Chronic	↑ PCO_2	↑ HCO_3^-	↑ HCO_3^- 3.5 mEq/L per 10 mm Hg ↑ PCO_2
Respiratory alkalosis			
Acute	↓ PCO_2	↓ HCO_3^-	↓ HCO_3^- 2 mEq/L per 10 mm Hg ↓ PCO_2
Chronic	↓ PCO_2	↓ HCO_3^-	↓ HCO_3^- 5 mEq/L per 10 mm Hg ↓ PCO_2
Metabolic acidosis	↓ HCO_3^-	↓ PCO_2	↓ PCO_2 1.3 mm Hg per 1 mEq/L ↓ HCO_3^-
Metabolic alkalosis	↑ HCO_3^-	↑ PCO_2	↑ PCO_2 0.7 mm Hg per 1 mEq/L ↑ HCO_3^-

The serum anion gap should subsequently be calculated (see below) for two reasons. First, it helps identify the cause of a metabolic acidosis, and second, to identify the presence of a gap metabolic acidosis, which may be present even without a decreased serum bicarbonate concentration. In patients with metabolic acidoses, clinicians should calculate the **delta gap**, which is the difference between the change in anion gap and the change in bicarbonate, to determine if there is a mixed anion gap or nonanion gap metabolic acidosis. In increased anion gap acidoses, there should be roughly a millimole for millimole decrease in HCO_3^- as the anion gap increases. The corrected serum HCO_3^- should be calculated by adding the change in serum anion gap to the serum HCO_3^- . A value higher or lower than normal (24 mEq/L) indicates the concomitant presence of metabolic alkalosis or normal anion gap metabolic acidosis, respectively.

Seifter JL et al. Disorders of acid-base balance: new perspectives. *Kidney Dis (Basel)*. 2017;2:170. [PMID: 28232934]

METABOLIC ACIDOSIS

ESSENTIALS OF DIAGNOSIS

- Decreased HCO_3^- with acidemia (low blood pH).
- Classified into increased anion gap acidosis and normal anion gap acidosis.
- Lactic acidosis, ketoacidosis, and toxins produce metabolic acidoses with the largest anion gaps.
- Normal anion gap acidosis is mainly caused by GI HCO_3^- loss or RTA.

General Considerations

The hallmark of metabolic acidosis is low serum bicarbonate concentration from loss of bicarbonate or gain of acid (Table 21–12); the anion gap detects an increase in plasma anions other than from measured bicarbonate and chloride.

Many clinicians use 12 mEq/L as the normal serum anion gap (range 4–12 mEq/L due to differences in analyzer methods).

$$\text{Anion Gap} = \text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)$$

If serum potassium is included in the formula, the range for anion gap increase by about 4 mEq/L:

$$\text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{HCO}_3^- + \text{Cl}^-)$$

The principle unmeasured anion usually responsible for the anion gap is albumin. The expected anion gap must be

Table 21–12. Anion gap in metabolic acidosis.¹

Decreased (< 6 mEq/L)

Hypoalbuminemia (decreased unmeasured anion)
Plasma cell dyscrasias

Monoclonal protein (cationic paraprotein accompanied by chloride and bicarbonate)

Bromide intoxication

Increased (> 12 mEq/L)

Metabolic anion

Diabetic ketoacidosis

Alcoholic ketoacidosis

Lactic acidosis

Chronic kidney disease (advanced stages) (PO_4^{3-} , SO_4^{2-})

Starvation ketoacidosis

Drug or chemical anion

Salicylate intoxication

Methanol (formic acid)

Ethylene glycol (oxalic acid)

5-Oxoprolidine acidosis from acetaminophen toxicity

Normal (4–12 mEq/L)

Loss of HCO_3^-

Diarrhea

Recovery from diabetic ketoacidosis

Pancreatic fluid loss, ileostomy (unadapted)

Carbonic anhydrase inhibitors

Chloride retention

Renal tubular acidosis

Ileal loop bladder

Administration of HCl equivalent or NH_4Cl

Arginine and lysine in parenteral nutrition

¹Reference ranges for anion gap may vary based on laboratory methods.

adjusted for hypoalbuminemia; the anion gap decreases by approximately 2.5 mEq/L for every 1 g/dL reduction in the serum albumin concentration.

$$\text{Corrected serum anion gap} = (\text{measured serum anion gap}) + (2.5 \times [4.0 - \text{serum albumin}])$$

In metabolic acidosis from a gain of acid, the anion gap will increase because the addition of acid includes the addition of anions. In nongap or hyperchloremic metabolic acidosis, the anion gap is normal because the rise in chloride parallels the fall in bicarbonate.

INCREASED ANION GAP ACIDOSIS

A gap metabolic acidosis is secondary to the addition of acid, either exogenous or endogenous. The major causes are lactic acidosis, ketoacidosis, kidney disease, and ingestions (Table 21–12). A useful mnemonic for the differential diagnosis of increased anion gap metabolic acidosis is GOLDMARK (glycols [ethylene glycol and propylene glycol], oxoproline, L-lactate, D-lactate, methanol, aspirin, renal failure, and ketoacidosis) (Table 21–13).

A. Lactic Acidosis

Lactic acidosis is a common cause of metabolic acidosis, producing an elevated anion gap and decreased serum pH when present without other acid-base disturbances. Lactate is formed from pyruvate in anaerobic glycolysis. Normally, lactate levels remain low (1 mEq/L) because of metabolism of lactate principally by the liver through gluconeogenesis or oxidation via the Krebs cycle. In lactic acidosis, lactate levels are at least 4–5 mEq/L but

commonly significantly higher. There are two basic types of lactic acidosis.

Type A (hypoxic) lactic acidosis is more common, resulting from tissue hypoxia, usually from septic, cardiogenic, or hemorrhagic shock; mesenteric ischemia; respiratory failure; and carbon monoxide poisoning. These conditions increase peripheral lactic acid production and decrease hepatic metabolism of lactate as liver perfusion declines.

Type B lactic acidosis is secondary to impaired mitochondrial oxygen utilization and may be due to metabolic causes (eg, diabetes mellitus, liver disease, kidney disease, thiamine deficiency, D-lactic acidosis, leukemia, or lymphoma) or toxins (eg, ethanol, methanol, ethylene glycol, cyanide, isoniazid, or metformin). Propylene glycol can cause lactic acidosis from decreased liver metabolism; it is used as a vehicle for intravenous medications, such as nitroglycerin, etomidate, and diazepam. Parenteral nutrition without thiamine causes severe refractory lactic acidosis from deranged pyruvate metabolism.

D-lactic acidosis may develop in patients with short bowel syndrome due to carbohydrate malabsorption and subsequent fermentation by colonic bacteria. Metabolic acidosis occurs after meals and is associated with neurologic changes (confusion, slurred speech, and ataxia). A specific D-lactic acid assay is required as the standard lactic acid assay only detects the L-isomer.

B. Ketoacidosis

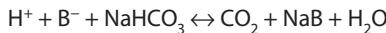
All forms of ketoacidosis share the physiologic state of insulin deficiency and glucagon excess, which shifts the body's primary fuel source from glucose to fatty acid

Table 21–13. Common causes and therapy for increased anion gap metabolic acidosis.

Cause	Treatment
Lactic acidosis	Therapy aimed at correcting the underlying cause. Treatment of type A requires improving perfusion and matching oxygen consumption with fluids, packed red cells, vasopressors, and inotropes as needed. Type B generally requires removal of the offending agent or supplementing key cofactors of anaerobic metabolism.
D-Lactic acidosis	Sodium bicarbonate may be administered in the setting of severe acidemia. Specific antimicrobial agents (metronidazole, neomycin) can be utilized in patients with short gut syndrome. A low carbohydrate diet can be effective by decreasing substrate delivery to the distal colon. Fecal transplant has been utilized successfully in patients unresponsive to conventional therapies.
Ketoacidosis Diabetes mellitus Starvation Alcoholic	Therapy involves correction of the state of insulin deficiency and glucagon excess. In diabetic ketoacidosis, this requires administration of exogenous insulin, generally with a continuous infusion. In starvation and alcoholic ketoacidosis, dextrose-containing fluids will stimulate endogenous insulin release. In all groups, correction of volume depletion with isotonic fluids as well as judicious repletion of electrolytes (particularly potassium and phosphorous) are imperative.
Kidney failure	Supplemental alkali therapy (sodium bicarbonate or sodium citrate). Hemodialysis when necessary.
Ingestions	
Ethylene glycol Methanol	See Chapter 38.
Salicylic acid	See Chapter 38.
Pyroglutamic acid (5-Oxoproline)	Therapy is directed at the underlying cause. Generally requires withdrawal of the offending agent (acetaminophen) and sodium bicarbonate therapy for severe acidemia. N-acetylcysteine may be effective in restoring glutathione stores.

metabolism. There are three types of ketones: acetone, acetoacetate, and beta-hydroxybutyrate.

1. Diabetic ketoacidosis (DKA)—DKA is characterized by hyperglycemia and metabolic acidosis with an increased anion gap from absolute or relative insulin deficiency:



where B^- is beta-hydroxybutyrate or acetoacetate, the ketones responsible for the increased anion gap. DKA may have an additional lactic acidosis from tissue hypoperfusion and increased anaerobic metabolism. The anion gap in DKA is generally large, often more than 20 mEq/L, though it can be variable. The elevated serum glucose leads to a marked osmotic diuresis with sizeable losses of sodium, water, and potassium.

Correction of ketoacidosis can be assessed by measurement of serum beta-hydroxybutyrate, pH, or by normalization of the anion gap. Urine ketones are detected by nitroprusside testing, results of which are rapidly available. However, urinary nitroprusside tests detect both acetoacetate and acetone (albeit to a lesser extent) but do not detect beta-hydroxybutyrate. Direct measurement of serum beta-hydroxybutyrate is preferred and can be used to monitor response to therapy.

2. Fasting ketoacidosis—Hepatic generation of ketones may occur as a normal response to fasting from relative hypoinsulinemia. Mild ketosis often occurs after 12–14 hours of fasting, peaking after 20–30 hours. The level of acidosis is generally small; overt ketoacidosis can occur in patients who consume very low carbohydrate diets.

3. Alcoholic ketoacidosis—Chronically malnourished patients who consume large quantities of alcohol may develop alcoholic ketoacidosis. Alcohol metabolism decreases gluconeogenesis, resulting in hepatic production of beta-hydroxybutyrate and, to a lesser degree, acetoacetate. Mixed acid-base disorders, such as metabolic alkalosis from vomiting, and respiratory alkalosis from alcohol withdrawal, aspiration, or cirrhosis are common.

In both of the above conditions, hypoglycemia, or stimulation of the sympathetic nervous system, suppresses insulin release allowing ketosis to occur. Patients with these disorders are able to sufficiently produce endogenous insulin and therefore do not require exogenous insulin administration. Treatment should commence with glucose administration to stimulate insulin release and suppress ketogenesis. Potassium should be repleted prior to glucose administration as insulin release will cause intracellular potassium shift, risking hypokalemia.

C. Toxins

(See also Chapter 38.) Multiple toxins and drugs increase the anion gap by increasing endogenous acid production. Common examples include methanol (metabolized to formic acid), ethylene glycol (glycolic and oxalic acid), and salicylates (salicylic acid and lactic acid). The latter can cause a mixed disorder of metabolic acidosis with respiratory alkalosis. In toluene poisoning, the metabolite hippurate is rapidly excreted by the kidney and may present as a normal anion gap acidosis. Isopropanol, which is metabolized to acetone, increases the osmolar gap, but not the anion gap. Long-term acetaminophen use, even at therapeutic doses, can result in an elevated anion gap acidosis from accumulation of 5-oxoproline.

D. Uremic Acidosis

As the GFR drops below 15–30 mL/min/1.73 m², the kidneys are increasingly unable to synthesize ammonium (NH_4^+). The reduced excretion of H^+ (as NH_4Cl) and accumulation of organic anions from decreased excretion (eg, phosphate and sulfate) results in an increased anion gap metabolic acidosis.

NORMAL ANION GAP ACIDOSIS

The two major causes of hyperchloremic metabolic acidosis are HCO_3^- loss from the GI tract or defects in renal acidification (RTA) (Table 21–12 and Table 21–14). The compensatory increase in serum chloride (hyperchloraemia) maintains

Table 21–14. Hyperchloremic, normal anion gap metabolic acidoses.

	Renal Defect	Serum [K ⁺]	Distal H ⁺ Secretion		Urinary Anion Gap	Treatment
			Urine pH	Titratable Acid		
Gastrointestinal HCO_3^- loss	None	↓	< 5.5	↑↑	Negative	Na^+ , K^+ , and HCO_3^- as required
Renal tubular acidosis						
I. Distal	Distal H ⁺ secretion	↓	> 5.3	↓	Positive	NaHCO_3 (1–3 mEq/kg/day)
II. Proximal	Proximal HCO_3^- reabsorption	↓	Variable	Normal	Positive	NaHCO_3 or KHCO_3 (10–15 mEq/kg/day), thiazide
IV. Hyporeninemic hypoaldosteronism	Distal Na^+ reabsorption, K^+ secretion, and H ⁺ secretion	↑	Variable	↓	Positive	Fludrocortisone (0.1–0.5 mg/day), dietary K ⁺ restriction, furosemide (40–160 mg/day), NaHCO_3 (1–3 mEq/kg/day)

Modified and reproduced, with permission, from Cogan MG. *Fluid and Electrolytes: Physiology and Pathophysiology*. McGraw-Hill, 1991.

electroneutrality and a normal anion gap. The urinary anion gap can help differentiate between these causes.

A. Gastrointestinal HCO₃⁻ Loss

The GI tract secretes bicarbonate at multiple sites. The most common cause of a non-anion gap metabolic acidosis from the GI tract is diarrhea (loss of bicarbonate rich stool fluid). An infrequent cause is a ureterosigmoidostomy, where ureters are implanted into the sigmoid colon for urinary diversion. Unlike the bladder, colonic mucosa secretes bicarbonate in exchange for chloride, resulting in metabolic acidosis. More commonly, a neobladder is created using a loop of bowel (generally ileum or colon), which has significantly decreased the incidence of metabolic acidosis, though it can still occur when contact time between urine and mucosa is increased, typically as a result of an anastomotic stricture.

B. Renal Tubular Acidosis

Hyperchloremic acidosis with a normal anion gap and normal (or near normal) GFR, in the absence of diarrhea, defines RTA. The defect is either an inability to excrete H⁺ as ammonium (inadequate generation of new HCO₃⁻) or inadequate reabsorption of filtered HCO₃⁻. Three major types can be differentiated by the clinical setting, urinary pH, urinary anion gap, and serum K⁺ level.

1. Distal RTA (type I)—This disorder is characterized by inability to excrete H⁺ by the distal nephron. The urine cannot be fully acidified (urine pH > 5.5), despite systemic acidosis. Urinary ammonium excretion is therefore decreased and the urinary anion gap is positive. Voltage dependent distal RTA (dRTA) is due to a defect in sodium reabsorption, which impairs hydrogen secretion by failure to generate a negative lumen potential. This is seen in obstructive uropathy; sickle cell disease; or medications, such as amiloride. This disorder also prevents the excretion of potassium, resulting in hyperkalemia. Classic distal RTA (the most common cause) is secondary to a congenital or acquired decrease in the number of functional H⁺ pumps, which reduces H⁺ secretion by alpha intercalated cells. This is associated with hypokalemia due to enhanced K⁺ excretion from a lack of competition from H⁺ in the tubular fluid. This form of dRTA is commonly due to Sjögren syndrome, SLE, plasma cell myeloma, toluene inhalation (glue sniffing), Wilson disease, and lithium. dRTA can also be caused by destruction of tubular integrity (eg, amphotericin B). This type of dRTA is also associated with hypokalemia as destruction of the tubular membrane allows potassium to freely flow down its concentration gradient into the tubular lumen. In all types of dRTA, buffering of acid by release of bicarbonate and calcium from bone results in hypercalciuria, which in addition to low urinary citrate from increased reabsorption, results in the often encountered complication of nephrolithiasis.

2. Proximal RTA (type II)—Proximal RTA is due to a defect in the ability of the proximal tubule to reabsorb filtered HCO₃⁻. The maximal rate of bicarbonate reabsorption is set by the tubular maximum (Tm), which is normally

26–28 mEq/L. The hallmark of a proximal RTA (pRTA) is a decrease in the Tm for bicarbonate, typically to 14–20 mEq/L. Therefore, this is a self-limited disease with serum bicarbonate levels predicated on the severity of the proximal defect and the ability of the distal nephron to reabsorb bicarbonate. This essentially creates a new steady state, when the Tm is equivalent to the serum HCO₃⁻ level, where the urine is acidic (no impairment of distal H⁺ secretion) and the urine anion gap is negative (no impairment of ammonium excretion). Bicarbonaturia, and hence an alkaline urine (greater than 5.5), only occurs when the bicarbonate level exceeds the Tm, which has implications in treatment. Fanconi syndrome is pRTA with other proximal reabsorption defects resulting in glucosuria, aminoaciduria, phosphaturia, and uricosuria. The most common cause of pRTA is proximal tubular toxicity from the monoclonal immunoglobulin light chains in plasma cell myeloma. Other causes include heavy metals; Sjögren syndrome; cystinosis; Wilson disease; and various medications, such as acetazolamide, topiramate, tenofovir, and ifosfamide. The increased delivery of HCO₃⁻ to the distal nephron enhances K⁺ secretion, and hypokalemia results when a patient is treated with HCO₃⁻ without adequate K⁺ supplementation. Similar to dRTA, bone loss from persistent acidosis is common. Untreated children can develop rickets, while adult patients can develop osteomalacia. Unlike dRTA, nephrolithiasis is uncommon in pRTA because of the increased citrate in the urine, which increases calcium solubility.

3. Hyporeninemic hypoaldosteronemic RTA (type IV)

Type IV is the most common RTA in clinical practice. This is primarily a disorder of hyperkalemia secondary to a decrease in aldosterone, which inhibits ammonium production. The clinical presentation is a hyperkalemic non-gap metabolic acidosis. Common causes include diabetic nephropathy and tubulointerstitial renal diseases. In patients with these disorders, drugs, such as ACE inhibitors, ARBs, spironolactone, and NSAIDs, can worsen the hyperkalemia and acidosis.

C. Other Causes of Nongap Acidosis

A dilutional acidosis may occur when the extracellular volume is rapidly expanded with normal saline since it contains neither bicarbonate nor sodium salts that can be metabolized to bicarbonate. Concerns have been raised regarding potential harm from volume expansion with normal saline. In clinical practice, balanced crystalloid solutions, such as lactated Ringer solution, are more commonly used.

1. Urine anion gap—The normal kidney response to a metabolic acidosis is to increase NH₄Cl excretion to enhance H⁺ removal. The daily urinary excretion of NH₄Cl can be increased from 30 mEq at baseline to 200–300 mEq in response to acidosis. Urine ammonium excretion can be estimated using the following urine anion gap equation:

$$\text{Urine anion gap} = U_{\text{Na}} + U_{\text{K}} - U_{\text{Cl}}$$

The urinary anion gap may help differentiate between GI and renal causes of hyperchloremic acidosis. If the cause

is GI HCO_3^- loss (diarrhea), renal acidification remains intact and NH_4^+ Cl excretion increases appropriately (urinary anion gap will be negative). In a distal RTA, ammonium excretion is impaired and the urinary anion gap is positive. In proximal (type II) RTA, the primary problem is impaired HCO_3^- reabsorption, leading to increased HCO_3^- excretion rather than decreased NH_4^+ Cl excretion and the urinary anion gap is often negative until treatment is initiated with exogenous bicarbonate therapy.

2. Urine osmolal gap—When large amounts of other anions (eg, hippurate in toluene poisoning, beta-hydroxybutyrate, acetacetate) are present in the urine, the urinary anion gap may not be reliable. In this situation, the urine osmolal gap may be a better indicator of NH_4^+ excretion, which can be estimated as 50% of the urinary osmolal gap where urine concentrations and osmolality are in mmol/L. A urine osmolal gap below 150 mOsmol/kg suggests impaired ammonium excretion, whereas a urine osmolal gap above 400 mOsmol/kg suggests an intact renal response to acidosis.

$$\text{Urine osmolal gap} = \text{U}_{\text{osm}} - 2(\text{U}_{\text{Na}} + \text{U}_{\text{K}}) + \text{U}_{\text{urea}} + \text{U}_{\text{glucose}}$$

Clinical Findings

A. Symptoms and Signs

Symptoms of metabolic acidosis are mainly those of the underlying disorder. Compensatory hyperventilation is an important clinical sign and may be misinterpreted as a primary respiratory disorder; Kussmaul breathing (deep, regular, sighing respirations) may be seen with severe metabolic acidosis.

B. Laboratory Findings

Blood pH, serum HCO_3^- , and PCO_2 are decreased. Anion gap may be normal (hyperchloremic metabolic acidosis) or increased. Hyperkalemia may be seen.

Treatment

A. Increased Anion Gap Acidosis

Treatment is aimed at the underlying disorder, such as insulin and fluid therapy for diabetes and appropriate volume resuscitation to restore tissue perfusion (see Table 21–13). NaHCO_3 therapy is controversial in the treatment of increased anion gap metabolic acidoses and is usually reserved for severe cases (arterial pH < 7.1–7.2). Large amounts of NaHCO_3 may have deleterious effects, including hypernatremia, hyperosmolality, volume overload, and worsening of intracellular acidosis.

B. Normal Anion Gap Acidosis

Treatment of RTA is mainly achieved by administration of alkali (bicarbonate or citrate) to correct metabolic abnormalities and prevent nephrocalcinosis and CKD.

Large amounts of oral alkali (NaHCO_3 or KHCO_3 , 10–15 mEq/kg/day) (Table 21–14) may be required to treat proximal RTA because much of the administered alkali is

excreted into the urine. This can exacerbate hypokalemia and a mixture of sodium and potassium salts is often required. Treatment of type I distal RTA requires less alkali (1–2 mEq/kg/day) than proximal RTA, and potassium supplementation is typically required.

For type IV RTA, dietary potassium restriction may be necessary and potassium-retaining drugs should be withdrawn. Loop diuretics may be beneficial. Fludrocortisone may be effective in some cases without significant volume expansion. In some cases, oral alkali supplementation (1–2 mEq/kg/day) may be required.

When to Refer

Most clinicians will refer patients with renal tubular acidosis to a nephrologist for evaluation and possible alkali therapy.

When to Admit

Patients will require emergency department evaluation or hospital admission depending on the severity of the acidosis and underlying conditions.

Chávez-Iñiguez JS et al. The Case | Severe hypokalemia and metabolic acidosis. *Kidney Int.* 2018;93:1255. [PMID: 29680030]

Palmer BF et al. Electrolyte and acid-base disturbances in patients with diabetes mellitus. *N Engl J Med.* 2015;373:548. [PMID: 26244308]

Palmer BF et al. Salicylate toxicity. *N Engl J Med.* 2020;382:2544. [PMID: 32579814]

Sharma S et al. Comprehensive clinical approach to renal tubular acidosis. *Clin Exp Nephrol.* 2015;19:556. [PMID: 25951806]

METABOLIC ALKALOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ High HCO_3^- with alkalemia (high pH).
- ▶ Evaluate effective circulating volume by physical examination.
- ▶ Urinary chloride concentration differentiates saline-responsive alkalosis from saline-unresponsive alkalosis.

General Considerations

Metabolic alkalosis is characterized by high serum HCO_3^- levels. The development of metabolic alkalosis requires its “generation” from loss of acid or gain of alkali, and its “maintenance” from the kidney’s inability to excrete excess bicarbonate.

The causes of metabolic alkalosis are classified into two groups based on chloride responsiveness and are generally distinguished using urine chloride values (Table 21–15). The compensatory increase in PCO_2 rarely exceeds 55 mm Hg; higher PCO_2 values imply a superimposed primary respiratory acidosis.

Table 21–15. Metabolic alkalosis.

Chloride-Responsive ($U_{Cl^-} < 20 \text{ mEq/L}$)	Chloride-Unresponsive ($U_{Cl^-} > 20 \text{ mEq/L}$)
Excessive body bicarbonate content	Excessive body bicarbonate content
Renal alkalosis	Normotensive
Diuretic therapy (after diuretic effect has ceased)	Bartter syndrome (renal salt wasting and secondary hyperaldosteronism)
Poorly reabsorbable anion therapy: carbenicillin, penicillin, sulfate, phosphate	Severe potassium depletion
Posthypercapnia	Refeeding alkalosis
Gastrointestinal alkalosis	Hypercalcemia and hypoparathyroidism
Loss of HCl from vomiting or nasogastric suction	Hypertensive
Intestinal alkalosis: chloride diarrhea	Endogenous mineralocorticoids
NaHCO_3 (baking soda)	Primary aldosteronism
Sodium citrate, lactate, gluconate, acetate	Hyperreninism
Transfusions	Adrenal enzyme (11-beta-hydroxylase and 17-alpha-hydroxylase) deficiency
Antacids	Liddle syndrome
Normal body bicarbonate content	Exogenous alkali
"Contraction alkalosis"	Exogenous mineralocorticoids
	Licorice

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A. Chloride-Responsive Metabolic Alkalosis (U_{Cl^-} less than 20 mEq/L)

Chloride-responsive metabolic alkalosis involves the loss of chloride and extracellular volume. In vomiting and nasogastric suction, loss of acid (HCl) generates the alkalosis and volume contraction from chloride loss maintains the alkalosis. Distally acting diuretics that cause chloride loss, eg, loop and thiazide diuretics, are a common cause of metabolic alkalosis. U_{Cl^-} levels can be unreliable in these settings since these diuretics increase U_{Cl^-} . These disorders cause concurrent hypokalemia, which can exacerbate metabolic alkalosis by stimulating H^+ secretion and ammonia-generation. In respiratory acidosis, the kidneys compensate by increasing renal HCO_3^- retention, which causes volume expansion and hence NaCl excretion. If the hypercapnia is corrected rapidly, the kidneys will attempt to correct the alkalosis by excreting HCO_3^- ; if sufficient Cl^- is unavailable, bicarbonaturia will halt and metabolic alkalosis will persist. This process has been termed **posthypercapneic metabolic alkalosis**.

In alkalosis, bicarbonaturia causes obligatory sodium excretion as the accompanying cation and U_{Na} levels are unreliable markers of extracellular volume.

B. Chloride-Unresponsive Alkalosis (U_{Cl^-} more than 20 mEq/L)

1. Excess mineralocorticoid activity—Mineralocorticoids act directly in the collecting duct to stimulate sodium reabsorption and hydrogen and potassium excretion. The effects on hydrogen excretion are important in the generation of a metabolic alkalosis. Table 21–15 lists important causes of excess mineralocorticoid activity. These disorders are typically associated with hypertension, hypokalemia, metabolic alkalosis, and mild hypernatremia.

2. Bartter and Gitelman syndromes—Metabolic alkalosis, hypokalemia, and normotension are features of both Bartter and Gitelman syndromes.

3. Alkali administration with decreased GFR—The normal kidney has a substantial capacity for bicarbonate excretion; therefore, metabolic alkalosis usually only develops with HCO_3^- intake when there is CKD (eg, intensive antacid therapy). In milk-alkali syndrome, sustained heavy ingestion of absorbable antacids and milk causes hypercalcemic kidney injury and metabolic alkalosis. Volume contraction from renal hypercalcemic effects exacerbates the alkalosis.

► Clinical Findings

A. Symptoms and Signs

There are no characteristic symptoms or signs. However, hypopnea can be present in severe cases. Concomitant hypokalemia may cause weakness and hyporeflexia. An increase in mortality has been observed with a $\text{pH} > 7.48$.

B. Laboratory Findings

The arterial blood pH and bicarbonate are elevated. With respiratory compensation, the arterial PCO_2 is increased. Serum potassium and chloride are decreased. The urine Cl^- can differentiate between chloride-responsive (less than 20 mEq/L) and unresponsive (greater than 20 mEq/L) causes.

► Treatment

Mild alkalosis is generally well tolerated. Severe or symptomatic alkalosis ($\text{pH} > 7.60$) requires urgent treatment.

A. Chloride-Responsive Metabolic Alkalosis

Therapy for chloride-responsive alkalosis involves volume expansion with chloride salts, generally in the form of intravenous normal saline, until a euvolemic state has been achieved. This reduces proximal tubular bicarbonate reabsorption and increases distal tubular delivery of chloride, where it is exchanged for bicarbonate by the luminal $\text{Cl}^-/\text{HCO}_3^-$ pendrin. In edematous patients with a contraindication to volume expansion (eg, heart failure), the carbonic anhydrase inhibitor acetazolamide can be given (250–500 mg orally twice daily) to increase renal bicarbonate excretion. Hypokalemia should be corrected by administering oral KCl.

B. Chloride-Unresponsive Metabolic Alkalosis

Therapy for chloride-unresponsive metabolic alkalosis requires therapy targeted to the underlying cause (see Chapter 26).

Emmett M. Metabolic alkalosis: a brief pathophysiologic review. *Clin J Am Soc Nephrol*. 2020;15:1848. [PMID: 32586924]

RESPIRATORY ACIDOSIS (Hypercapnia)

► General Considerations

Respiratory acidosis results from hypoventilation and subsequent hypercapnia. Both pulmonary and extrapulmonary disorders can cause hypoventilation.

Acute respiratory acidosis is associated with only a modest increase in bicarbonate since serum bicarbonate is an ineffective buffer because of impaired elimination of carbon dioxide. After 6–12 hours, the primary increase in PCO_2 evokes a renal compensation to excrete more acid and to generate more HCO_3^- . Complete metabolic compensation by the kidney takes several days. In acute respiratory acidosis, HCO_3^- increases by 1 mEq/L for every 10 mm Hg increase in PCO_2 .

Chronic respiratory acidosis is generally seen in patients with underlying lung disease, such as chronic obstructive pulmonary disease. Renal excretion of acid as NH_4^+Cl results in a compensatory metabolic alkalosis. In this situation, HCO_3^- increases by 3 mEq/L for every 10 mm Hg increase in PCO_2 .

► Clinical Findings

A. Symptoms and Signs

With acute onset, somnolence, confusion, mental status changes, asterixis, and myoclonus may develop. Severe hypercapnia increases cerebral blood flow, cerebrospinal fluid pressure, and intracranial pressure; papilledema and seizures may be seen.

B. Laboratory Findings

Arterial pH is low and PCO_2 is increased. Serum HCO_3^- is elevated but does not fully correct the pH. Respiratory etiologies of respiratory acidosis usually have a wide A-a difference; a relatively normal A-a difference in the presence of respiratory acidosis is highly suggestive of global hypoventilation.

► Treatment

If opioid overdose is a possible diagnosis or there is no other obvious cause for hypoventilation, the clinician should consider a diagnostic and therapeutic trial of intravenous naloxone (see Chapter 38). Noninvasive or mechanical ventilation may be necessary.

Adrogué HJ et al. Alkali therapy for respiratory acidosis: a medical controversy. *Am J Kidney Dis*. 2020;75:265. [PMID: 31473018]

RESPIRATORY ALKALOSIS

► General Considerations

Respiratory alkalosis is always a disorder of hyperventilation, reducing the PCO_2 and increasing serum pH (Table 21–16). In pregnancy, progesterone stimulates the respiratory center, producing an average PCO_2 of 30 mm Hg and respiratory alkalosis. Salicylates directly stimulate respiration and aspirin toxicity should be suspected when both respiratory alkalosis and an anion gap metabolic acidosis are present, particularly with alkalemia. Symptoms of acute respiratory alkalosis are related to decreased cerebral blood flow induced by the disorder.

Table 21–16. Causes of respiratory alkalosis.

Hypoxia

Decreased inspired oxygen tension
High altitude
Ventilation/perfusion inequality
Hypotension
Severe anemia

CNS-mediated disorders

Voluntary hyperventilation
Anxiety-hyperventilation syndrome
Neurologic disease
Cerebrovascular accident (infarction, hemorrhage)
Infection
Trauma
Tumor
Pharmacologic and hormonal stimulation

Salicylates
Nicotine
Xanthines
Pregnancy (progesterone)

Liver failure
Gram-negative septicemia
Recovery from metabolic acidosis
Heat exposure

Pulmonary disease

Interstitial lung disease
Pneumonia
Pulmonary embolism
Pulmonary edema

Mechanical overventilation

Adapted, with permission, from Gennari FJ. Respiratory acidosis and alkalosis. In: Maxwell and Kleeman's *Clinical Disorders of Fluid and Electrolyte Metabolism*, 5th ed. Narins RG (editor). McGraw-Hill, 1994.

Table 21–17. Replacement guidelines for sweat and gastrointestinal fluid losses.

	Average Electrolyte Composition					Replacement Guidelines per Liter Lost			
	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	Cl ⁻ (mEq/L)	HCO ₃ ⁻ (mEq/L)	0.9% Saline (mL)	0.45% Saline (mL)	D ₅ W (mL)	KCl (mEq/L)	7.5% NaHCO ₃ (45 mEq HCO ₃ ⁻ /amp)
Sweat	30–50	5	30–50			500	500	5	
Gastric secretions	20	10	10			300	700	20	
Pancreatic juice	130	5	35	115		400	600	5	2 amps
Bile	145	5	100	25	600		400	5	0.5 amp
Diarrhea ¹	140	15	110–115	40–45					

¹In the absence of diarrhea, colonic fluid Na⁺ levels are low (40 mEq/L).

Determination of appropriate metabolic compensation may reveal an associated metabolic disorder.

As in respiratory acidosis, the metabolic compensation is greater if the respiratory alkalosis is chronic (see Table 21–11). In acute respiratory alkalosis, HCO₃⁻ decreases by 2 mEq/L for every 10 mm Hg decrease in PCO₂, whereas in chronic respiratory alkalosis, HCO₃⁻ decreases by 4 mEq/L for every 10 mm Hg decrease in PCO₂.

Clinical Findings

A. Symptoms and Signs

In acute cases (hyperventilation), there is light-headedness, anxiety, perioral numbness, and paresthesias. Tetany occurs from a low ionized calcium, since severe alkalosis increases calcium binding to albumin.

B. Laboratory Findings

Arterial blood pH is elevated, and PCO₂ is low. Serum bicarbonate is decreased in chronic respiratory alkalosis.

Treatment

Treatment is directed toward the underlying cause. In acute hyperventilation syndrome from anxiety, the traditional treatment of breathing into a paper bag should be discouraged because it does not correct PCO₂ and may decrease PO₂. Reassurance may be sufficient for the anxious patient, but sedation may be necessary if the process persists. Hyperventilation is usually self-limited since muscle weakness caused by the respiratory alkalemia will suppress ventilation. Rapid correction of chronic respiratory alkalosis may result in metabolic acidosis as PCO₂ is increased with a previous compensatory decrease in HCO₃⁻. The severity of hypocapnia in critically ill patients has been associated with adverse outcomes.

Scheiner B et al. Acid-base disorders in liver disease. *J Hepatol.* 2017;67:1062. [PMID: 28684104]

FLUID MANAGEMENT

Daily parenteral maintenance fluids and electrolytes for an average adult of 70 kg would include at least 2 L of water in the form of 0.45% saline with 20 mEq/L of potassium chloride. Patients with hypoglycemia, starvation ketosis, or ketoacidosis being treated with insulin may require 5% dextrose-containing solutions. Guidelines for GI fluid losses are shown in Table 21–17.

Weight loss or gain is the best indication of water balance. Insensible water loss should be considered in febrile patients. Water loss increases by 100–150 mL/day for each degree of body temperature over 37°C.

In patients requiring maintenance and possibly replacement of fluid and electrolytes by parenteral infusion, the total daily ration should be administered continuously over 24 hours to ensure optimal utilization.

If intravenous fluids are the only source of water, electrolytes, and calories for longer than a week, parenteral nutrition containing amino acids, lipids, trace metals, and vitamins may be indicated. (See Chapter 29.)

Balanced crystalloid-like lactated Ringer solution, rather than normal saline, is the resuscitation fluid of choice in most settings (see Chapter 12). Excessive fluid resuscitation and maintenance are complications in hospitalized patients, especially those with critical illness or acute kidney injury. These complications have been associated with worsened outcomes, such as prolonged mechanical ventilation, dependence on dialysis, and longer hospitalization with increased mortality.

Bentzer P et al. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA.* 2016;316:1298. [PMID: 27673307]

Moritz ML et al. Maintenance intravenous fluids in acutely ill patients. *N Engl J Med.* 2015;373:1350. [PMID: 26422725]

Schindler AW et al. Evidence-based fluid management in the ICU. *Curr Opin Anaesthesiol.* 2016;29:158. [PMID: 26784351]

22

Kidney Disease

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Although some patients with kidney disease experience hypertension, edema, nausea, or hematuria that may lead to its discovery, kidney disease is often discovered incidentally during a routine medical evaluation. The initial approach to kidney disease is to assess the cause and severity of renal abnormalities. In all cases, this evaluation includes (1) estimation of disease duration, (2) careful examination of the urine, and (3) assessment of the glomerular filtration rate (GFR). The history and physical examination, though equally important, are variable among renal syndromes—thus, specific symptoms and signs are discussed under each disease entity.

ASSESSMENT OF KIDNEY DISEASE

Kidneys may be damaged by a variety of injuries; data helpful in the evaluation of kidney disease include estimation of disease duration, estimation of the glomerular filtration rate (eGFR), examination of the urine, and quantification of urinary protein excretion. Additionally, renal imaging (most often ultrasonography) can be helpful. Kidney biopsy may be performed in select cases as noted below, particularly when glomerular disease is suspected.

Disease Duration

Kidney disease can be acute or chronic. Acute kidney injury (AKI) is worsening of kidney function over hours to days, resulting in retention of waste products (such as urea nitrogen) and creatinine in the blood. Retention of these substances is called azotemia. Chronic kidney disease (CKD) is the loss of kidney function over months to years. Differentiating between AKI and CKD is important for diagnosis and treatment, and certain clues may help distinguish the two. For instance, oliguria is only observed in AKI, whereas anemia (from low kidney erythropoietin production) suggests CKD. Additionally, small kidney size on imaging is more consistent with CKD, whereas normal to large kidney size can be seen with both AKI and CKD.

Urinalysis

Examination of the urine can provide important clues when evaluating kidney disease. A urine specimen should

be collected midstream or by bladder catheterization and examined within 1 hour after collection to avoid destruction of formed elements. Urinalysis includes dipstick examination followed by microscopy if the dipstick has positive findings. The dipstick examination measures urinary pH, specific gravity, protein, hemoglobin, glucose, ketones, bilirubin, nitrites, and leukocyte esterase. Microscopy of centrifuged urinary sediment permits examination of formed elements—crystals, cells, casts, and infectious organisms. A bland (normal) sediment is common, especially in CKD and acute nonparenchymal disorders, such as limited effective blood flow to the kidney or urinary obstruction. Urinary casts form when urine flow is slow, leading to precipitation of Tamm-Horsfall mucoprotein in the renal tubule; if there are many red or white blood cells in the urine, cellular casts may form. The presence of protein on dipstick examination suggests underlying glomerular disease. If the glomerular basement membrane (GBM) is damaged (eg, by inflammation), red blood cells may leak into the urinary space and appear dysmorphic. Thus, proteinuria, dysmorphic hematuria, and red blood cells casts are highly suggestive of glomerulonephritis. Heavy proteinuria and lipiduria are indicative of nephrotic syndrome. Granular casts (also called “muddy brown casts”) and renal tubular epithelial cells alone or in casts are hallmarks of acute tubular necrosis (ATN). White blood cells (including neutrophils and eosinophils), white blood cell casts (Table 22–1), and proteinuria of varying degree can be seen with pyelonephritis and interstitial nephritis; pyuria alone can indicate urinary tract infection. Proteinuria and hematuria are further discussed below.

A. Proteinuria

Proteinuria is defined as excessive protein excretion in the urine, generally greater than 150 mg/24 hours in adults. Proteinuria more than 1–2 g/day is usually a sign of underlying glomerular kidney disease, whereas proteinuria less than 1 g/day can be due to multiple causes along the nephron segment, as listed below. Proteinuria can be accompanied by other clinical abnormalities—elevated blood urea nitrogen (BUN) and serum creatinine levels, abnormal urine sediment, or evidence of systemic illness (eg, fever, rash, vasculitis).

Table 22–1. Significance of specific urinary casts.

Type	Significance
Hyaline casts	Not indicative of kidney disease Concentrated urine, febrile disease, diuretic therapy, after strenuous exercise
Red cell casts	Glomerulonephritis
White cell casts	Indicative of infection or inflammation Pyelonephritis, interstitial nephritis
Renal tubular cell casts	Acute tubular necrosis, interstitial nephritis
Granular (muddy brown) casts	Nonspecific; can indicate acute tubular necrosis
Broad waxy casts	Indicative of stasis in enlarged collecting tubules Chronic kidney disease

There are several reasons proteinuria may develop: (1) **Functional proteinuria** is a benign process stemming from stressors such as acute illness, exercise, and “orthostatic proteinuria.” The latter condition, generally found in people under 30 years of age, usually causes protein excretion less than 1 g/day. The orthostatic nature of the proteinuria is confirmed by measuring an 8-hour overnight supine urinary protein excretion, which should be less than 50 mg. (2) **Overload proteinuria** occurs when the reabsorptive capacity of tubules is overwhelmed, which can result from excess production of low-molecular-weight plasma proteins (eg, Bence Jones proteins associated with plasma cell myeloma). In the case of plasma cell myeloma, protein electrophoresis from serum or urine will exhibit a discrete, monoclonal protein spike. Other examples of overload proteinuria include myoglobinuria in rhabdomyolysis and hemoglobinuria in hemolysis. (3) **Glomerular proteinuria** results from effacement of epithelial cell foot processes and altered glomerular permeability with an increased filtration fraction of normal plasma proteins, as in diabetic nephropathy. Protein electrophoresis will exhibit a large albumin spike indicative of the increased permeability of albumin across the damaged GBM. (4) **Tubular proteinuria** occurs as a result of faulty reabsorption of normally filtered proteins in the proximal tubule, such as beta-2-microglobulin. Causes may include ATN, toxic injury (lead, aminoglycosides, and certain antiretrovirals), drug-induced interstitial nephritis, and hereditary metabolic disorders (Wilson disease and Fanconi syndrome).

Evaluation of proteinuria by urine dipstick does not actually measure protein but instead detects the negative electrochemical charge that characterizes albumin. As a result, positively charged Bence Jones proteins are missed with dipstick analysis. Bence Jones proteins can be detected by the addition of sulfosalicylic acid to the urine specimen or, more commonly, directly measuring urine protein. It should be noted that, because urine dipstick simply detects negative electrochemical charge, alkaline urine ($\text{pH} > 7.0$) can cause false-positive results.

While urine dipstick is commonly used to screen for proteinuria, quantitative investigation requires direct evaluation

of urine protein excretion. This can be estimated with a random urine sample or measured from a timed urine collection (typically 24 hours). Collection of a random urine sample is far simpler, and the ratio of urine protein-to-creatinine concentration ($[\text{U}_{\text{protein}}]/[\text{U}_{\text{creatinine}}]$) correlates with a 24-hour urine protein collection (less than 0.2 is normal and corresponds to excretion of less than 200 mg/24 hours). In a 24-hour collection, proteinuria above 150 mg is abnormal and above 3 g is classified as nephrotic-range. One benefit of a random protein-to-creatinine ratio is the minimization of error from overcollection or undercollection of urine in the 24-hour specimen. A kidney biopsy may be indicated to determine the cause of abnormal proteinuria, particularly if accompanied by abnormal GFR or hematuria. The clinical sequelae of proteinuria are discussed in the section on Nephrotic Spectrum Glomerular Diseases.

B. Hematuria

Hematuria is considered clinically significant if there are more than three red blood cells per high-power field on at least two occasions. It is usually detected incidentally on urine dipstick or following an episode of macroscopic hematuria. The diagnosis must be confirmed via microscopic examination, as false-positive dipstick tests can be caused by myoglobin, oxidizing agents, beets and rhubarb, hydrochloric acid, and bacteria. Transient hematuria is common but is less often clinically significant in patients younger than 40 years due to lower concern for malignancy.

Hematuria may be due to renal or extrarenal causes. Extrarenal causes are addressed in Chapter 23. Renal causes account for approximately 10% of cases and are classified as either glomerular or extraglomerular. Glomerular causes include glomerulonephritis (eg, immunoglobulin A [IgA] nephropathy), thin basement membrane disease and other hereditary disorders (eg, Alport syndrome), and systemic nephritic syndromes (eg, lupus nephritis). Extraglomerular sources include cysts; calculi; interstitial nephritis; and, most worrisome, genitourinary neoplasms from the kidney, prostate, or bladder (see Chapter 39).

► Glomerular Filtration Rate

The GFR provides a useful measure of kidney function at the level of the glomerulus and can either be measured directly using biomarkers (most commonly creatinine) or estimated using validated formulae. The GFR measures the amount of plasma ultrafiltered across the glomerular capillaries per unit time and reflects the kidneys' ability to filter fluids and substances, including medications; it is often used to determine drug dosing. Daily GFR in normal individuals is variable, with a range of 150–250 L/24 h or 100–120 mL/min/1.73 m² of body surface area. Patients with kidney disease can have decreased GFR from any process that causes loss of functional glomeruli. However, they can also have normal or increased GFR, either from glomerular hyperfiltration or disease at a different segment of the nephron, interstitium, or vascular supply.

GFR can be measured by determining the renal clearance of plasma substances that are not bound to plasma

proteins, are freely filterable across the glomerulus, and are neither secreted nor reabsorbed along the renal tubules. The renal clearance of a substance is defined as:

$$C = \frac{U \times \dot{V}}{P}$$

where C is the clearance, U and P are the respective urine and plasma concentrations of the substance (mg/dL), and \dot{V} is volume of urine per unit time (typically mL/min). In clinical practice, the clearance of endogenous creatinine (termed **creatinine clearance**) is the primary way to measure GFR. The creatinine clearance (C_{cr}) is approximately 100 mL/min in healthy young women and 120 mL/min in healthy young men. The creatinine clearance declines by an average of 0.8 mL/min/yr after age 40 years as part of the aging process. Creatinine is a product of muscle metabolism produced at a relatively constant rate and cleared by renal excretion. It is freely filtered by the glomerulus and not reabsorbed by the renal tubules. However, creatinine is not a perfect indicator of GFR for the following reasons: (1) a small amount is normally eliminated by tubular secretion, and it progressively increases as GFR declines (thus overestimating GFR); (2) with severe kidney failure, gut microorganisms degrade creatinine; (3) dietary meat intake and muscle mass affect plasma creatinine levels; (4) medications such as aspirin, dolutegravir, probenecid, and trimethoprim reduce tubular secretion of creatinine, increasing the plasma creatinine concentration and falsely suggesting kidney dysfunction; and (5) the measurement assumes a stable plasma creatinine concentration over a 24-hour period, so when values are changing during the development of and recovery from AKI, creatinine clearance is inaccurate.

One way to measure creatinine clearance is to perform a timed urine collection and determine the plasma creatinine level midway through the collection. An incomplete or prolonged urine collection is a common source of error. The completeness of the collection can be estimated by comparing the amount of creatinine excreted in the collection to that expected over a 24-hour period, which should be constant:

$$U_{cr} \times \dot{V} = 15 - 20 \text{ mg/kg for healthy young women}$$

$$U_{cr} \times \dot{V} = 20 - 25 \text{ mg/kg for healthy young men}$$

Given the tedious nature of timed urine collections for measuring GFR, GFR is more commonly estimated (denoted eGFR) using formulae that have been validated using patient characteristics (such as age, weight, race, and sex) and plasma creatinine levels. The Kidney Disease Improving Global Outcomes workgroup recommends eGFR formulae as the primary method for determining GFR. The preferred eGFR formula is the 2009 CKD-Epidemiology (EPI) Collaboration creatinine equation (<https://www.kidney.org/content/ckd-epi-creatinine-equation-2009>). An alternative creatinine-based GFR estimating equation is acceptable if it improves accuracy over the CKD-EPI equation. Several web-based calculators will calculate the eGFR (eg, <http://touchcalc.com/calculators/epi>). The Cockcroft-Gault formula is commonly used to determine drug dosing, but it is no longer recommended since it was developed

before the standardization of creatinine assays currently in use. **Cystatin C** is another endogenous marker of GFR that is filtered freely at the glomerulus, produced at a relatively constant rate, and less dependent on muscle mass. It is reabsorbed and partially metabolized in the renal tubular epithelial cells. Adding the measurement of cystatin C to serum creatinine can improve the accuracy of the eGFR. A large meta-analysis showed that cystatin C alone or in combination with serum creatinine is a stronger predictor of important clinical events, such as end-stage kidney disease (ESKD) or death, than serum creatinine alone. However, because cystatin C is not universally available or standardized across assays, it remains a complementary biomarker for estimating GFR.

BUN is another index used in assessing kidney function. It is synthesized mainly in the liver and is the end product of protein catabolism. Urea is freely filtered by the glomerulus, but about 30–70% is reabsorbed in the renal tubules. As such, it underestimates GFR. Renal urea reabsorption increases (in conjunction with increased sodium reabsorption) in hypovolemic patients (who, therefore, have an increased BUN). A normal BUN:creatinine ratio is approximately 10:1, although this varies between individuals. With volume depletion, the ratio can increase to 20:1 or higher. Other causes of increased BUN include increased catabolism (gastrointestinal [GI] bleeding, cell lysis, and corticosteroid usage), increased dietary protein, and decreased renal perfusion prompting increased sodium (and therefore BUN) reabsorption (eg, heart failure, renal artery stenosis) (Table 22–2). Reduced BUN levels are seen in liver disease and in the syndrome of inappropriate antidiuretic hormone (SIADH).

In summary, creatinine and urea clearances overestimate and underestimate GFR, respectively. Because each of these estimates become more inaccurate as kidney disease advances, a more accurate measure of GFR as patients approach ESKD is the average of the creatinine and urea clearances.

KIDNEY BIOPSY

Indications for percutaneous needle biopsy include (1) unexplained AKI or CKD; (2) unexplained proteinuria or hematuria, or both; (3) previously identified and treated

Table 22–2. Conditions affecting BUN independently of GFR.

Increased BUN

Reduced effective circulating blood volume (prerenal azotemia)
Catabolic states (gastrointestinal bleeding, corticosteroid use)
High-protein diets
Tetracycline

Decreased BUN

Liver disease
Malnutrition
Sickle cell anemia
SIADH

BUN, blood urea nitrogen; GFR, glomerular filtration rate; SIADH, syndrome of inappropriate antidiuretic hormone.

lesions to guide future therapy; (4) systemic diseases associated with kidney dysfunction, such as systemic lupus erythematosus (SLE), anti-GBM disease, and granulomatosis with polyangiitis; and (5) kidney transplant dysfunction, to evaluate for transplant rejection or other abnormalities. Kidney biopsies should only be performed if the results will influence the treatment plan or facilitate discussion about prognosis. Relative contraindications include a solitary or ectopic kidney (exception for transplant allografts), horseshoe kidney, ESKD, congenital anomalies, and multiple cysts. Absolute contraindications include an uncorrected bleeding disorder; severe uncontrolled hypertension; renal infection or neoplasm; hydronephrosis; or uncooperative patients, including those who are unable to lie flat for the procedure.

Percutaneous kidney biopsies are generally safe. The major risk is bleeding, which may occur up to 72 hours post biopsy. More than half of patients will have at least a small hematoma; approximately 1–5% of patients will experience significant bleeding requiring a blood transfusion. Anticoagulation should be held for 5–7 days post biopsy if possible. The risks of nephrectomy and mortality are about 0.06–0.08%. When a percutaneous needle biopsy is technically not feasible and kidney tissue is deemed clinically essential, a closed biopsy via interventional radiologic techniques or open biopsy under general anesthesia can be performed.

Bökenkamp A. Proteinuria—take a closer look! *Pediatr Nephrol*. 2020;35:533. [PMID: 31925536]

Cavanaugh C et al. Urine sediment examination in the diagnosis and management of kidney disease: Core Curriculum 2019. *Am J Kidney Dis*. 2019;73:258. [PMID: 30249419]

Levey AS et al. Measured and estimated glomerular filtration rate: current status and future directions. *Nat Rev Nephrol*. 2020;16:51. [PMID: 31527790]

3.0-fold or greater increase in serum creatinine, an increase in serum creatinine to greater than or equal to 4 mg/dL, a decline in urinary output to less than 0.3 mL/kg/h for 24 hours or longer, anuria for 12 hours or longer, or initiation of renal replacement therapy. In the absence of functioning kidneys, serum creatinine concentration will typically increase by 1–1.5 mg/dL daily, although with certain conditions, such as rhabdomyolysis, serum creatinine can increase more rapidly. On average, 5% of hospital admissions and 30% of intensive care unit (ICU) admissions include a diagnosis of AKI, and AKI develops in 25% of hospitalized patients. The rates of AKI in the hospital setting have increased steadily since the 1980s and continue to rise.

► Clinical Findings

A. Symptoms and Signs

Although many patients will not experience any symptoms or exhibit any signs of AKI, the buildup of waste products can cause nonspecific symptoms and signs collectively termed **uremia**: nausea, vomiting, malaise, and altered sensorium. More commonly, patients experience symptoms and signs of the underlying disease causing their AKI (eg, lupus). Hypertension can occur, and fluid homeostasis is often impaired. Hypovolemia can cause states of low blood flow to the kidneys, sometimes termed **prerenal azotemia**, whereas hypervolemia can result from intrinsic or postrenal disease. Pericardial effusions can occur with uremia and may result in cardiac tamponade; a pericardial friction rub can be present, signaling pericarditis. With hyperkalemia, ventricular tachycardia and other tachyarrhythmias can occur. The lung examination may reveal rales in the presence of hypervolemia. AKI can cause non-specific diffuse abdominal pain and ileus. Platelet dysfunction with bleeding and clotting disorders can occur. The neurologic examination sometimes reveals encephalopathic changes with asterixis and confusion; uncommonly seizures may ensue.

B. Laboratory Findings

By definition, elevated serum creatinine (and often BUN) levels are present, though these elevations do not distinguish AKI from CKD. Metabolic acidosis (due to decreased clearance of organic and inorganic acids) is often noted. Hyperkalemia can occur from impaired renal potassium excretion or from shifting of potassium from cells into the blood as a result of metabolic acidosis. With hyperkalemia, ECG can reveal peaked T waves, PR prolongation, and QRS widening. A long QT segment can occur with hypocalcemia. Hyperphosphatemia occurs when phosphorus cannot be secreted by damaged tubules either with or without increased cell catabolism. Anemia can occur as a result of decreased erythropoietin production over weeks, and platelet dysfunction is typical.

► Classification & Etiology

AKI is commonly divided into three categories: prerenal causes (kidney hypoperfusion), intrinsic kidney disease,

ACUTE KIDNEY INJURY



ESSENTIALS OF DIAGNOSIS

- Rapid increase in serum creatinine.
- Oliguria may be present.
- Symptoms and signs depend on cause.

► General Considerations

AKI is defined as an absolute increase in serum creatinine by 0.3 mg/dL or more within 48 hours or a relative increase of at least 1.5 times baseline that is known or presumed to have occurred within 7 days. AKI is characterized as oliguric if urine production is less than roughly 400–500 mL/day. Clinically, AKI is characterized by an inability to maintain acid-base, fluid, and electrolyte balance and to excrete nitrogenous wastes. **Stage 1** is a 1.5- to 1.9-fold increase in serum creatinine or a decline in urinary output to less than 0.5 mL/kg/h over 6–12 hours; **stage 2** is a 2.0- to 2.9-fold increase in serum creatinine or decline in urinary output to less than 0.5 mL/kg/h over 12 hours or longer; **stage 3** is a

Table 22–3. Classification and differential diagnosis of acute kidney injury.

	Prerenal Azotemia	Postrenal Azotemia	Intrinsic Renal Disease		
			Acute Tubular Necrosis	Acute Glomerulonephritis	Acute Interstitial Nephritis
Etiology	Poor renal perfusion	Obstruction of the urinary tract	Ischemia, nephrotoxins	Immune complex-mediated, pauci-immune, anti-GBM related, monoclonal immunoglobulin-mediated, C3 glomerulopathy	Allergic reaction; drug reaction; infection; autoimmune disease
Serum BUN:Cr ratio	> 20:1	> 20:1	< 20:1	> 20:1	< 20:1
U_{Na} (mEq/L)	< 20	Variable	> 20	< 20	Variable
FE_{Na} (%)	< 1	Variable	> 1 (when oliguric)	< 1	Variable
Urine osmolality (mOsm/kg)	> 500	< 400	250–300	Variable	Variable
Urinary sediment	Benign or hyaline casts	Normal or red cells, white cells, or crystals	Granular (muddy brown) casts, renal tubular cell casts	Red cells, dysmorphic red cells, and red cell casts	White cells, white cell casts, with or without eosinophils

BUN:Cr, blood urea nitrogen:creatinine ratio; FE_{Na} , fractional excretion of sodium; GBM, glomerular basement membrane; U_{Na} , urinary concentration of sodium.

and postrenal causes (obstruction to urinary outflow). Identifying the cause is the first step toward treatment (Table 22–3).

A. Prerenal Causes

Prerenal causes are the most common etiology of AKI, accounting for 40–80% of cases. Prerenal azotemia is a physiologic response to renal hypoperfusion. If reversed quickly with restoration of renal blood flow (eg, fluid resuscitation), renal parenchymal damage often does not occur. If hypoperfusion persists, prerenal azotemia can lead to intrinsic kidney injury.

Decreased renal perfusion can occur in several ways, such as a decrease in intravascular volume, a change in vascular resistance, or low cardiac output. Causes of volume depletion include hemorrhage (eg, from trauma), GI losses, excessive diuresis, and extravascular fluid sequestration (eg, pancreatitis, burns, and peritonitis).

Changes in systemic vascular resistance can occur with sepsis, anaphylaxis, anesthesia, and afterload-reducing drugs. Blockade of the renin-angiotensin-aldosterone system, such as with angiotensin-converting enzyme (ACE) inhibitors, limits efferent renal arteriolar constriction out of proportion to afferent arteriolar constriction and thereby decreases GFR. Nonsteroidal anti-inflammatory drugs (NSAIDs) minimize afferent arteriolar vasodilation by inhibiting prostaglandin-mediated signals. NSAIDs may have particularly deleterious effects on renal perfusion in cirrhosis and heart failure when prostaglandins are recruited to increase renal blood flow. Epinephrine, norepinephrine, high-dose dopamine, anesthetic agents, and calcineurin inhibitors also can cause renal vasoconstriction. Renal artery stenosis causes increased resistance and decreased renal perfusion.

Low cardiac output is a state of low effective renal arterial blood flow. This occurs in states of heart failure (including cardiogenic shock), pulmonary embolism, and pericardial tamponade. Arrhythmias and valvular disorders can also reduce cardiac output. In the intensive care setting, positive pressure ventilation will decrease venous return and, in effect, cardiac output.

When GFR falls acutely, it is important to determine whether AKI is due to prerenal or intrinsic causes. The history, physical examination, and laboratory data may be helpful in distinguishing between these causes. In prerenal AKI, the BUN:creatinine ratio often exceeds 20:1 due to increased urea reabsorption. In oliguric patients, another useful index is the fractional excretion of sodium (FE_{Na}). With decreased GFR, the kidney reabsorbs salt and water avidly if there is no intrinsic tubular dysfunction. Thus, oliguric patients with prerenal AKI should have a low fractional excretion of sodium (less than 1%). Oliguric patients with intrinsic kidney dysfunction typically have a high FE_{Na} (greater than 1–2%), indicating loss of tubular cells' ability to reabsorb sodium. The FE_{Na} is calculated as follows: $FE_{Na} = \text{clearance of } Na^+/\text{GFR} = \text{clearance of } Na^+/C_{cr}$:

$$FE_{Na} = \frac{\text{Urine}_{Na} / \text{Serum}_{Na}}{\text{Urine}_{cr} / \text{Serum}_{cr}} \times 100\%$$

The equation was created and validated to assess the difference between *oliguric* ATN and prerenal AKI; its utility in nonoliguric patients is limited. Further, because diuretics act by increasing sodium excretion, a high FE_{Na} within 12–24 hours after diuretic administration cannot be meaningfully interpreted. In contrast, a low FE_{Na} despite receiving diuretics offers strong evidence of prerenal states in oliguric patients. Given the limitations of FE_{Na} ,

calculations, urine microscopy is a much more valuable tool for determining cause of AKI. Patients with prerenal azotemia typically have bland urine sediments, though some have hyaline casts. In contrast, patients with ATN often have renal tubular epithelial cells or muddy brown casts visible.

Treatment of prerenal AKI depends on the underlying cause, but achievement of euolemia, attention to serum electrolytes, and avoidance of nephrotoxic drugs are benchmarks of therapy. This involves careful assessment of volume status, cardiac function, diet, and drug usage.

B. Postrenal Causes

Postrenal causes of AKI are the least common, accounting for approximately 5–10% of cases, but are important to detect because of their reversibility. Postrenal azotemia occurs when urinary flow from both kidneys, or a single functioning kidney, is obstructed. Obstruction leads to elevated intraluminal pressure and resultant kidney parenchymal damage, with marked effects on renal blood flow and tubular function.

Postrenal causes of AKI include urethral obstruction, bladder dysfunction or obstruction, and obstruction of both ureters or renal pelvises. In men, benign prostatic hyperplasia is the most common cause. Patients taking anticholinergic drugs are at risk for urinary retention. Obstruction can also be caused by bladder, prostate, and cervical cancers; retroperitoneal fibrosis; and neurogenic bladder (eg, from diabetes mellitus). Less common causes include blood clots, bilateral ureteral stones, urethral stones or strictures, and bilateral papillary necrosis.

Patients may be anuric or polyuric and may experience lower abdominal or back pain. Polyuria can occur in the setting of partial obstruction with resultant tubular dysfunction and an inability to appropriately reabsorb salt and water loads. Obstruction can be constant or intermittent and partial or complete. On examination, the patient may have an enlarged prostate, distended bladder, or mass detected on abdominal examination.

Laboratory examination may initially reveal high urine osmolality, low urine sodium, high BUN:creatinine ratio, and low Fe_{Na} (as tubular function may not be compromised initially). These indices are similar to a prerenal state because extensive intrinsic renal damage has not yet occurred. After several days, however, the urine sodium increases as the kidneys fail and are unable to concentrate the urine; this inability to concentrate the urine is called isosthenuria. The urine sediment is generally bland, though hematuria may be seen if the obstruction is due to stones, blood clots, or papillary necrosis.

Patients with AKI due to suspected postrenal causes should undergo bladder catheterization and ultrasonography to assess for hydronephrosis, or large bladder volume. After reversal of the underlying process, some patients experience significant urinary output (called postobstructive diuresis). In such settings, care should be taken to avoid volume depletion or electrolyte derangements. Prompt treatment of obstruction within days by catheters, stents, or other surgical procedures can result in partial or complete reversal of AKI.

C. Intrinsic Acute Kidney Injury

Intrinsic renal disorders account for up to 50% of all cases of AKI. Intrinsic dysfunction is considered after prerenal and postrenal causes have been excluded. The potential sites of injury are the tubules, interstitium, vasculature, and glomeruli. Intrinsic AKI is discussed in greater detail in the following sections.

► When to Refer

- If a patient has signs of AKI that have not reversed over 1–2 weeks, or if the degree of AKI is concerning (eg, doubling of creatinine) and without an immediately reversible cause such as obstruction.
- If a patient has signs of urinary tract obstruction, the patient should be referred to a urologist.

► When to Admit

The patient should be admitted if there is sudden loss of kidney function resulting in abnormalities that cannot be handled expeditiously in an outpatient setting (eg, hyperkalemia, volume overload, uremia) or an acute intervention is needed, such as emergent urologic procedures or dialysis.

Ostermann et al. Recommendations on acute kidney injury biomarkers from the Acute Disease Quality Initiative Consensus Conference: a consensus statement. *JAMA Netw Open*. 2020;3:e2019209. [PMID: 33021646]

Ronco C et al. Acute kidney injury. *Lancet*. 2019;394:1949. [PMID: 31773789]

Srisawat N et al. The role of biomarkers in acute kidney injury. *Crit Care Clin*. 2020;36:125. [PMID: 31733675]

ACUTE TUBULAR NECROSIS



ESSENTIALS OF DIAGNOSIS

- AKI.
- Ischemic or toxic insult or underlying sepsis.
- Urine sediment with granular (muddy brown) casts and renal tubular epithelial cells is pathognomonic but not essential.

► General Considerations

AKI due to tubular damage is termed **acute tubular necrosis (ATN)** and accounts for approximately 85% of intrinsic AKI. The two major causes of ATN are ischemia and nephrotoxin exposure. Ischemic ATN is characterized not only by inadequate GFR but also by renal blood flow that is inadequate to maintain parenchymal cellular perfusion. Renal tubular damage can be caused by low effective arterial blood flow to the kidneys in the setting of prolonged hypotension or hypoxemia, such as volume depletion or shock. Underlying sepsis is an independent risk factor for ATN, even in the absence of hemodynamic compromise.

Prolonged periods of renal hypoperfusion can occur with major surgical procedures, which are exacerbated by vaso-dilating anesthetic agents.

A. Exogenous Nephrotoxins

Exogenous nephrotoxins more commonly cause damage than endogenous nephrotoxins.

Aminoglycosides cause some degree of ATN in up to 25% of hospitalized patients receiving therapeutic levels of the drugs. Nonoliguric kidney injury typically occurs after 5–10 days of exposure. Predisposing factors include underlying kidney damage, volume depletion, and advanced age. Monitoring drug levels is important, and troughs are particularly helpful in predicting renal toxicity.

Amphotericin B is typically nephrotoxic after a dose of 2–3 g. This causes a type 1 (distal) renal tubular acidosis with severe vasoconstriction and tubular damage, which can lead to hypokalemia and nephrogenic diabetes insipidus. **Vancomycin**, intravenous **acyclovir**, and several **cephalosporins** have also been known to cause or be associated with ATN.

Radiographic contrast media may be directly nephrotoxic. Contrast nephropathy is the third leading cause of incident AKI in hospitalized patients and is thought to result from the synergistic combination of direct renal tubular epithelial cell toxicity and renal medullary ischemia. The combination of preexisting diabetes mellitus and CKD is associated with the greatest risk (15–50%) of contrast nephropathy. Other risk factors include advanced age; volume depletion; heart failure; plasma cell myeloma; repeated doses of contrast; and recent exposure to other nephrotoxic agents, including NSAIDs and ACE inhibitors. Lower volumes of contrast with low osmolality are recommended in high-risk patients. Toxicity usually occurs within 24–48 hours after the radiocontrast study. Nonionic contrast media may be less toxic, but this has not been well proven. Prevention of contrast nephropathy is the goal when using these agents. The mainstay of prophylaxis is 1–3 mL/kg or 500–1000 mL of intravenous 0.9% (normal) saline over 6 hours both before and after the contrast administration—cautiously in patients with preexisting cardiac dysfunction; oral intake of fluids is an acceptable alternative for outpatient studies. Isotonic intravenous volume repletion is superior to hypotonic intravenous solutions, and both are superior to oral solutions in small studies. Other nephrotoxic agents should be avoided during the day before and after dye administration. Alternative prophylactic strategies involving *N*-acetylcysteine, sodium bicarbonate, mannitol, and furosemide do not show benefit over 0.9% (normal) saline administration. In fact, furosemide may lead to increased rates of kidney dysfunction in this setting.

Calcineurin inhibitor toxicity (from tacrolimus or cyclosporine) is usually dose dependent. It causes distal tubular dysfunction (a type 4 renal tubular acidosis) and severe vasoconstriction. Regular blood level monitoring is important to prevent both acute and chronic nephrotoxicity. Kidney function usually improves after reducing the dose or stopping the drug.

Other exogenous nephrotoxins include antineoplastics, such as cisplatin and organic solvents, and heavy metals

such as mercury, cadmium, and arsenic. Herbal medicines are also increasingly recognized as potentially nephrotoxic.

B. Endogenous Nephrotoxins

Endogenous nephrotoxins include pigment-containing products (myoglobin and hemoglobin), uric acid, and paraproteins.

Pigment-containing products can cause direct tubular toxicity, resulting in ATN. The most common type of pigment nephropathy is rhabdomyolysis, caused by release of myoglobin from muscle. Massive intravascular hemolysis is seen in transfusion reactions and in certain hemolytic anemias, and causes release of hemoglobin. Reversal of the underlying disorder and hydration are the mainstays of treatment.

Hyperuricemia can occur in the setting of rapid cell turnover and lysis. Chemotherapy for germ cell and hematologic malignancies (leukemia and lymphoma) is the primary cause; spontaneous tumor lysis syndrome can also occur, though is less common. AKI occurs with intratubular precipitation of uric acid crystals; serum uric acid levels often exceed 15–20 mg/dL and urine uric acid levels are typically greater than 600 mg/24 h. A urine uric acid to urine creatinine ratio greater than 1.0 identifies individuals at risk for AKI. Allopurinol or rasburicase can be used prophylactically, and rasburicase with or without dialysis is often used for treatment in established cases.

Paraproteins seen in conjunction with plasma cell myeloma can cause direct tubular toxicity and tubular obstruction. Other renal complications from plasma cell myeloma include hypercalcemia and renal tubular dysfunction, including proximal renal tubular acidosis (see Plasma Cell Myeloma below).

► Clinical Findings

A. Symptoms and Signs

See Acute Kidney Injury.

B. Laboratory Findings

Hyperkalemia and hyperphosphatemia are commonly present. The BUN:creatinine ratio is usually less than 20:1 because tubular function is not intact, as described in the general section on AKI (Table 22–3). Urinary output can be oliguric or nonoliguric, with oliguria portending a worse prognosis. Urine sodium concentration and Fe_{Na} are typically elevated, indicative of tubular dysfunction. Urine microscopy may show evidence of acute tubular damage; the presence of two or more granular casts or renal tubular epithelial cells is strongly predictive of ATN but has a low negative predictive value (see Table 22–1). Although not usually performed in cases of ATN, kidney biopsy is sometimes helpful in cases of diagnostic uncertainty.

► Treatment

Treatment of ATN is aimed at hastening recovery and avoiding complications. Preventive measures should be taken to avoid volume overload and hyperkalemia. A prospective randomized controlled trial did not show a benefit

of loop diuretics on either recovery from AKI or death. Widespread use of diuretics in critically ill patients with AKI should be used only when otherwise clinically indicated (eg, in states of volume overload), although unresponsiveness to high-dose diuretics has been shown to predict future need for acute dialysis in this population (termed “furosemide stress test”). A 2012 randomized controlled trial did not show a benefit on mortality from plasma ultrafiltration compared to intravenous diuretics in patients with decompensated heart failure. Thus, ultrafiltration should generally be reserved for ICU patients with AKI in need of volume removal who are nonresponsive to diuretics, with the recognition that this has not ultimately improved survival in this patient population. Nutritional support should meet daily needs while preventing excessive catabolism. Dietary protein restriction of 0.6 g/kg/day helps prevent metabolic acidosis. Hypocalcemia and hyperphosphatemia can be improved with dietary modification and phosphate-binding agents taken with meals; examples include aluminum hydroxide (500 mg orally) over the short term, and calcium carbonate (500–1500 mg orally), calcium acetate (667 mg, two or three tablets), sevelamer carbonate (800–1600 mg orally), and lanthanum carbonate (1000 mg orally) over longer periods. Hypocalcemia should not be treated in patients with rhabdomyolysis unless they are symptomatic. Hypermagnesemia can occur because of reduced magnesium excretion by the renal tubules, so magnesium-containing antacids and laxatives should be avoided in these patients. Dosages of all medications must be adjusted for drugs eliminated by the kidney.

Indications for dialysis in AKI from ATN or other intrinsic disorders include life-threatening electrolyte disturbances (such as hyperkalemia), volume overload unresponsive to diuresis, refractory acidosis, and uremic complications (eg, encephalopathy, pericarditis, and seizures). In gravely ill patients, less severe but worsening abnormalities may also be indications for dialytic support. Unfortunately, there is no evidence that more intensive or earlier initiation of renal replacement therapy for patients with AKI confers any survival benefit.

Course & Prognosis

The clinical course of ATN is often divided into three phases: initial injury, maintenance, and recovery. The maintenance phase is expressed as either oliguric (urinary output less than 500 mL/day) or nonoliguric. Nonoliguric ATN is associated with better outcomes than oliguric ATN; conversion from oliguric to nonoliguric states with the use of diuretics does not alter prognosis. While dopamine has sometimes been used for this purpose, numerous studies have shown that its use in this setting is not beneficial. Average duration of the maintenance phase is 1–3 weeks, but some cases may last several months. Cellular repair and removal of tubular debris occur during this period. The recovery phase can be heralded by diuresis, due to inability of recovering renal tubules to reabsorb salt and water appropriately, and a solute diuresis from elevated BUN levels. As GFR begins to rise, BUN and serum creatinine fall.

The mortality rate associated with AKI is 20–50% in hospitalized settings, and up to 70% for those in the ICU

requiring dialysis with additional comorbid illnesses. Increased mortality is associated with advanced age, severe underlying disease, and multisystem organ failure. Leading causes of death are infections, fluid and electrolyte disturbances, and worsening of underlying disease.

When to Refer

- When uncertainty exists as to the cause of or treatment for AKI.
- For fluid, electrolyte, and acid-base abnormalities that are recalcitrant to interventions.
- Nephrology referral improves outcomes in AKI.

When to Admit

A patient with symptoms or signs of AKI that require immediate intervention, such as administration of intravenous fluids or dialytic therapy, or that require a team approach that cannot be coordinated as an outpatient.

Griffin BR et al. Critical care nephrology: Core Curriculum 2020. Am J Kidney Dis. 2020;75:435. [PMID: 31982214]

Peerapornratana S et al. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int. 2019;96:1083. [PMID: 31443997]

STARTR-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group, Bagshaw SM et al. Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med. 2020;383:240. [PMID: 32668114]

Rhabdomyolysis



ESSENTIALS OF DIAGNOSIS

- Associated with crush injuries to muscle, immobility, drug toxicities, and hypothermia.
- Characterized by serum elevations in muscle enzymes, including creatine kinase, and marked electrolyte abnormalities.
- Release of myoglobin leads to direct renal toxicity.

General Considerations

Rhabdomyolysis is a syndrome of acute skeletal muscle necrosis, leading to myoglobinuria and markedly elevated creatine kinase levels. Acute tubular necrosis is a common complication of rhabdomyolysis and is due to the filtration of excessive quantities of myoglobin, which can be exacerbated by volume depletion. Distal tubular obstruction from pigmented casts and intrarenal vasoconstriction can also occur. Rhabdomyolysis can result from crush injuries, prolonged immobility, seizures, substance abuse (eg, cocaine), and medications (especially statins). The presence of kidney or liver dysfunction, diabetes mellitus, and hypothyroidism increase the risk of

rhabdomyolysis in patients taking statins. Concurrent use of drugs that inhibit cytochrome P450 (including protease inhibitors, erythromycin or clarithromycin, itraconazole, diltiazem, and verapamil) with statins (except pravastatin or rosuvastatin) as well as concurrent use of niacin and fibrate-containing therapy can increase the risk of development of rhabdomyolysis.

► Clinical Findings

A. Symptoms and Signs

Patients with rhabdomyolysis may have myalgias or weakness or both, though it is not uncommon for them to be asymptomatic. Urine may appear dark.

B. Laboratory Findings

Rhabdomyolysis of clinical importance commonly occurs with a serum creatine kinase greater than 20,000–50,000 international units/L; one study showed that 58% of patients with AKI from rhabdomyolysis had creatine kinase levels greater than 16,000 international units/L, while only 11% of patients without kidney injury had creatine kinase values greater than 16,000 international units/L. Often, there are elevated serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LD) (due to release of these enzymes from skeletal muscle). The massive acute elevations of muscle enzymes peak quickly and usually resolve within days once the inciting injury has been removed.

The classic laboratory finding in rhabdomyolysis is a urine dipstick test that is positive for “blood” but without red blood cells on microscopy. This false-positive result is due to detection of myoglobin. Additionally, clinically meaningful rhabdomyolysis causes injured muscle cells to release intracellular components, leading to electrolyte derangements (including hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia).

► Treatment

The mainstay of treatment is aggressive volume repletion with 0.9% normal saline (ie, more than 4 L/day) and removal of offending medications if thought to have caused the disorder. Adjunctive treatments with mannitol and alkalinization of the urine have not been proven to change outcomes in human trials. As patients recover, calcium can move back from tissues to plasma, so early exogenous calcium administration for hypocalcemia is not recommended unless the patient is symptomatic or the level becomes exceedingly low in an unconscious patient; calcium repletion can cause precipitation of calcium phosphate given the frequently concurrent hyperphosphatemia.

Myopathic complications of statins usually resolve within several weeks of discontinuing the drug.

► When to Refer

Clinically meaningful rhabdomyolysis requires immediate attention and inpatient management, so affected patients should not be referred to outpatient nephrology clinics unless to follow up after a hospital admission.

► When to Admit

Patients whose serum creatine kinase levels are greater than 15,000–20,000 international units/L or patients with AKI or electrolyte derangements should be admitted for fluid repletion and serial monitoring of creatine kinase and electrolytes.

Long B et al. An evidence-based narrative review of the emergency department evaluation and management of rhabdomyolysis. *Am J Emerg Med*. 2019;37:518. [PMID: 30630682]

INTERSTITIAL NEPHRITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Fever.
- ▶ Transient maculopapular rash.
- ▶ Acute or chronic in nature.
- ▶ Pyuria, white blood cell casts, and hematuria.

► General Considerations

Acute interstitial nephritis accounts for 10–15% of cases of intrinsic renal failure. An interstitial inflammatory response with edema and possible tubular cell damage is the typical pathologic finding.

Although drugs account for over 70% of cases, acute interstitial nephritis also occurs in infectious diseases, autoimmune disorders, or as idiopathic conditions. The most common drugs implicated are penicillins and cephalosporins, immune checkpoint inhibitors, sulfonamides and sulfonamide-containing diuretics, NSAIDs, proton pump inhibitors, rifampin, and allopurinol. Infectious causes include streptococcal infections, leptospirosis, cytomegalovirus, histoplasmosis, and Rocky Mountain spotted fever. SLE, Sjögren syndrome, sarcoidosis, and cryoglobulinemia can also cause interstitial nephritis, though they are more classically associated with glomerulonephritis.

► Clinical Findings

Clinical features include fever (more than 80% of cases), rash (25–50%), arthralgias, and peripheral blood eosinophilia (80%). The classic triad of fever, rash, and arthralgias is present in only 10–15% of cases. The urine often contains white cells (95%), red cells, and white cell casts. Proteinuria is often present, particularly in NSAID-induced interstitial nephritis, but is usually modest (less than 2 g/24 h). Eosinophiluria is neither very sensitive nor specific for interstitial nephritis; evaluation for eosinophiluria is not advised. Although the clinical history and laboratory data often give clues to the diagnosis, kidney biopsy is sometimes needed.

► Treatment & Prognosis

Acute interstitial nephritis often carries a good prognosis, with recovery occurring over weeks to months. Urgent

dialytic therapy may be necessary in up to one-third of all referred patients before resolution, but patients rarely progress to ESKD. Those with prolonged oliguria and advanced age have a worse prognosis. Treatment consists of supportive measures and removal of the inciting agent. If kidney injury persists, a short course of corticosteroids can be considered, although the data to support their use are not substantial, and their efficacy may depend on the elapsed time between onset of AKI and their initiation. Short-term, high-dose methylprednisolone (0.5–1 g/day intravenously for 1–4 days) or prednisone (60 mg/day orally for 1–2 weeks) followed by a prednisone taper can be used in more severe cases of drug-induced interstitial nephritis.

- Moledina DG et al. Treatment of drug-induced acute tubulointerstitial nephritis: the search for better evidence. *Clin J Am Soc Nephrol*. 2018;13:1785. [PMID: 30397028]
 Shingarev R et al. Kidney complications of immune checkpoint inhibitors: a review. *Am J Kidney Dis*. 2019;74:529. [PMID: 31303350]

GLOMERULONEPHRITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Hematuria, subnephrotic proteinuria.
- ▶ Red cell casts pathognomonic but not required for diagnosis.
- ▶ Dependent edema and hypertension.
- ▶ AKI.

► General Considerations

Acute glomerulonephritis is a relatively uncommon cause of AKI, accounting for about 5% of cases. Pathologically, inflammatory glomerular lesions are seen. These include mesangioliferative, focal and diffuse endocapillary proliferative, and crescentic lesions. The larger the percentage of glomeruli involved and the more severe the lesion, the more likely it is that the patient will have a poor clinical outcome.

Glomerulonephritides are classified into five pathophysiologic processes, which can be characterized by serologic analysis. Markers include anti-GBM antibodies, antineutrophil cytoplasmic antibodies (ANCA), and other immune markers of disease.

Immune complex deposition occurs when there is moderate overproduction of antigen compared to antibody production. Complexes formed with marked antigen excess tend to remain in the circulation. Antibody excess with large antigen–antibody aggregates usually results in phagocytosis and clearance of the precipitates by the mononuclear phagocytic system in the liver and spleen. Causes include IgA nephropathy, infection-related glomerulonephritis, lupus nephritis, and cryoglobulinemic glomerulonephritis (often associated with hepatitis C virus [HCV]).

Anti-GBM-associated acute glomerulonephritis is either confined to the kidney or associated with pulmonary hemorrhage. The latter is termed “Goodpasture syndrome.”

Injury is related to autoantibodies against type IV collagen in the GBM.

Pauci-immune acute glomerulonephritis is a form of small-vessel vasculitis associated with ANCA, causing kidney diseases without direct immune complex deposition or antibody binding. Tissue injury is believed to be due to cell-mediated immune processes. An example is granulomatosis with polyangiitis, a systemic necrotizing vasculitis of small arteries and veins associated with intravascular and extravascular granuloma formation. In addition to glomerulonephritis, these patients can have upper airway, pulmonary, and skin manifestations. Cytoplasmic ANCA (c-ANCA) is the common staining pattern. Microscopic polyangiitis is another pauci-immune vasculitis causing acute glomerulonephritis, which is more commonly associated with perinuclear staining (p-ANCA). ANCA-associated and anti-GBM-associated acute glomerulonephritides can evolve to crescentic glomerulonephritis and often have poor outcomes unless treatment is started early.

Monoclonal immunoglobulin-mediated glomerulonephritis is characterized by the deposition of a monoclonal immunoglobulin in glomeruli or tubular basement membrane or both. It is detected on immunofluorescent or immunohistochemical staining of kidney biopsies as monotypic immunoglobulin deposits. Serum protein electrophoresis and serum free light chains are useful diagnostic tests to perform when monoclonal immunoglobulin-mediated glomerulonephritis is suspected or confirmed. While many cases will occur in the setting of a monoclonal gammopathy, this is not always the case.

C3 glomerulopathy results from predominant C3 deposition in the glomeruli with or without minimal deposition of immunoglobulins. It is also identified by immunofluorescence or immunohistochemistry. The pathogenesis of C3 glomerulonephropathy stems from abnormalities in regulation of the alternative pathway of complement. While checking serum C3 levels may be helpful, normal levels do not rule out C3 glomerulopathy.

Other vascular causes of glomerulonephritis include hypertensive emergencies and the thrombotic microangiopathies such as hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (see Chapter 14).

► Clinical Findings

A. Symptoms and Signs

Patients with acute glomerulonephritis are often hypertensive and edematous with an abnormal urinary sediment. The edema is found first in body parts with low tissue tension, such as the periorbital and scrotal regions.

B. Laboratory Findings

Serum creatinine can rise over days to months, depending on the rapidity of the underlying process. The BUN:creatinine ratio is not a reliable marker of kidney function and is more reflective of the patient's underlying volume status. Dipstick and microscopic evaluation reveal evidence of hematuria and typically subnephrotic proteinuria; there may be cellular elements such as dysmorphic red cells, red cell casts, and white cells. Red cell casts are

specific for glomerulonephritis, and a detailed search on urine microscopy is warranted.

Additional tests include serum complement levels (C3, C4) that may be low in immune complex glomerulonephritis (except for IgA nephropathy) or C3 glomerulopathy and normal in pauci-immune, anti-GBM-related, and monoclonal immunoglobulin-mediated glomerulonephritides. Other tests include ASO titers, anti-GBM antibody levels, ANCA, antinuclear antibody titers, cryoglobulins, hepatitis serologies, serum protein electrophoresis and serum free light chains, blood cultures, and renal ultrasound. With few exceptions, a kidney biopsy is ultimately necessary to confirm the diagnosis, irrespective of laboratory data.

Treatment

Depending on the nature and severity of disease, treatment might include high-dose corticosteroids, rituximab, and cytotoxic agents (such as cyclophosphamide). Plasma exchange can be used in Goodpasture syndrome as a temporizing measure until chemotherapy can take effect. Treatment and prognosis for specific diseases are discussed more fully below.

Geetha D et al. ANCA-associated vasculitis: Core Curriculum 2020. Am J Kidney Dis. 2020;75:124. [PMID: 31358311]
Sethi S et al. Standardized classification and reporting of glomerulonephritis. Nephrol Dial Transplant. 2019;34:193. [PMID: 30124958]

COVID-19 & THE KIDNEY



ESSENTIALS OF DIAGNOSIS

- ▶ Broad array of clinical presentation and kidney pathology.

Clinical Findings & Treatment

Nearly half of patients hospitalized with COVID-19 present with or develop AKI, which is associated with poorer prognosis. Many causes of AKI are described in patients with COVID-19, but the most common is ATN related to a high inflammatory state (termed “cytokine storm”).

Urinalysis may reveal hematuria, reflecting endothelial injury and fibrin thrombi that are commonly observed on biopsy. Another emerging entity is COVID-19-associated collapsing glomerulopathy, which is a type of focal segmental glomerulosclerosis (see section on “Nephrotic Spectrum Glomerular Diseases” below). Patients with collapsing glomerulopathy present with nephrotic syndrome and are typically of African ancestry, highlighting a suspected genetic predisposition. Treatment of COVID-19-related AKI is largely supportive; the role of corticosteroids in COVID-19-associated collapsing glomerulopathy is under investigation.

Chan L et al; Mount Sinai COVID Informatics Center (MSCIC). AKI in hospitalized patients with COVID-19. J Am Soc Nephrol. 2021;32:151. [PMID: 32883700]

Nasr SH et al. COVID-19-associated collapsing glomerulopathy: an emerging entity. Kidney Int Rep. 2020;5:759. [PMID: 32368701]
Ronco C et al. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8:738. [PMID: 32416769]
Shetty AA et al. COVID-19-associated glomerular disease. J Am Soc Nephrol. 2021;32:33. [PMID: 33214201]

CARDIORENAL SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ **Cardiac dysfunction:** acute or chronic heart failure, ischemic injury, or arrhythmias.
- ▶ **Kidney disease:** acute or chronic, depending on the type of cardiorenal syndrome.

General Considerations

Cardiorenal syndrome is a pathophysiologic disorder of the heart and kidneys wherein the acute or chronic deterioration of one organ results in the acute or chronic deterioration of the other. This syndrome is classified into five types as a matter of convention. Achieving euvolemia is the overarching therapeutic goal regardless of type (see Heart Failure section in Chapter 10).

Type 1 consists of AKI stemming from acute cardiac disease. Type 2 is CKD due to chronic cardiac disease. Type 3 is acute cardiac disease as a result of AKI. Type 4 is chronic cardiac decompensation from CKD. Type 5 consists of heart and kidney dysfunction due to other acute or chronic systemic disorders (such as sepsis). Although novel agents are being examined for future therapies, the mainstay of treatment is to address the primary underlying heart or kidney dysfunction.

Kumar U et al. Cardiorenal syndrome: pathophysiology. Cardiol Clin. 2019;37:251. [PMID: 31279419]

Raina R et al. An update on the pathophysiology and treatment of cardiorenal syndrome. Cardiol Res. 2020;11:76. [PMID: 32256914]

CHRONIC KIDNEY DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Decline in the GFR over months to years.
- ▶ Persistent proteinuria or abnormal renal morphology may be present.
- ▶ Hypertension in most cases.
- ▶ Symptoms and signs of uremia when nearing end-stage disease.
- ▶ Bilateral small or echogenic kidneys on ultrasound in advanced disease.

Table 22–4. Stages of chronic kidney disease: a clinical action plan.^{1,2}

Stage ³	Description	GFR (mL/min/1.73 m ²)	Action
1	Kidney damage with normal or ↑↑ GFR	≥ 90	Diagnosis and treatment of underlying etiology if possible. Treatment of comorbid conditions. Estimate progression, work to slow progression. Cardiovascular disease risk reduction.
2	Kidney damage with mildly ↓ GFR	60–89	
3a	Mildly-moderately ↓ GFR	45–59	As above, and evaluating and treating complications.
3b	Moderately-severely ↓ GFR	30–44	
4	Severely ↓ GFR	15–29	Preparation for end-stage kidney disease.
5	End-stage kidney disease	< 15 (or dialysis)	Dialysis, transplant, or palliative care.

¹Based on National Kidney Foundation, KDOQI, and KDIGO Chronic Kidney Disease Guidelines.

²Chronic kidney disease is defined as either kidney damage or GFR < 60 mL/min/1.73 m² for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

³At all stages, persistent albuminuria confers added risk for chronic kidney disease progression and cardiovascular disease in the following gradations: < 30 mg/day = lowest added risk, 30–300 mg/day = mildly increased risk, > 300–1000 mg/day = moderately increased risk, > 1000 mg/day = severely increased risk.

GFR, glomerular filtration rate.

Modified and reproduced, with permission, from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2013 Jan;3(1) (Suppl):1–150.

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► General Considerations

CKD affects at least 10% of Americans. Many are unaware of the condition because they remain asymptomatic until the disease is near end stage. The National Kidney Foundation's staging system helps clinicians formulate practice plans (Table 22–4). Over 70% of cases of late-stage CKD (stage 5 CKD and ESKD) in the United States are due to diabetes mellitus or hypertension/vascular disease. Glomerulonephritis, cystic diseases, chronic tubulointerstitial diseases, and other urologic diseases account for the remainder (Table 22–5). Genetic polymorphisms of the *APOL-1* gene have been shown to be associated with an increased risk of the development of CKD in persons of African ancestry.

CKD usually leads to a progressive decline in kidney function even if the inciting cause can be identified and treated or removed. Destruction of nephrons leads to compensatory hypertrophy and supranormal GFR of the remaining nephrons in order to maintain overall homeostasis. As a result, the serum creatinine may remain relatively normal even in the face of significant loss of renal mass and is, therefore, an insensitive marker for early renal damage and scarring. In addition, compensatory hyperfiltration leads to overwork injury in the remaining nephrons, which in turn causes progressive glomerular sclerosis and interstitial fibrosis. Angiotensin receptor blockers (ARBs) and ACE inhibitors can help reduce hyperfiltration injury and may slow the progression of proteinuric CKD.

While CKD is an independent risk factor for cardiovascular disease (CVD), proteinuric CKD confers the highest risk. Most patients with stage 3 CKD die of underlying CVD prior to progression to ESKD.

► Clinical Findings

A. Symptoms and Signs

Stages 1–4 CKD are asymptomatic. Symptoms develop slowly with the progressive decline in GFR, are nonspecific, and do not manifest until kidney disease is far advanced (GFR less than 5–10 mL/min/1.73 m²). At this point, the accumulation of metabolic waste products, or uremic toxins, results in the **uremic syndrome**. General symptoms of uremia may include fatigue, anorexia, nausea, and a metallic taste in the mouth. Neurologic symptoms such as memory impairment, insomnia, restless legs, and twitching may be due to uremia. Generalized pruritus (without rash) may occur, as may decreased libido and menstrual irregularities. Pericarditis, a rare complication of CKD, may present with pleuritic chest pain. Medications that are cleared by the kidneys will accumulate as kidney function worsens and toxicity may ensue; an important example is insulin and an increasing risk of significant hypoglycemia if doses are not appropriately reduced.

The most common physical finding in CKD is hypertension; this is due in part to impaired sodium excretion. It is often present in early stages of CKD and tends to worsen with CKD progression. In later stages of CKD, sodium retention may lead to clinically apparent volume overload. Uremic signs are seen with a profound decrease in GFR (less than 5–10 mL/min/1.73 m²) and may include a generally sallow and ill appearance, halitosis (uremic fetor), and the uremic encephalopathic signs of decreased mental status, asterixis, myoclonus, and possibly seizures.

Symptoms and signs of uremia warrant immediate hospital admission and nephrology consultation for initiation of dialysis. The uremic syndrome is ameliorated with dialytic therapy.

Table 22–5. Causes of chronic kidney disease.

Glomerular Diseases
Primary glomerular diseases
Focal segmental glomerulosclerosis
Membranoproliferative glomerulonephritis
IgA nephropathy
Membranous nephropathy
Alport syndrome (hereditary nephritis)
Secondary glomerular diseases
Diabetic nephropathy
Renal amyloidosis
Postinfectious glomerulonephritis
HIV-associated nephropathy
Collagen-vascular diseases (eg, SLE)
HCV-associated membranoproliferative glomerulonephritis
Tubulointerstitial Nephritis
Drug hypersensitivity
Heavy metals
Analgesic nephropathy
Reflux/chronic pyelonephritis
Sickle cell nephropathy
Idiopathic
Cystic Diseases
Polycystic kidney disease
Medullary cystic disease
Obstructive Nephropathies
Prostatic disease
Nephrolithiasis
Retroperitoneal fibrosis/tumor
Congenital/reflux
Vascular Diseases
Hypertensive nephrosclerosis
Renal artery stenosis

HCV, hepatitis C virus; SLE, systemic lupus erythematosus.

In any patient with kidney disease, it is important to identify and correct all possibly reversible insults or exacerbating factors (Table 22–6). Urinary obstruction, hypovolemia, hypotension, nephrotoxins (such as NSAIDs, aminoglycosides, or proton pump inhibitors), severe or emergent hypertension, and heart failure exacerbation should be excluded.

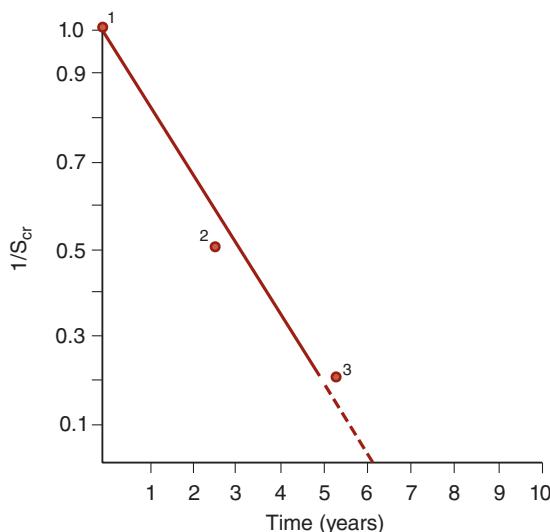
B. Laboratory Findings

CKD is usually defined by an abnormal GFR persisting for at least 3 months. Persistent proteinuria or abnormalities on renal imaging (eg, polycystic kidneys or a single kidney) are also diagnostic of CKD, even when eGFR is normal. If multiple measurements of eGFR over time are available, the rate of progression should be assessed (Figure 22–1). If the slope of the line acutely declines, potentially reversible renal insults should be excluded. Anemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and metabolic acidosis are common complications of advanced CKD. The urinary sediment may show broad waxy casts as a result of

Table 22–6. Reversible causes of kidney injury.

Reversible Factors	Diagnostic Clues
Obstruction	Post-void residual, bladder catheterization, renal ultrasound
Extracellular fluid volume depletion or significant hypotension relative to baseline	Blood pressure and pulse, including orthostatic pulse
Hypercalcemia	Serum electrolytes, calcium, phosphate
Nephrotoxic agents	Drug history
Severe/urgent hypertension	Blood pressure, chest radiograph
Heart failure exacerbation	Physical examination, chest radiograph

dilated, hypertrophic nephrons. If proteinuria is present, it should be quantified as described above. This can help narrow the differential diagnosis of the etiology of the CKD (Table 22–5); for example, glomerular diseases tend to present with protein excretion of more than 1 g/day. Additionally, higher urinary protein excretion is associated with more rapid progression of CKD and increased risk of cardiovascular mortality.

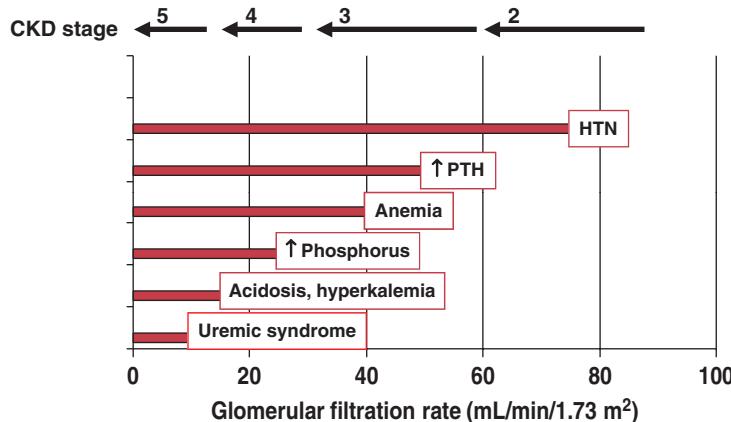


¹ Value of serum creatinine level = 1.0 mg/dL

² Value of serum creatinine level = 2.0 mg/dL

³ Value of serum creatinine level = 5.0 mg/dL

▲ Figure 22–1. Decline in kidney function (expressed as the reciprocal of serum creatinine as shown here, or as estimated glomerular filtration rate [eGFR]) plotted against time to ESKD. The solid line indicates the linear decline in kidney function over time. The dotted line indicates the approximate time to ESKD.



▲ Figure 22-2. Complications of chronic kidney disease (CKD) by stage and glomerular filtration rate (GFR). Complications arising from CKD tend to occur at the stages depicted, although there is considerable variability noted in clinical practice. HTN, hypertension; PTH, parathyroid hormone. (Adapted, with permission, from William Bennett, MD.)

C. Imaging

The finding of small, echogenic kidneys bilaterally (less than 9–10 cm) by ultrasonography suggests the chronic scarring of advanced CKD. Large kidneys can be seen with adult polycystic kidney disease, diabetic nephropathy, HIV-associated nephropathy, plasma cell myeloma, amyloidosis, and obstructive uropathy.

► Complications

The complications of CKD tend to occur at relatively predictable stages of disease as noted in Figure 22-2.

A. Cardiovascular Complications

Patients with CKD experience greater morbidity and mortality from CVD in comparison to the general population. Roughly 80% of patients with CKD die before reaching ESKD, primarily of CVD. Of those undergoing dialysis, 45% will die of a cardiovascular cause. The mechanisms for enhanced cardiovascular mortality in CKD are complex and include abnormal phosphorus and calcium homeostasis, increased burden of oxidative stress, increased vascular reactivity, left ventricular hypertrophy, and coexistent conditions such as hypertension and diabetes mellitus.

1. Hypertension—Hypertension is the most common complication of CKD; it tends to be progressive and salt-sensitive. Hyperreninemic states and exogenous erythropoietin administration can exacerbate hypertension.

As with other patient populations, control of hypertension should focus on both pharmacologic and nonpharmacologic therapy (eg, diet, exercise, weight loss, treatment of obstructive sleep apnea). CKD results in disturbed sodium homeostasis such that the ability of the kidney to adjust to variations in sodium and water intake becomes limited as GFR declines. A low salt diet (2 g/day) is often essential to control blood pressure and help avoid overt volume overload. Diuretics are nearly always needed to help control hypertension (see Table 11-8); thiazides work well in early CKD, but loop diuretics may be more effective in those

with a GFR less than 30 mL/min/1.73 m². However, volume contraction as a result of very low sodium intake (especially with intercurrent illness) or over-diuresis in the presence of impaired sodium homeostasis can result in AKI. Initial drug therapy for proteinuric patients should include ACE inhibitors or ARBs (see Table 11-6); however, there is no evidence of superiority of these drugs over other drug classes for nonproteinuric CKD. When an ACE inhibitor or an ARB is initiated or uptitrated, patients must have serum creatinine and potassium checked within 7–14 days. A rise in serum creatinine greater than 30% from baseline mandates dose reduction or cessation of the drug. Hyperkalemia may also warrant drug cessation, except in the reliable patient who can follow a low-potassium diet and adhere to a potassium-binding resin; such patients should be monitored closely. An ACE inhibitor and ARB should not be used in combination. CKD is a common cause of refractory hypertension for which agents from multiple classes are often needed. Current guidelines differ with respect to blood pressure goals in CKD; those from the Joint National Commission suggest a goal of less than 140/90 mm Hg, while the American Heart Association advocates for less than 130/80 mm Hg. As patients with CKD are at risk for renal hypoperfusion and AKI with overtreatment of hypertension, it is prudent to individualize the approach to blood pressure control to each patient.

2. Coronary artery disease—Patients with CKD are at higher risk for death from CVD than the general population. Traditional modifiable risk factors for CVD, such as hypertension, tobacco use, and hyperlipidemia, should be aggressively treated. Uremic vascular calcification involving disordered phosphorus homeostasis and other mediators may also be a cardiovascular risk factor in these patients.

3. Heart failure—CKD complications result in increased cardiac workload due to hypertension, volume overload, and anemia. Patients may also have accelerated rates of atherosclerosis and vascular calcification resulting in vessel stiffness. All of these factors contribute to left ventricular

hypertrophy and heart failure with preserved ejection fraction, which is common in CKD. Over time, heart failure with decreased ejection fraction may develop. Diuretic therapy, in addition to fluid and salt restriction, is usually necessary; diuretic dose escalation may be needed as kidney function declines. ACE inhibitors and ARBs can be used for patients with advanced CKD with close monitoring of blood pressure as well as for hyperkalemia and worsening kidney function; mineralocorticoid receptor antagonists may be used with similar precautions but should be discontinued when eGFR is less than 30 mL/min/1.73 m². SGLT2 inhibitors have been shown to improve outcomes for both heart failure and CKD.

4. Atrial fibrillation—Patients with advanced CKD and ESKD suffer disproportionate rates of atrial fibrillation, which approach 20% in patients receiving dialysis. While those with up to CKD stage 4 should be treated as the general population, anticoagulation for prevention of thromboembolic events becomes challenging in those with ESKD due to competing risks of bleeding and clotting as well as a lack of data supporting its routine use.

5. Pericarditis—Pericarditis rarely develops in uremic patients; typical findings include pleuritic chest pain and a friction rub. Cardiac tamponade can occur; therefore, uremic pericarditis is a mandatory indication for hospitalization and initiation of hemodialysis.

Bangalore S et al. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med*. 2020;382:1608. [PMID: 32227756]

Fay KS et al. Resistant hypertension in people with CKD: a review. *Am J Kidney Dis*. 2021;77:110. [PMID: 32712185]

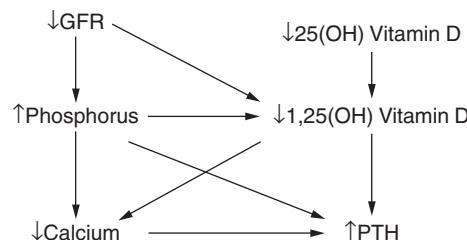
Guerrot D et al. Blood pressure targets in chronic kidney disease: an update on the evidence. *Curr Opin Nephrol Hypertens*. 2020;29:327. [PMID: 32167996]

Packer M et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413. [PMID: 32865377]

Palmer BF. Potassium binders for hyperkalemia in chronic kidney disease—diet, renin-angiotensin-aldosterone system inhibitor therapy, and hemodialysis. *Mayo Clin Proc*. 2020;95:339. [PMID: 31668450]

B. Metabolic Bone Disease

The metabolic bone disease of CKD refers to the complex disturbances of calcium and phosphorus metabolism, parathyroid hormone (PTH), active vitamin D, and fibroblast growth factor-23 (FGF-23) homeostasis (see Chapter 21 and Figure 22–3). A typical pattern seen as early as CKD stage 3 is hyperphosphatemia, hypocalcemia, and hypovitaminosis D, resulting in secondary hyperparathyroidism. These abnormalities can contribute to vascular calcification and may be responsible in part for the accelerated CVD and excess mortality seen in the CKD population. Epidemiologic studies show an association between elevated phosphorus levels and increased risk of cardiovascular mortality in early CKD through ESKD. As yet, there are no intervention trials suggesting the best course of treatment in these patients; control of mineral and PTH levels per current guidelines is discussed below.



▲ Figure 22–3. Mineral abnormalities of CKD. Decline in glomerular filtration rate (GFR) and loss of renal mass lead directly to increased serum phosphorus and hypovitaminosis D. Both of these abnormalities result in hypocalcemia and hyperparathyroidism. Many CKD patients also have nutritional 25(OH) vitamin D deficiency. PTH, parathyroid hormone.

Bone disease, or renal osteodystrophy, in advanced CKD is common and there are several types of lesions. Renal osteodystrophy can be diagnosed only by bone biopsy, which is rarely done. The most common bone disease, osteitis fibrosa cystica, is a result of secondary hyperparathyroidism and the osteoclast-stimulating effects of PTH. This is a high-turnover disease with bone resorption and subperiosteal lesions; it can result in bone pain and proximal muscle weakness. Adynamic bone disease, or low-bone turnover, is becoming more common; it may result iatrogenically from suppression of PTH or via spontaneously low PTH production. Osteomalacia is characterized by lack of bone mineralization. In the past, osteomalacia was associated with aluminum toxicity—either as a result of chronic ingestion of prescribed aluminum-containing phosphorus binders or from high levels of aluminum in impure dialysate water. Currently, osteomalacia is more likely to result from hypovitaminosis D; there is also theoretical risk of osteomalacia associated with use of bisphosphonates in advanced CKD.

All of the above entities increase the risk of fractures. Treatment may involve correction of calcium, phosphorus, and 25-OH vitamin D levels toward normal values, and mitigation of hyperparathyroidism. Understanding the interplay between these abnormalities can help target therapy (Figure 22–3). Declining GFR leads to phosphorus retention. This results in hypocalcemia as phosphorus complexes with calcium, deposits in soft tissues, and stimulates PTH. Loss of renal mass and low 25-OH vitamin D levels often seen in CKD patients result in low 1,25(OH) vitamin D production by the kidney. Because 1,25(OH) vitamin D is a suppressor of PTH production, hypovitaminosis D also leads to secondary hyperparathyroidism.

The first step in treatment of metabolic bone disease is control of hyperphosphatemia. This involves dietary phosphorus restriction initially (see section on dietary management), followed by the administration of oral phosphorus binders if targets are not achieved. Oral phosphorus binders block absorption of dietary phosphorus in the gut and are given thrice daily with meals. These should be titrated to a near-normal serum phosphorus level. Calcium-containing binders (calcium carbonate, 650 mg/tablet, or calcium acetate, 667 mg/capsule, used at doses of one to three

pills per meal) are relatively inexpensive but may contribute to positive calcium balance and vascular calcification; overt hypercalcemia may also occur. Current guidelines suggest limiting their use in favor of the non-calcium-containing binders sevelamer carbonate (800–3200 mg/meal) and lanthanum carbonate (500–1000 mg/meal). Newer, iron-based phosphorus binders include ferric citrate and sucroferric oxyhydroxide and may be considered when other binders are not tolerated either due to hypercalcemia or constipation. They should be avoided in patients with iron overload. Aluminum hydroxide is a highly effective phosphorus binder but can cause osteomalacia and neurologic complications when used long-term; it can be used in the acute setting for severe hyperphosphatemia or for short periods (eg, 3 weeks) in CKD patients.

Once serum phosphorus levels are controlled, active vitamin D (1,25[OH] vitamin D, or calcitriol) or other vitamin D analogs are used to treat secondary hyperparathyroidism in advanced CKD and ESKD. Serum 25-OH vitamin D levels should be measured and brought to normal (see Chapter 26) prior to considering administration of active vitamin D. Active vitamin D (calcitriol) increases serum calcium and phosphorus levels; both need to be monitored closely during calcitriol therapy, and its dose should be decreased if hypercalcemia or hyperphosphatemia occurs. Typical calcitriol dosing is 0.25 or 0.5 mcg orally daily or every other day. Cinacalcet targets the calcium-sensing receptors of the parathyroid gland and suppresses PTH production. Cinacalcet, 30–90 mg orally once a day, can be used if elevated serum phosphorus or calcium levels prohibit the use of vitamin D analogs; it can cause serious hypocalcemia, and patients should be closely monitored for this complication. Optimal PTH levels in CKD are not known, but because skeletal resistance to PTH develops with uremia, relatively high levels are targeted in advanced CKD to avoid adynamic bone disease. Expert guidelines suggest goal PTH levels near or just above the upper limit of normal for moderate CKD, and at least twofold and up to ninefold the upper limit of normal for ESKD.

Evenepoel P et al. European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4-G5D. *Nephrol Dial Transplant*. 2021;36:42. [PMID: 33098421]

Scialla JJ et al. State-of-the-art management of hyperphosphatemia in patients with CKD: an NKF-KDOQI controversies perspective. *Am J Kidney Dis*. 2021;77:132. [PMID: 32771650]

C. Hematologic Complications

1. Anemia—The anemia of CKD, primarily due to decreased erythropoietin production, often becomes clinically significant during stage 3 CKD. CKD is also associated with high levels of hepcidin, which blocks GI iron absorption and mobilization of iron from body stores; this results in a functional iron deficiency—the so-called “anemia of chronic disease.” The approach to a patient with CKD and anemia begins with ensuring that the bone marrow can respond to erythropoietin. Thus, thyroid function tests, serum vitamin B₁₂ levels, and iron stores (ferritin and iron saturation) should be checked. Iron stores are targeted

to higher goals due to a functional blockade of iron utilization in this population. In CKD, a serum ferritin below 100–200 ng/mL or iron saturation less than 20% is suggestive of iron deficiency. Iron stores may be repleted with oral or parenteral iron; iron therapy should probably be withheld if the serum ferritin is greater than 500–800 ng/mL, even if the iron saturation is less than 20%. Oral therapy with ferrous sulfate, gluconate, or fumarate, 325 mg once daily, is the initial therapy in pre-ESKD CKD; higher doses will result in increasing hepcidin levels. For those who do not respond due to poor GI absorption or lack of tolerance, intravenous iron (eg, iron sucrose or iron gluconate) may be necessary.

Erythropoiesis-stimulating agents (ESAs, eg, recombinant erythropoietin [epoetin alfa or beta] and darbepoetin) are used to treat the anemia of CKD if other treatable causes are excluded. There is likely no benefit of starting an ESA before hemoglobin (Hgb) values are less than 9 g/dL. The starting dose of epoetin alfa is 50–100 units/kg once or twice a week, and darbepoetin is started at 0.45 mcg/kg and administered every 2–4 weeks; epoetin beta at a starting dose of 60–100 mcg is given every 2–4 weeks. These agents can be given intravenously (eg, to the hemodialysis patient) or subcutaneously (to both the predialysis or dialysis patient); subcutaneous dosing of epoetin alfa is roughly 30% more effective than intravenous dosing. ESAs should be titrated to an Hgb of 10–11 g/dL for optimal safety; studies show that targeting a higher Hgb increases the risk of stroke and possibly other cardiovascular events. When titrating doses, Hgb levels should rise no more than 1 g/dL every 3–4 weeks. Hypertension is a common complication of treatment with ESAs.

2. Coagulopathy—The bleeding diathesis that may occur in stage 4–5 CKD is mainly due to platelet dysfunction, but severe anemia may also contribute.

Treatment is required only in patients who are symptomatic. Raising the Hgb to 9–10 g/dL in anemic patients can reduce risk of bleeding via improved clot formation. Desmopressin (25 mcg intravenously every 8–12 hours for two doses) is a short-lived but effective treatment for platelet dysfunction and it is often used in preparation for surgery or kidney biopsy; hyponatremia is a potential adverse effect of this treatment. Dialysis improves the bleeding time.

Locatelli F et al. Are all erythropoiesis-stimulating agents created equal? *Nephrol Dial Transplant*. 2020. [Epub ahead of print] [PMID: 32206785]

D. Hyperkalemia

Potassium balance generally remains intact in CKD until stages 4–5. However, hyperkalemia may occur at earlier stages when certain conditions are present, such as type 4 renal tubular acidosis (seen in patients with diabetes mellitus), high potassium diets, or medications that decrease renal potassium secretion (amiloride, triamterene, spironolactone, eplerenone, NSAIDs, ACE inhibitors, ARBs) or block cellular potassium uptake (beta-blockers). Other causes include acidemic states and any type of cellular destruction causing release of intracellular contents, such as hemolysis and rhabdomyolysis.

Treatment of acute hyperkalemia is discussed in Chapter 21 (see Table 21–5). Cardiac monitoring is indicated for any ECG changes seen with hyperkalemia or a serum potassium level greater than 6.0–6.5 mEq/L or mmol/L. Chronic hyperkalemia is best treated with dietary potassium restriction (2 g/day) and minimization or elimination of any medications that may impair renal potassium excretion, as noted above. Loop diuretics may be administered for their kaliuretic effect as long as the patient is not volume-depleted, and oral potassium-binding resins may be considered.

Palmer BF et al. Clinical management of hyperkalemia. Mayo Clin Proc. 2021;96:744. [PMID: 33160639]

E. Acid-Base Disorders

Damaged kidneys are unable to excrete the 1 mEq/kg/day of acid generated by metabolism of dietary animal proteins in the typical Western diet. The resultant metabolic acidosis is primarily due to decreased GFR; proximal or distal tubular defects may contribute to or worsen the acidosis. Excess hydrogen ions are buffered by bone; the consequent leaching of calcium and phosphorus from the bone contributes to the metabolic bone disease described above. Chronic acidosis can also result in muscle protein catabolism as well as growth retardation in children with CKD and may accelerate progression of CKD. Reduction of dietary animal protein and increased fruit and vegetable intake, and the administration of oral sodium bicarbonate (in doses of 0.5–1.0 mEq/kg/day divided twice daily and titrated as needed) are strategies to bring serum bicarbonate levels toward normal. Citrate salts increase the absorption of dietary aluminum and should be avoided in CKD.

Navaneethan SD et al. Effects of treatment of metabolic acidosis in CKD: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2019;14:1011. [PMID: 31196951]

F. Neurologic Complications

Uremic encephalopathy, resulting from the aggregation of uremic toxins, does not occur until GFR falls below 5–10 mL/min/1.73 m². Symptoms begin with difficulty in concentrating and can progress to lethargy, confusion, seizure, and coma. Physical findings may include altered mental status, weakness, and asterixis. These findings improve with dialysis.

Other neurologic complications that can manifest with advanced CKD include peripheral neuropathies (stocking-glove or isolated mononeuropathies), erectile dysfunction, autonomic dysfunction, and restless leg syndrome. These may not improve with dialysis therapy.

G. Endocrine Disorders

Decreased libido and erectile dysfunction are common in advanced CKD. Men have decreased testosterone levels; women are often anovulatory. Women with serum creatinine less than 1.4 mg/dL are not at increased risk for poor outcomes in pregnancy; however, those with serum

creatinine greater than 1.4 mg/dL may experience faster progression of CKD with pregnancy. Fetal survival is not compromised, however, unless CKD is advanced.

Treatment

A. Slowing Progression

Treatment of the underlying cause of CKD is vital. Control of diabetes should be aggressive in early CKD; however, risk of hypoglycemia increases in advanced CKD, and glycemic targets may need to be relaxed to avoid this dangerous complication. Blood pressure control is vital to slow progression of all forms of CKD; agents that block the renin-angiotensin-aldosterone system are particularly important in proteinuric patients. Obese patients should be encouraged to lose weight. Management of traditional cardiovascular risk factors is vital. Risks for AKI should be minimized or avoided, including long-term use of NSAIDs. Treatment of metabolic acidosis may be helpful. The efficacy of SGLT2 inhibition for slowing progression of CKD in those with and without diabetes or significant proteinuria has been demonstrated in several recent trials.

Hannan M et al. Risk factors for CKD progression: overview of findings from the CRIC study. Clin J Am Soc Nephrol. 2021;16:648. [PMID: 33177074]

Heerspink HJL et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436. [PMID: 32970396]

Kelly JT et al. Modifiable lifestyle factors for primary prevention of CKD: a systematic review and meta-analysis. J Am Soc Nephrol. 2021;32:239. [PMID: 32868398]

B. Dietary Management

Patients with CKD should be evaluated by a renal nutritionist. Patient-specific recommendations should be made concerning protein, salt, water, potassium, and phosphorus intake to help manage CKD progression and complications.

1. Protein restriction—There is increasing interest in plant-based diets for the treatment of CKD. Reduced intake of animal protein to 0.6–0.8 g/kg/day may slow CKD progression. However, significant protein restriction is not advisable in those with cachexia or low serum albumin in the absence of the nephrotic syndrome.

2. Salt and water restriction—In advanced CKD, the kidney is unable to adapt to large changes in sodium intake. Intake of greater than 3–4 g/day can lead to hypertension and hypervolemia, whereas intake of less than 1 g/day can lead to volume depletion and hypotension. A goal of 2 g/day of sodium is reasonable for most patients. Daily fluid restriction to 2 L may be needed if volume overload is present.

3. Potassium restriction—Restriction is needed once the GFR has fallen below 10–20 mL/min/1.73 m², or earlier if the patient is hyperkalemic. Patients should receive detailed lists describing potassium content of foods and should limit their intake to less than 50–60 mEq/day (2 g/day). An aggressive bowel regimen should be instituted for patients with hyperkalemia (more than two bowel movements

daily), since a higher percentage of potassium is excreted through the GI tract as GFR declines. Potassium-binding resins may be used (see section on Hyperkalemia).

4. Phosphorus restriction—Guidelines suggest lowering elevated serum phosphorus levels toward normal in all stages of CKD. Dietary phosphate restriction to 800–1000 mg/day is the first step. Processed foods and cola beverages are often preserved with highly bioavailable phosphorus and should be avoided. Foods rich in phosphorus such as eggs, dairy products, nuts, beans, and meat may also need to be limited, although care must be taken to avoid protein malnutrition. When GFR is less than 20–30 mL/min/1.73 m², dietary restriction is rarely sufficient to reach target levels, and phosphorus binders are usually required (see section on Metabolic Bone Disease).

Ikizler TA et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis. 2020;76:S1. [PMID: 32829751]

Joshi S et al. Plant-based diets for kidney disease: a guide for clinicians. Am J Kidney Dis. 2021;77:287. [PMID: 33075387]

C. Medication Management

Many drugs are excreted by the kidney; dosages should be adjusted for GFR. Decreased renal elimination of insulin in advanced CKD confers risk for hypoglycemia in treated diabetic patients. Doses of oral hypoglycemics and insulin may need reduction. The risk of lactic acidosis with metformin is due to both dose and eGFR; it should be discontinued when eGFR is less than 30 mL/min/1.73 m².

Magnesium-containing medications, such as laxatives or antacids, and phosphorus-containing medicines (eg, cathartics) should be avoided. Active morphine metabolites can accumulate in advanced CKD; this problem is not encountered with other opioid agents. Drugs with potential nephrotoxicity (NSAIDs, intravenous contrast, as well as others noted in the Acute Kidney Injury section) should be avoided. Proton pump inhibitors should be used only when medically necessary.

Shaddock R et al. Renal repercussions of medications. Prim Care. 2020;47:691. [PMID: 33121637]

D. Treatment of ESKD

When GFR declines to 5–10 mL/min/1.73 m², renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation) is required to sustain life. Patient education is important in understanding which mode of therapy is most suitable, as is timely preparation for treatment. Referral to a nephrologist has been shown to improve mortality and therefore should take place in late stage 3 CKD or when the GFR is declining rapidly. Preparation for ESKD treatment requires a team approach with the involvement of dieticians, social workers, primary care clinicians, and nephrologists. For very elderly patients, or those with multiple debilitating or life-limiting comorbidities, dialysis therapy may not meaningfully prolong life, and the option of palliative care should be discussed with the patient and

family. Conversely, for patients who are otherwise relatively healthy, evaluation for possible kidney transplantation should be considered prior to initiation of dialysis.

1. Dialysis—Dialysis initiation should be considered when GFR is near 10 mL/min/1.73 m² and uremic symptoms are present. Other indications for dialysis, which may occur when GFR is 10–15 mL/min/1.73 m², are fluid overload unresponsive to diuresis and refractory hyperkalemia.

A. HEMODIALYSIS—Vascular access for hemodialysis can be accomplished by an arteriovenous fistula (the preferred method) or prosthetic graft; creation of dialysis access should be considered well before dialysis initiation. An indwelling catheter is used when there is no useable vascular access. Because catheters confer a high risk of bloodstream infection, they should be considered a temporary measure. Native fistulas typically last longer than prosthetic grafts but require a longer time after surgical construction for maturation (6–8 weeks for a fistula versus 2 weeks for a graft). Infection, thrombosis, and aneurysm formation are complications seen more often in grafts than fistulas. *Staphylococcus* species are the most common cause of soft tissue infections and bacteremia.

Treatment at a hemodialysis center typically occurs three times a week. Sessions last 3–5 hours, depending on patient size and type of dialysis access. Home hemodialysis is often performed more frequently (3–6 days per week for shorter sessions) and requires a trained helper. Results of trials comparing quotidian modalities (nocturnal and frequent home hemodialysis) to conventional in-center dialysis have not thus far shown significant mortality differences, but there may be improvements in blood pressure control, mineral metabolism, and quality of life.

B. PERITONEAL DIALYSIS—With peritoneal dialysis, the peritoneal membrane is the “dialyzer.”

There are different kinds of peritoneal dialysis: continuous ambulatory peritoneal dialysis (CAPD), in which the patient exchanges the dialysate four to six times a day manually; and continuous cyclic peritoneal dialysis (CCPD), which utilizes a cycler machine to automatically perform exchanges at night.

The most common complication of peritoneal dialysis is peritonitis. Peritonitis may present with nausea and vomiting, abdominal pain, diarrhea or constipation, and fever. The normally clear dialysate becomes cloudy; and a diagnostic peritoneal fluid cell count greater than 100 white blood cells/mcL ($0.1 \times 10^9/L$) with a differential of greater than 50% polymorphonuclear neutrophils is present. *Staphylococcus aureus* is the most common infecting organism, but streptococci and gram-negative species may also be causative. Empiric intraperitoneal administration of either vancomycin or a first-generation cephalosporin (cefazolin) plus a third-generation cephalosporin (ceftazidime) should be instituted with the first signs of peritonitis and subsequently tailored based on culture results.

2. Kidney transplantation—Many patients with ESKD are otherwise healthy enough to be suitable for transplantation, although standard criteria for recipient selection

are lacking between transplant centers. Two-thirds of kidney allografts come from deceased donors, with the remainder from living related or unrelated donors. Over 100,000 patients are on the waiting list for a deceased donor transplant in the United States; the average wait is 3–7 years, depending on geographic location and recipient blood type.

3. Medical management of ESKD—As noted above, some patients are not candidates for kidney transplantation and may not benefit from dialysis. Very elderly persons may die soon after dialysis initiation; those who do not may nonetheless rapidly lose functional status in the first year of treatment. The decision to initiate dialysis in patients with limited life expectancy should be weighed against possible deterioration in quality of life. For patients with ESKD who elect not to undergo dialysis or who withdraw from dialysis, progressive uremia with gradual suppression of sensorium results in a painless death within days to months. Involvement of a palliative care team is essential.

Foster JG et al. Care of the renal transplant patient. *Prim Care*. 2020;47:703. [PMID: 33121638]

Zarantonello D et al. Novel conservative management of chronic kidney disease via dialysis-free interventions. *Curr Opin Nephrol Hypertens*. 2021;30:97. [PMID: 33186220]

► Prognosis in ESKD

Compared with kidney transplant recipients and age-matched controls, mortality is higher for patients undergoing dialysis. There is likely little difference in survival for well-matched peritoneal versus hemodialysis patients.

Survival rates on dialysis depend on the underlying disease process. Five-year Kaplan-Meier survival rates vary from 37% for patients with diabetes to 54% for patients with glomerulonephritis. Overall 5-year survival is currently estimated at 40%. Patients undergoing dialysis have an average life expectancy of 3–5 years, but survival for as long as 25 years may be achieved depending on comorbidities. The most common cause of death is cardiac disease (more than 50%). Other causes include infection, cerebrovascular disease, and malignancy.

► When to Refer

- A patient with stage 3–5 CKD should be referred to a nephrologist for management in conjunction with the primary care provider.
- A patient with other forms of CKD such as those with proteinuria greater than 1 g/day or polycystic kidney disease should be referred to a nephrologist at earlier stages.

► When to Admit

- Admission should be considered for decompensation of problems related to CKD, such as worsening of acid-base status, electrolyte abnormalities, and volume overload, that cannot be appropriately treated in the outpatient setting.

- Admission is appropriate when a patient needs to start dialysis and is not stable for its outpatient initiation.

Charles C et al. Chronic kidney disease. *Prim Care*. 2020;47:585. [PMID: 33121630]

Li PK et al. Kidney health for everyone everywhere—from prevention to detection and equitable access to care. *Clin Nephrol*. 2020;93:111. [PMID: 32017699]

Shlipak MG et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2021;99:34. [PMID: 33127436]

Stenvinkel P et al. A planetary health perspective for kidney disease. *Kidney Int*. 2020;98:261. [PMID: 32709283]

RENAL ARTERY STENOSIS

ESSENTIALS OF DIAGNOSIS

- Produced by atherosclerotic occlusive disease (80–90% of patients) or fibromuscular dysplasia (10–15%).
- Hypertension.
- AKI in patients starting ACE inhibitor therapy if stenosis is bilateral.

► General Considerations

Approximately 5% of Americans with hypertension suffer from renal artery stenosis. Atherosclerotic ischemic renal disease accounts for most cases of renal artery stenosis. It typically occurs among persons over 45 years of age with additional risk factors such as CKD, diabetes mellitus, and tobacco use. Fibromuscular dysplasia is a less common cause of renal artery stenosis that most commonly occurs in young women.

► Clinical Findings

A. Symptoms and Signs

Patients with atherosclerotic ischemic renal disease may have refractory hypertension, new-onset hypertension (in an older patient), pulmonary edema with poorly controlled blood pressure, and AKI upon starting an ACE inhibitor or ARB. Physical examination may reveal an audible abdominal bruit on the affected side. Unexplained hypertension in a woman younger than 40 years should raise suspicion for fibromuscular dysplasia.

B. Laboratory Findings

BUN and serum creatinine may be elevated if there is significant renal ischemia. Patients with bilateral renal artery stenosis may have hypokalemia, a finding that reflects activation of the renin-angiotensin-aldosterone system in response to reduced blood flow (a “prerenal” state).

C. Imaging

Abdominal ultrasound can reveal either asymmetric kidney size if one renal artery is affected more than the other or small hyperechoic kidneys if both are affected.

Screening with Doppler ultrasonography, CT angiography, or magnetic resonance angiography (MRA) is recommended if a corrective procedure would be performed when a positive test result is found. **Doppler ultrasonography** is highly sensitive and specific (85% and 92%, respectively) and relatively inexpensive but is extremely operator and patient dependent.

CT angiography consists of intravenous contrast injection with digital subtraction arteriography. The sensitivities from various studies range from 77% to 98%, with specificities of 90–94%.

MRA is an excellent but expensive way to screen for renal artery stenosis, particularly in those with atherosclerotic disease. Sensitivity is 77–100% and specificity ranges from 71% to 96%. The imaging agent for MRA (gadolinium) has been associated with nephrogenic systemic fibrosis, which is discussed elsewhere under Nephrogenic Systemic Fibrosis.

Renal angiography is the gold standard for diagnosis, but it is more invasive than the three screening tests discussed above. Thus, it is performed after a positive screening test. Lesions are most commonly found in the proximal third or ostial region of the renal artery. The risk of atheroembolic phenomena after angiography ranges from 5% to 10%. Fibromuscular dysplasia has a characteristic “beads-on-a-string” appearance on angiography.

► Treatment

Treatment of atherosclerotic ischemic renal disease is controversial. Options include medical management, angioplasty with or without stenting, and surgical bypass. Two large randomized trials showed that vascular intervention is no better than optimal medical management in patients with renal artery stenosis, except in selected circumstances (eg, patients with recurrent episodes of flash pulmonary edema). Angioplasty might reduce the number of antihypertensive medications but does not significantly change the progression of kidney dysfunction. Stenting produces significantly better results than angioplasty. However, blood pressure and serum creatinine are similar at 6 months with medical management as with either angioplasty and stents.

Treatment of fibromuscular dysplasia with percutaneous transluminal angioplasty is often curative, which is in stark contrast to treatments for atherosclerotic disease.

Gornik HL et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. *Vasc Med.* 2019;24:164. [PMID: 30648921]

Mannemuddhu SS et al. Renovascular hypertension. *Prim Care.* 2020;47:631. [PMID: 33121633]

Prince M et al. Renal revascularization in resistant hypertension. *Prog Cardiovasc Dis.* 2020;63:58. [PMID: 31821813]

► GLOMERULAR DISEASES

Glomerular diseases can be challenging to understand clinically because the glomerulus is a histologically complex structure (consisting of the epithelial cells [podocytes], basement membrane, capillary endothelium, and mesangium). The following are examples of injuries that can affect any or all of the constituents of the glomerulus: (1) overwork injury, as in CKD; (2) an inflammatory process, such as SLE; (3) a podocyte protein mutation, as in hereditary focal segmental glomerulosclerosis (FSGS); or (4) a deposition disease, as in diabetes or amyloidosis. When a glomerular disease is suspected, a kidney biopsy may be needed to clarify the etiology.

► Classification

Glomerular diseases can be classified in one of two clinical spectra—the nephritic spectrum or the nephrotic spectrum (Figure 22–4). At the “least severe” end of the **nephritic spectrum**, the findings of asymptomatic glomerular hematuria (ie, dysmorphic red blood cells with or without some proteinuria [less than 1 g/day]) are characteristic. The nephritic *syndrome*, comprising glomerular hematuria, subnephrotic proteinuria (less than 3 g/day), edema, and elevated creatinine, falls in the midportion of the spectrum. The rapidly progressive glomerulonephritides (RPGNs), with systemic symptoms, are at the “most severe” and clinically urgent end of the spectrum. The **nephrotic spectrum** is comprised of diseases that present primarily with proteinuria of at least 0.5–1 g/day and a bland urine sediment (no cells or cellular casts). At the more severe end of the nephrotic spectrum is the nephrotic *syndrome*, consisting of nephrotic-range proteinuria (greater than 3 g/day), hypoalbuminemia, edema, hyperlipidemia, and urinary oval fat bodies. Differentiating between a clinical presentation within the nephritic spectrum versus the nephrotic spectrum is important because it helps narrow the differential diagnosis of the underlying glomerular disease (Tables 22–7 and 22–8).

Glomerular diseases can also be classified according to whether they cause renal abnormalities alone (primary renal disease) or whether the renal abnormalities result from a systemic disease (secondary renal disease).

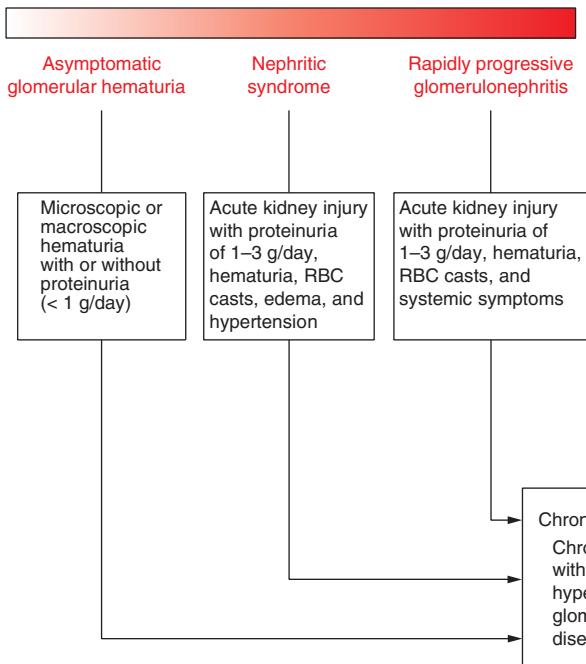
Further evaluation prior to kidney biopsy may include serologic testing for systemic diseases that can result in glomerular damage (Figure 22–5).

Cavanaugh C et al. Urine sediment examination in the diagnosis and management of kidney disease: Core Curriculum 2019. *Am J Kidney Dis.* 2019;73:258. [PMID: 30249419]

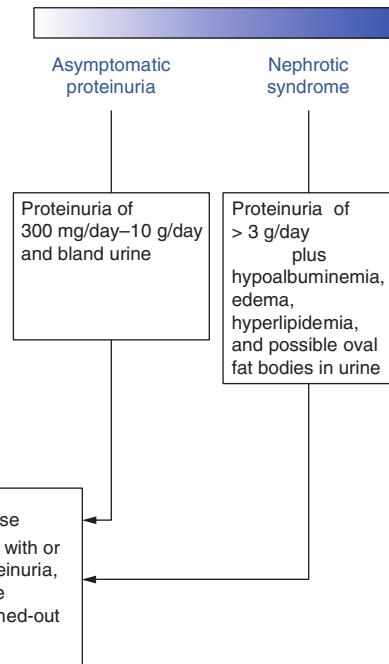
Floege J et al. Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2019;95:268. [PMID: 30665568]

Rovin BH et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2019;95:281. [PMID: 30665569]

Nephritic Spectrum



Nephrotic Spectrum



▲ **Figure 22–4.** Glomerular diseases present within one of the clinical spectra shown; the exact presentation is determined by the severity of the underlying disease and the pattern of injury. Nephritic diseases are characterized by the presence of an active urine sediment with glomerular hematuria and often with proteinuria. Nephrotic spectrum diseases are proteinuric with bland urine sediments (no cells or cellular casts). All glomerular diseases may progress to a chronic, scarred state. (Adapted, with permission, from Megan Troxell, MD, PhD.)

NEPHRITIC SPECTRUM GLOMERULAR DISEASES



ESSENTIALS OF DIAGNOSIS

- ▶ **Asymptomatic glomerular hematuria**
 - Hematuria with dysmorphic RBCs
 - Proteinuria < 1 g/day
- ▶ **Nephritic syndrome in more severe cases**
 - Glomerular hematuria (and RBC casts if glomerular bleeding is heavy)
 - Proteinuria of 1–3 g/day
 - Hypertension
 - Edema
 - Rising creatinine over days to months
- ▶ **Rapidly progressive glomerulonephritis in most severe cases**
 - AKI with rising creatinine over days to months
 - Glomerular hematuria (and RBC casts)
 - Proteinuria of 1–3 g/day
 - Systemic symptoms
 - Hypertension and edema uncommon

► General Considerations

“Glomerulonephritis” is a term given to those diseases that present in the nephritic spectrum and usually signifies an inflammatory process causing renal dysfunction. It can be acute, developing over days to weeks, with or without resolution, or may be chronic and indolent with progressive scarring. As noted above, diseases that cause a nephritic spectrum presentation may present with glomerular hematuria and proteinuria, with nephritic syndrome, or with RPGN (Figure 22–4). The presentation depends on the severity of the underlying inflammation and the pattern of injury caused by the disease process.

► Clinical Findings

A. Symptoms and Signs

Nephritic syndrome usually leads to an acute decrease in GFR and resultant sodium retention. This is manifested by hypertension and edema, which is first seen in regions of low tissue pressure such as the periorbital and scrotal areas. Heavy glomerular bleeding from inflammation may result in gross hematuria (smoky or cola-colored urine).

B. Laboratory Findings

1. **Serologic testing**—Serologic tests based on the history and physical examination help narrow the differential

Table 22–7. Classification and findings in glomerulonephritis: nephritic spectrum presentations.

	Typical Presentation	Association/Notes	Serology
Postinfectious glomerulonephritis	Children: abrupt onset of nephritic syndrome and acute kidney injury but can present anywhere in nephritic spectrum	Streptococci, other bacterial infections (eg, staphylococci, endocarditis, shunt infections)	Rising ASO titers, low complement levels
IgA nephropathy (Berger disease) and Henoch-Schönlein purpura, systemic IgA vasculitis	Classically: gross hematuria with respiratory tract infection, but can present anywhere in nephritic spectrum; Henoch-Schönlein purpura with vasculitic rash and gastrointestinal hemorrhage	Abnormal IgA glycosylation in both primary (familial predisposition) and secondary disease (associated with cirrhosis, HIV, celiac disease) Henoch-Schönlein purpura in children after an inciting infection	No serologic tests helpful; complement levels are normal
Pauci-immune (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, polyarteritis, idiopathic crescentic glomerulonephritis)	Classically: crescentic or RPGN, but can present anywhere in nephritic spectrum; may have respiratory tract/sinus symptoms in granulomatosis with polyangiitis	See Figure 22–5	ANCA: MPO or PR3 titers high; complement levels normal
Anti-GBM glomerulonephritis; Goodpasture syndrome	Classically: crescentic or RPGN, but can present anywhere in nephritic spectrum; pulmonary hemorrhage in Goodpasture syndrome	May develop as a result of respiratory irritant exposure (chemicals or tobacco use)	Anti-GBM antibody titers high; complement levels normal
Cryoglobulin-associated glomerulonephritis	Often acute nephritic syndrome; often with systemic vasculitis including rash and arthritis	Most commonly associated with chronic hepatitis C; may occur with other chronic infections or some connective tissue diseases	Cryoglobulins positive; rheumatoid factor may be elevated; complement levels low
MPGN	Classically: acute nephritic syndrome, but can also have nephrotic syndrome features	Most patients are < 30 years old Immune complex MPGN most common C3 glomerulonephritis	Low complement levels, may have findings of underlying infection or paraproteinemia
Hepatitis C infection	Anywhere in nephritic spectrum	Can cause MPGN pattern of injury or cryoglobulinemic glomerulonephritis; membranous nephropathy pattern of injury uncommon	Low complement levels; positive hepatitis C serology; rheumatoid factor may be elevated
Systemic lupus erythematosus	Anywhere in nephritic spectrum, depending on pattern/severity of injury	Treatment depends on clinical course and International Society of Nephrology and Renal Pathology Society classification on biopsy	High ANA and anti-double-stranded DNA titers; low complement levels

ANA, antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane; MPGN, membranoproliferative glomerulonephritis; MPO, myeloperoxidase; PR3, proteinase 3; RPGN, rapidly progressive glomerulonephritis.

diagnosis. These tests may include C3 and C4 complement levels, antinuclear antibodies, cryoglobulins, hepatitis serologies, serum and urine protein electrophoreses, serum free light chains, ANCA, anti-GBM antibodies, and anti-streptolysin O (ASO) titers (Figure 22–5).

2. Urinalysis—The urine dipstick is positive for protein and blood. Urinary microscopy reveals red blood cells that are misshapen or dysmorphic from traversing a damaged glomerular filtration barrier. Red blood cell casts are seen with heavy glomerular bleeding and tubular stasis. When quantified, proteinuria is usually subnephrotic range (less than 3 g/day).

3. Biopsy—Definitive diagnosis of the underlying glomerular disease cannot be made without a kidney biopsy. Candidates for biopsy are patients for whom test results would influence management; exceptions include those

with advanced underlying CKD, those who cannot adhere to medical therapy, those for whom immunosuppressive therapy is not appropriate, or those for whom the presentation is “classic” for a particular disease (eg, post-streptococcal glomerulonephritis, childhood minimal change disease, and diabetic nephropathy). The major risk of biopsy is bleeding. Contraindications include a bleeding diathesis, thrombocytopenia, and uncontrolled hypertension.

► Treatment

General measures include treatment of hypertension and fluid overload, if present. Antiproteinuric therapy with an ACE inhibitor or ARB should be considered for those without AKI. For those with profound AKI, dialysis may be needed. The inflammatory glomerular injury may require immunosuppressive agents (see specific diseases discussed below).

Table 22–8. Classification and findings in glomerulonephritis: nephrotic spectrum presentations.

Disease	Typical Presentation	Association/Notes
Minimal change disease (nil disease; lipid nephrosis)	Child with sudden onset of full nephrotic syndrome	Children: associated with allergy or viral infection Adults: associated with Hodgkin disease, NSAIDs
Membranous nephropathy	Anywhere in nephrotic spectrum, but nephrotic syndrome not uncommon; particular predisposition to hypercoagulable state	Primary (idiopathic) may be associated with antibodies to PLA ₂ R Secondary may be associated with non-Hodgkin lymphoma, carcinoma (gastrointestinal, renal, bronchogenic, thyroid), gold therapy, penicillamine, SLE, chronic hepatitis B or C infection
Focal and segmental glomerulosclerosis	Anywhere in nephrotic spectrum; children with congenital disease have nephrotic syndrome	Children: congenital disease with podocyte gene mutation, or in spectrum of disease with minimal change disease Adults: associated with heroin abuse, HIV infection, reflux nephropathy, obesity, pamidronate, podocyte protein mutations, <i>APOL1</i> mutations
Amyloidosis	Anywhere in nephrotic spectrum	AL: plasma cell dyscrasia with Ig light chain overproduction and deposition; check SPEP and UPEP AA: serum amyloid protein A overproduction and deposition in response to chronic inflammatory disease (rheumatoid arthritis, inflammatory bowel disease, chronic infection)
Diabetic nephropathy	High GFR (hyperfiltration) → microalbuminuria → frank proteinuria → decline in GFR	Diabetes diagnosis precedes diagnosis of nephropathy by years
HIV-associated nephropathy	Heavy proteinuria, often nephrotic syndrome, progresses to ESKD relatively quickly	Usually seen in antiviral treatment-naïve patients (rare in antiretroviral therapy era), predilection for those of African descent (<i>APOL1</i> mutations)
Membranoproliferative glomerulonephropathy	Classically presents with acute nephritic syndrome, some may also exhibit nephrotic features	Immune complex–MPGN are idiopathic or secondary to infections, paraproteinemia, or systemic autoimmune disease; C3 glomerulopathies are due to alternative complement pathway dysregulation

ESKD, end-stage kidney disease; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; PLA₂R, phospholipase A₂ receptor; SLE, systemic lupus erythematosus; SPEP/UPEP, serum and urine protein electrophoresis.

► When to Refer

Any patient in whom a glomerulonephritis is suspected should be referred to a nephrologist.

► When to Admit

Any suspicion of acute nephritic syndrome or RPGN warrants consideration of immediate hospitalization.

Lamba P et al. Nephritic syndrome. Prim Care. 2020;47:615. [PMID: 33121632]
Poppelaars F et al. Complement-mediated kidney diseases. Mol Immunol. 2020;128:175. [PMID: 33137606]

1. Infection-Related & Postinfectious Glomerulonephritis



ESSENTIALS OF DIAGNOSIS

- ▶ Proteinuria.
- ▶ Glomerular hematuria.
- ▶ Symptoms 1–3 weeks after some infections (often pharyngitis or impetigo) or during course of other infections (eg, pneumonia or endocarditis).

► General Considerations

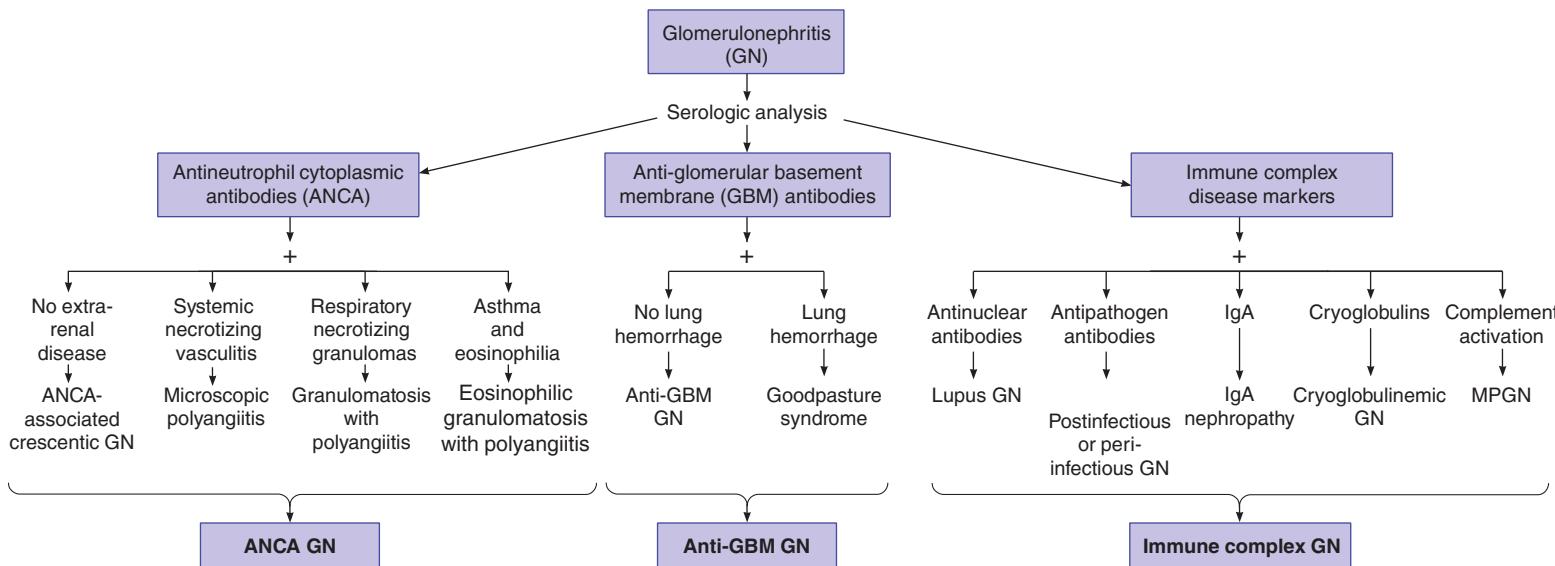
Postinfectious glomerulonephritis is most often due to infection with nephritogenic group A beta-hemolytic streptococcal infections (pharyngitis or impetigo). It can occur sporadically or in clusters and during epidemics, with onset up to 1–3 weeks after infection (average 7–10 days).

Other infections have been associated with glomerulonephritis including bacteremia (especially *S aureus*), bacterial pneumonias, deep-seated abscesses, gram-negative infections, infective endocarditis, and shunt infections; viral, fungal, and parasitic causes of glomerulonephritis include hepatitis B or C, HIV, cytomegalovirus infection, infectious mononucleosis, coccidioidomycosis, malaria, mycobacteria, syphilis, and toxoplasmosis. These entities result in glomerular injury during active infection, and are better termed “infection-related glomerulonephritis” rather than “postinfectious glomerulonephritis.”

► Clinical Findings

A. Symptoms and Signs

Disease presentation varies across the nephritic spectrum from asymptomatic glomerular hematuria (especially in epidemic cases) with minimal change in kidney function, to nephritic syndrome with hypertension, edema, and



▲ **Figure 22–5.** Serologic analysis of patients with glomerulonephritis. MPGN, membranoproliferative glomerulonephritis. (Modified, with permission, from Greenberg A et al. *Primer on Kidney Diseases*. Academic Press, 1994; and Jennette JC, Falk RJ. Diagnosis and management of glomerulonephritis and vasculitis presenting as acute renal failure. *Med Clin North Am*. 1990;74(4):893–908. © Elsevier.)

perhaps gross glomerular hematuria (smokey-colored urine); the most severe cases may result in oliguric AKI requiring dialysis.

B. Laboratory Findings

Serum complement levels are low; in postinfectious glomerulonephritis due to group A streptococcal infection, anti-streptolysin O (ASO) titers can be high unless the immune response has been blunted with previous antibiotic treatment. Glomerular hematuria and proteinuria are present. In children with a recent streptococcal infection and nephritic features, a diagnosis may be made empirically without a biopsy. When performed, kidney biopsy shows a diffuse proliferative pattern of injury on light microscopy. Immunofluorescence demonstrates granular deposition of IgG and C3 in the mesangium and along the capillary basement membrane. Electron microscopy shows large, dense subepithelial deposits or “humps.” Kidney biopsy findings in infection-related glomerulonephritis are varied and may show overlap with immune-complex membranoproliferative glomerulonephritis or C3 glomerulonephritis.

Treatment

Any active infection should be identified and treated appropriately; otherwise, treatment for postinfectious glomerulonephritis is supportive. Antihypertensives, salt restriction, and diuretics should be used if needed. Corticosteroids have not been shown to improve outcomes. Prognosis depends on the severity of the glomerular injury and age of the patient. Children are more likely to fully recover; adults are more prone to the development of severe disease (RPGN with crescent formation) and CKD.

Mohammad D et al. Postinfectious glomerulonephritis. *Pediatr Ann.* 2020;49:e273. [PMID: 32520369]
 Satoskar AA et al. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. *Nat Rev Nephrol.* 2020;16:32. [PMID: 31399725]

2. IgA Nephropathy



ESSENTIALS OF DIAGNOSIS

- ▶ Proteinuria: minimal to nephrotic range.
- ▶ Glomerular hematuria: microscopic is common; macroscopic (gross) after infection.
- ▶ Positive IgA staining on kidney biopsy.

General Considerations

IgA nephropathy (Berger disease) is a primary renal disease of IgA deposition in the glomerular mesangium. The inciting cause is unknown. IgA nephropathy can be a primary (renal-limited) disease or secondary to hepatic cirrhosis, celiac disease, and infections such as HIV and cytomegalovirus. Susceptibility to IgA nephropathy is inheritable.

IgA nephropathy is the most common primary glomerular disease worldwide, particularly in Asia. It is most often seen in children and young adults, with males affected two to three times more commonly than females.

Clinical Findings

The classical presentation of IgA nephropathy is an episode of gross hematuria associated with a mucosal viral infection, often of the upper respiratory tract. The urine becomes red or smokey-colored 1–2 days after illness onset—a so-called synpharyngitic presentation in contradistinction to the latent period seen in postinfectious glomerulonephritis. However, IgA nephropathy can present anywhere along the nephritic spectrum from asymptomatic microscopic hematuria with minimal proteinuria and preserved eGFR to RPGN (Figure 22–4). Rarely, nephrotic syndrome can be present.

There are no serologic tests that aid in this diagnosis; serum complements are normal. The typical pattern of injury seen on kidney biopsy is a focal glomerulonephritis with mesangial proliferation; immunofluorescence demonstrates diffuse mesangial IgA and C3 deposits.

Treatment

The disease course of primary IgA nephropathy varies widely among patients; treatment approach needs to be tailored to risk for progression. Patients with low risk for progression (no hypertension, normal GFR, minimal proteinuria) can be monitored annually. Patients at higher risk (proteinuria greater than 1.0 g/day, decreased GFR, or hypertension or any combination of these three conditions) should be treated with an ACE inhibitor or ARB. Therapy should be titrated to reduce proteinuria to less than 1 g/day and to control blood pressure in the range of 125/75 mm Hg to 130/80 mm Hg. Prior trials suggested that corticosteroids reduced proteinuria when administered to patients with GFR greater than 50 mL/min/1.73 m² and persistent proteinuria greater than 1 g/day. However, more recent data failed to demonstrate slowing of GFR loss with corticosteroid therapy compared with use of ACE inhibitor or ARB alone; enthusiasm for glucocorticoid therapy therefore has waned. For the rare patient with IgA nephropathy and a rapidly progressive clinical course with crescent formation on biopsy, cyclophosphamide and corticosteroid therapy should be considered (see section on ANCA-associated vasculitis below). Kidney transplantation is an excellent option for patients with ESKD, but recurrent disease has been documented in 30% of patients 5–10 years posttransplant.

Prognosis

Approximately one-third of patients experience spontaneous clinical remission. Progression to ESKD occurs in 20–40% of patients. The most unfavorable prognostic indicator is proteinuria greater than 1 g/day; other include hypertension, tubulointerstitial fibrosis, glomerulosclerosis, or glomerular crescents on biopsy, and abnormal GFR on presentation.

Cambier A et al. New therapeutic perspectives for IgA nephropathy in children. *Pediatr Nephrol*. 2021;36:497. [PMID: 32040630]
 Rauen T et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. *Kidney Int*. 2020;98:1044. [PMID: 32450154]

Trimarchi H et al. IgA nephropathy: “State of the art”: a report from the 15th International Symposium on IgA Nephropathy celebrating the 50th anniversary of its first description. *Kidney Int*. 2019;95:750. [PMID: 30904065]

3. Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a systemic small-vessel leukocytoclastic vasculitis associated with IgA subclass 1 deposition in vessel walls. It is most common in children and is often associated with an inciting infection, such as group A streptococcus or other exposure. There is a male predominance. It classically presents with palpable purpura in the lower extremities and buttock area; arthralgias; abdominal symptoms, such as nausea, colic, and melena; and AKI with nephritic urine sediment. The renal lesions can be identical to those found in IgA nephropathy, and the underlying pathophysiology appears to be similar. Most patients with microscopic hematuria and minimal proteinuria recover fully over several weeks. Progressive CKD and possibly ESKD are more likely to develop in adults and in those with both nephritic and nephrotic syndromes. Although several treatment regimens of various immunosuppressive agents have been clinically tested, none are proven to alter the course of severe nephritis. Rituximab treatment and plasma exchange have been successful for severe disease according to several case reports, but clinical trials are lacking. Rapidly progressive disease with crescent formation on biopsy may be treated as in ANCA-associated vasculitis (see section below). Further details about Henoch-Schönlein purpura are provided in Chapter 20.

Maritati F et al. Adult-onset IgA vasculitis (Henoch-Schönlein): update on therapy. *Presse Med*. 2020;49:104035. [PMID: 32645417]

4. Pauci-Immune Glomerulonephritis (ANCA-Associated)

Pauci-immune necrotizing glomerulonephritis is caused by the following systemic ANCA-associated small-vessel vasculitides: granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss disease; see Chapter 20). ANCA-associated glomerulonephritis can also present as a primary renal lesion without systemic involvement; this is termed “idiopathic” crescentic glomerulonephritis.” The pathogenesis of these entities appears to involve cytokine-primed neutrophils presenting cytoplasmic antigens on their surfaces (proteinase 3 and myeloperoxidase). Circulating ANCAs then bind to these antigens and activate a neutrophil respiratory burst with consequent vascular damage; primed neutrophils also appear to activate the alternative complement pathway. Putative environmental exposures that may incite the initial response include *S aureus*

and silica. Immunofluorescence of kidney biopsy specimens demonstrates lack of immunoglobulin or complement deposition, hence the term “pauci-immune.” Renal involvement classically presents as an RPGN, but more indolent presentations can be seen.

► Clinical Findings

A. Symptoms and Signs

Symptoms of a systemic inflammatory disease, including fever, malaise, and weight loss, may be present and usually precede initial presentation by several months. In addition to hematuria and proteinuria from glomerular inflammation, some patients exhibit purpura from dermal capillary involvement and mononeuritis multiplex from nerve arteriolar involvement. Ninety percent of patients with granulomatosis with polyangiitis have upper (especially sinus) or lower respiratory tract symptoms with nodular lesions that can cavitate and bleed. Hemoptysis is a concerning sign and usually warrants hospitalization and aggressive immunosuppression.

B. Laboratory Findings

Serologically, ANCA subtype analysis is done to determine whether antiproteinase-3 antibodies (PR3-ANCA) or anti-myeloperoxidase antibodies (MPO-ANCA) are present. Most patients with granulomatosis with polyangiitis are PR3 positive; the remainder are MPO positive or, more rarely, do not demonstrate circulating ANCA. Microscopic angiitis is generally associated with MPO ANCA. Renal biopsy demonstrates necrotizing lesions and crescents on light microscopy; immunofluorescence is negative for immune complex deposition.

► Treatment

Treatment should be instituted early if aggressive disease is present. Induction therapy of high-dose corticosteroids (methylprednisolone, 1–2 g/day intravenously for 3 days, followed by prednisone, 1 mg/kg orally for 1 month, with a slow taper over the next 6 months) and cytotoxic agents (cyclophosphamide, 0.5–1 g/m² intravenously per month or 1.5–2 mg/kg orally for 3–6 months) is followed by long-term azathioprine or mycophenolate mofetil. Rituximab has been shown to be noninferior to cyclophosphamide for induction and is also used in refractory or relapsing cases and as an alternative to azathioprine for maintenance of remission. Plasma exchange is likely helpful in conjunction with induction therapy for cases complicated by pulmonary hemorrhage. Trials using the complement inhibitor avacopan in place of glucocorticoids in cyclophosphamide- or rituximab-based regimens are ongoing and appear promising.

► Prognosis

Without treatment, prognosis is extremely poor. With aggressive treatment, complete remission can be achieved in 75% of patients. Prognosis depends on the extent of renal involvement before treatment is started and may be worse in those with PR3-associated disease. ANCA titers may be monitored to follow treatment efficacy; rising titers may herald relapse.

- Geetha D et al. ANCA-associated vasculitis: Core Curriculum 2020. Am J Kidney Dis. 2020;75:124. [PMID: 31358311]
- Smith RM et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. Ann Rheum Dis. 2020;79:1243. [PMID: 32581088]
- Walsh M et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382:622. [PMID: 32053298]

5. Anti-Glomerular Basement Membrane Glomerulonephritis & Goodpasture Syndrome

Autoantibodies to epitopes of the GBM cause a glomerulonephritis (anti-GBM disease); concomitant immune attack on alveolar basement membranes results in pulmonary hemorrhage as well (Goodpasture syndrome) (Figure 22–5). Anti-GBM–associated glomerulonephritis accounts for 10–20% of patients with acute RPGN. The incidence peaks in the third decade of life during which time males are predominantly affected and lung involvement is more common, and again in the sixth and seventh decades with less gender specificity and pulmonary involvement. Goodpasture syndrome has been associated with pulmonary infection, tobacco use, and exposure to hydrocarbon solvents or alemtuzumab; HLA-DR2 and -B7 antigens may predispose as well.

Clinical Findings

A. Symptoms and Signs

The onset of disease may be preceded by an upper respiratory tract infection; hemoptysis, dyspnea, and possible respiratory failure may ensue. Other findings are consistent with an RPGN, although rare cases may present with much milder forms of the nephritic spectrum of disease (eg, glomerular hematuria and proteinuria with minimal kidney dysfunction).

B. Laboratory Findings

Chest radiographs may demonstrate pulmonary infiltrates if pulmonary hemorrhage is present. Serum complement levels are normal. Circulating anti-GBM antibodies are present in over 90% of patients. A small percentage of patients have elevated ANCA titers; these patients should be treated with plasma exchange as for anti-GBM disease. Kidney biopsy typically shows crescent formation with light microscopy, with linear IgG staining along the GBM with immunofluorescence.

Treatment

Patients with pulmonary hemorrhage and strong clinical suspicion of Goodpasture syndrome should be treated emergently—possibly prior to confirming the diagnosis with serology and kidney biopsy. Treatment is a combination of plasma exchange therapy daily for up to 2 weeks to remove circulating antibodies, and administration of corticosteroids and cyclophosphamide to prevent formation of new antibodies and control the inflammatory response. Rituximab has been used in a small number of patients

with refractory disease. Patients with oliguric AKI or who require dialysis upon presentation have a poor prognosis. Anti-GBM antibody titers should decrease as the clinical course improves.

Segelmark M et al. Anti-glomerular basement membrane disease: an update on subgroups, pathogenesis and therapies. Nephrol Dial Transplant. 2019;34(11):1826. [PMID: 30371823]

Uematsu-Uchida M et al. Rituximab in treatment of anti-GBM antibody glomerulonephritis: a case report and literature review. Medicine (Baltimore). 2019;98:e17801. [PMID: 31689860]

6. Membranoproliferative Glomerulonephritis & C3 Glomerulopathies

MPGN is a relatively rare pattern of glomerular injury that can present anywhere along the nephritic spectrum from asymptomatic glomerular hematuria to acute nephritic syndrome with bouts of gross hematuria to RPGN; nephrotic syndrome can also be seen. MPGN is classified pathologically and mechanistically into immune complex– and C3-related disease. Etiologies of immune complex–mediated MPGN include chronic infection (most commonly HCV, but also bacterial and parasitic infections), a paraproteinemia, or an underlying autoimmune disease (such as lupus); it can also be idiopathic (especially in children and young adults). In these cases, the pathogenesis is likely a chronic antigenemia leading to classical complement pathway activation with immune complex deposition; however, some cases may result from alternative complement pathway dysregulation. C3 glomerulopathies are caused by several inherited or acquired abnormalities in the alternative complement pathway. Both types result in low circulating C3 complement; C4 is low in immune complex disease. Light microscopy of both types shows varying degrees of mesangial hypercellularity, endothelial proliferation and capillary wall remodeling resulting in double contours of the GBM (“tram track” appearance). Immunofluorescence and electron microscopy provide distinguishing information. Immune complex–mediated MPGN reveals C3 and IgG or IgM staining (or both) on immunofluorescence; electron microscopy demonstrates mesangial and subepithelial deposits. C3 glomerulonephritis is distinguished by lack of immunoglobulin staining on immunofluorescence, but can appear similar to immune complex disease with respect to light and electron microscopy. An additional but rare type of C3 glomerular injury is “dense deposit disease” based on thick ribbon-like deposits seen on electron microscopy. Together, dense deposit disease and C3 glomerulonephritis are termed “C3 glomerulopathies.”

Treatment of immune complex MPGN should be directed at any identifiable underlying cause; idiopathic immune complex disease treatment is controversial and controlled trial data are lacking. For those with mild disease, ACE inhibitors and ARBs should be used. For severe disease, a combination of oral cyclophosphamide or mycophenolate mofetil plus corticosteroids could be considered; rituximab is also sometimes used. Those with RPGN and crescents on biopsy may be treated the same as those with

ANCA-associated disease provided secondary causes have been ruled out. Despite therapy, most will progress to ESKD. Treatment for the C3 glomerulopathies is in evolution as novel therapies to target the dysregulated alternative complement cascade are being explored; small, uncontrolled series suggest a possible benefit of eculizumab in some patients; others may respond to mycophenolate mofetil. Less favorable prognostic findings include dense deposit disease, early decline in GFR, hypertension, and persistent nephrotic syndrome. All types of MPGN recur with high frequency after kidney transplantation; however, dense deposit disease recurs more commonly. Plasma exchange, with or without eculizumab, has been used with mixed results to treat posttransplant recurrence of MPGN.

Fakhouri F et al. Practical management of C3 glomerulopathy and Ig-mediated MPGN: facts and uncertainties. *Kidney Int.* 2020;98:1135. [PMID: 32622830]

7. Cryoglobulin-Associated Glomerulonephritis

Essential (mixed) cryoglobulinemia is a vasculitis caused by cold-precipitable immunoglobulins (cryoglobulins). The most common underlying etiology is HCV infection; in these cases, there is clonal expansion of B lymphocytes, which produce IgM rheumatoid factor. Rheumatoid factor, HCV antigen, and polyclonal anti-HCV IgG form complexes that deposit in vessels and incite inflammation. Other overt or occult infections (eg, viral, bacterial, and fungal) as well as some autoimmune diseases and lymphoproliferative disorders can cause cryoglobulinemic vasculitis.

Patients exhibit purpuric and necrotizing skin lesions in dependent areas, arthralgias, fever, and hepatosplenomegaly. Serum complement levels are low and rheumatoid factor is often elevated. Kidney biopsy may show several different patterns of injury; there may be crescent formation, glomerular capillary thrombi, or MPGN (see above). Treatment consists of aggressively targeting the causative infection. Pulse corticosteroids, plasma exchange, rituximab, and cytotoxic agents have been used when there is little risk of exacerbating the underlying infection or when no infection is present. See also Hepatitis C Virus-Associated Kidney Disease.

Kolopp-Sarda MN et al. Cryoglobulinemic vasculitis: pathophysiological mechanisms and diagnosis. *Curr Opin Rheumatol.* 2021;33:1. [PMID: 33186245]

8. Hepatitis C Virus-Associated Kidney Disease

Kidney disease can occur in the setting of HCV infection. The three patterns of kidney injury associated with HCV are secondary MPGN (most common), cryoglobulinemic glomerulonephritis, and membranous nephropathy. The clinical presentation is dictated by the underlying pattern of injury. Many patients have elevated serum transaminases and an elevated rheumatoid factor. Hypocomplementemia is very common, with C4 typically more reduced than C3; complement levels and rheumatoid factor tend to be normal if there is a membranous pattern of injury.

Treatment

Viral suppression or eradication is the cornerstone of treatment of HCV-associated kidney disease (see Chapter 16). Use of most direct-acting antiviral agents appears to be safe in those with reduced GFR, with the exception of sofosbuvir. Therapy with rituximab and possibly corticosteroids and plasmapheresis should be initiated in patients with severe vasculitis prior to the initiation of antiviral therapy.

Comarmond C et al. Treatment of chronic hepatitis C-associated cryoglobulinemia vasculitis at the era of direct-acting antivirals. *Therap Adv Gastroenterol.* 2020;13:1756284820942617. [PMID: 32782479]

Roth D et al. KDOQI US commentary on the 2018 KDIGO clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C. *Am J Kidney Dis.* 2020;75:665. [PMID: 32279907]

9. Systemic Lupus Erythematosus

Renal involvement occurs in 35–90% of patients who have SLE, with higher estimates encompassing subclinical disease. Rates of lupus nephritis are highest in non-Whites. The pathogenesis may be dysregulated cellular apoptosis resulting in autoantibodies against nucleosomes; antibody/nucleosome complexes then bind to components of the glomerulus to form immune complex glomerular disease. See Chapter 20 for further discussion of SLE.

The term “lupus nephritis” encompasses many possible patterns of renal injury—most cases present within the nephritic spectrum (class I–IV). Nonglomerular syndromes include tubulointerstitial nephritis and vasculitis. All patients with SLE should have routine urinalyses to monitor for the appearance of hematuria or proteinuria. If urinary abnormalities are detected, kidney biopsy is often performed. The International Society of Nephrology and Renal Pathology Society classification of renal glomerular lesions is class I, minimal mesangial nephritis; class II, mesangial proliferative nephritis; class III, focal (less than 50% of glomeruli affected with capillary involvement) proliferative nephritis; class IV, diffuse (greater than 50% of glomeruli affected with capillary involvement) proliferative nephritis; class V, membranous nephropathy; and class VI, advanced sclerosis without residual disease activity. Classes III and IV, the most severe forms of lupus nephritis, are further classified as active or chronic, and global or segmental, which confers additional prognostic value.

Treatment

Individuals with class I and class II lesions generally require no treatment; corticosteroids or calcineurin inhibitors should be considered for those with class II lesions with nephrotic-range proteinuria. Transformation of these types to a more active lesion may occur and is usually accompanied by an increase in lupus serologic activity (eg, rising titers of anti-double-stranded DNA antibodies and falling C3 and C4 levels) and increasing proteinuria or falling GFR. Repeat biopsy in such patients is recommended. Hydroxychloroquine should be considered for all patients with lupus nephritis, regardless of histological class.

Patients with extensive **class III lesions** and all **class IV lesions** should receive aggressive immunosuppressive therapy. Poor prognostic indicators in patients with class III or IV lesions include elevated serum creatinine, lower complement levels, male sex, presence of antiphospholipid antibodies, nephrotic-range proteinuria, African descent (possibly in association with *APOL1* risk alleles), and poor response to therapy. Immunosuppressive therapy for class V lupus nephritis is indicated if superimposed proliferative lesions exist. Class VI lesions should not be treated.

Treatment of class III or IV lupus nephritis consists of induction therapy, followed by maintenance therapy. Induction therapy includes corticosteroids (eg, methylprednisolone 1 g intravenously daily for 3 days followed by prednisone, 1 mg/kg orally daily with subsequent taper over 6–12 months) in combination with either cyclophosphamide or mycophenolate mofetil. Data suggest that Blacks and Hispanics respond more favorably to mycophenolate mofetil than cyclophosphamide; in addition, mycophenolate mofetil has a more favorable side-effect profile than cyclophosphamide and should be favored when preservation of fertility is a consideration. Mycophenolate mofetil induction is typically given at 2–3 g orally daily, then tapered to 1–2 g/day for maintenance. Cyclophosphamide induction regimens vary but usually involve monthly intravenous pulse doses (500–1000 mg/m²) for 6 months. Induction is followed by daily oral mycophenolate mofetil or azathioprine maintenance therapy; mycophenolate mofetil may be superior to azathioprine maintenance and causes few adverse effects. Maintenance with calcineurin inhibitors may also be considered, but the relapse rate is high upon discontinuation of these agents. With standard therapy, remission rates with induction vary from 80% for partial remission to 50–60% for full remission; it may take more than 6 months to see these effects. Relapse is common and rates of disease flare are higher in those who do not experience complete remission; similarly, progression to ESKD is more common in those who relapse more frequently, or in whom no remission has been achieved. The use of add-on B-cell-targeted therapy with rituximab or belimumab for class III, IV, and/or V disease may be considered. Pure class V disease is treated with mycophenolate mofetil with or without rituximab.

The levels of various disease activity markers (double-stranded DNA antibodies, serum C3, C4, CH₅₀ levels) and the urinary protein levels and sediment activity can be useful in monitoring response to treatment; however, repeat renal biopsy yields more reliable information regarding disease activity and may be used to guide maintenance therapy withdrawal. Patients with SLE who undergo dialysis have a favorable prospect for long-term survival; interestingly, systemic lupus symptoms may become quiescent with the development of ESKD. Patients with SLE undergoing kidney transplants can have recurrent renal disease, although rates are relatively low.

Furie R et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med*. 2020;383:1117. [PMID: 32937045]
Parikh SV et al. Update on lupus nephritis: Core Curriculum 2020. *Am J Kidney Dis*. 2020;76:265. [PMID: 32220510]

NEPHROTIC SPECTRUM GLOMERULAR DISEASES



ESSENTIALS OF DIAGNOSIS

- ▶ Proteinuria with bland urine sediment (few if any cells or cellular casts).
- ▶ Nephrotic syndrome (if present) manifestations:
 - Nephrotic-range proteinuria (urine protein excretion > 3 g per 24 hours).
 - Hypoalbuminemia (albumin < 3 g/dL).
 - Peripheral edema.
 - Hyperlipidemia.
 - Oval fat bodies may be seen in the urine.

General Considerations

In American adults, the most common cause of nephrotic spectrum glomerular disease is diabetes mellitus. Other causes include minimal change disease, FSGS, membranous nephropathy, and amyloidosis. Any of these entities can present on the less severe end of the nephrotic spectrum with a bland urinalysis and proteinuria or on the most severe end of the full nephrotic syndrome. Serum creatinine may be abnormal at the time of presentation, depending on the severity and chronicity of the disease.

Clinical Findings

A. Symptoms and Signs

Patients with subnephrotic range proteinuria do not manifest symptoms of kidney disease. In those with the nephrotic syndrome, peripheral edema is present—most likely due both to sodium retention and hypoalbuminemia-induced low plasma oncotic pressure. Edema may develop solely in dependent regions, such as the lower extremities, or it may become generalized and include periorbital edema. Dyspnea due to pulmonary edema, pleural effusions, and diaphragmatic compromise due to ascites can occur.

B. Laboratory Findings

1. Urinalysis—Proteinuria occurs as a result of podocytopathy and variable alterations of the GBM. The urine dipstick is a good screening test for albuminuria; if positive, urinary protein excretion should be quantified (see earlier Proteinuria section). A spot urine protein to urine creatinine ratio gives a reasonable approximation of grams of protein excreted per day; a 24-hour urine sample for protein excretion is rarely needed.

Microscopically, the urinary sediment has relatively few cellular elements or casts. However, if marked hyperlipidemia is present, urinary oval fat bodies may be seen. They appear as “grape clusters” under light microscopy and “Maltese crosses” under polarized light.

2. Blood chemistries—The nephrotic syndrome results in hypoalbuminemia (less than 3 g/dL [30 g/L]). Hyperlipidemia, due both falling oncotic pressure triggering increased hepatic production of lipids and to decreased clearance of very low-density lipoproteins causing hypertriglyceridemia, occurs in over 50% of patients with early nephrotic syndrome, and becomes more frequent and worsens in degree as the severity of the nephrotic syndrome increases. An elevated erythrocyte sedimentation rate may be seen as a result of increased levels of fibrinogen. Heavy urinary excretion of binding proteins may result in deficiencies of vitamin D, zinc, and copper.

Laboratory testing to help elucidate the underlying cause of the glomerular disease includes complement levels, serum and urine protein electrophoresis, serum free light chains, antinuclear antibodies, PLA₂R antibody titers, HbA_{1c}, and serologic testing for hepatitis B and C, HIV, and syphilis.

3. Kidney biopsy—Kidney biopsy is often performed in adults with new-onset idiopathic nephrotic syndrome if a primary renal disease that may require immunosuppressive therapy is suspected. Chronically and significantly decreased GFR indicates irreversible kidney disease mitigating the usefulness of kidney biopsy. In the setting of long-standing diabetes mellitus type 1 or 2, proteinuric renal disease is rarely biopsied unless atypical features (such as significant glomerular hematuria or cellular casts) are also present, or if there is other reason to suspect an additional renal lesion.

Treatment

A. Protein Loss

In those with subnephrotic proteinuria, dietary protein restriction may be helpful in slowing progression of kidney disease (see CKD section).

In both diabetic and nondiabetic patients, anti-proteinuric therapy should also slow progression of kidney disease. ACE inhibitors and ARBs reduce urine protein excretion by decreasing glomerular capillary pressure and also have antifibrotic effects. They can be used in patients with reduced GFR as long as significant hyperkalemia (potassium greater than 5.2–5.5 mEq/L or mmol/L) does not occur and serum creatinine rises less than 30% after drug initiation or dose titration; patients should be monitored closely to avoid AKI and hyperkalemia. Combination therapy of an ARB and an ACE inhibitor increases risk for AKI and hyperkalemia and is not recommended.

B. Edema

Dietary salt restriction is essential for managing edema; most patients also require diuretic therapy. A combination of loop and thiazide diuretics may be needed for refractory fluid retention. Both thiazide and loop diuretics are highly protein bound; therefore, with hypoalbuminemia and decreased GFR, diuretic delivery to the kidney is reduced and larger doses often are required.

C. Hyperlipidemia

Hypercholesterolemia and hypertriglyceridemia occur as noted above. Dietary modification and exercise should be advocated; however, effective lipid-lowering usually also requires pharmacologic treatment (see Chapter 28). There is significant risk of rhabdomyolysis in patients with CKD who take gemfibrozil in combination with statins; combining fenofibrate or niacin with a statin is preferred.

D. Hypercoagulable State

Patients with nephrotic syndrome have urinary losses of antithrombin, protein C, and protein S and increased platelet activation. Patients with serum albumin less than 2 g/dL (20 g/L) have considerable risk for thrombophilia and may develop renal vein thrombosis, pulmonary embolus, and other venous thromboemboli; this is particularly likely with membranous nephropathy. Anticoagulation therapy with warfarin is warranted for at least 3–6 months in patients with evidence of thrombosis in any location and may be required indefinitely for renal vein thrombosis, pulmonary embolus, recurrent thromboemboli or when ongoing nephrotic syndrome poses a risk of thrombosis recurrence.

When to Refer

Any patient with the nephrotic syndrome should be referred immediately to a nephrologist for volume and blood pressure management, assessment for kidney biopsy, and treatment of the underlying disease. Proteinuria of more than 1 g/24 hours without the nephrotic syndrome also merits nephrology referral, though with less urgency.

When to Admit

Patients with edema refractory to outpatient therapy or rapidly worsening kidney function that may require inpatient interventions should be admitted.

- Bökenkamp A. Proteinuria—take a closer look! *Pediatr Nephrol*. 2020;35:533. [PMID: 31925536]
- Politano SA et al. Nephrotic syndrome. *Prim Care*. 2020;47:597. [PMID: 33121631]
- Wang CS et al. Nephrotic syndrome. *Pediatr Clin North Am*. 2019;66:73. [PMID: 30454752]

NEPHROTIC SPECTRUM DISEASE IN PRIMARY RENAL DISORDERS

MINIMAL CHANGE DISEASE

-  **ESSENTIALS OF DIAGNOSIS**
 - Nephrotic-range proteinuria.
 - Kidney biopsy shows no changes on light microscopy.
 - Characteristic foot-process effacement on electron microscopy.

► General Considerations

Minimal change disease is the most common cause of proteinuric renal disease in children, accounting for about 80% of cases. It often remits upon treatment with a course of corticosteroids. Indeed, children with nephrotic syndrome are often treated for minimal change disease empirically without a biopsy diagnosis. Minimal change disease is less common in adults, accounting for 20–25% of cases of primary nephrotic syndrome in those over age 40 years. This entity can be idiopathic but also occurs following viral upper respiratory infections (especially in children), in association with neoplasms such as Hodgkin disease, with drugs (lithium), and with hypersensitivity reactions (especially to NSAIDs and bee stings).

► Clinical Findings

A. Symptoms and Signs

Patients present with nephrotic syndrome, which confers susceptibility to infection, tendency toward thromboembolic events, severe hyperlipidemia, and possibly protein malnutrition. Minimal change disease can cause AKI due to renal tubular damage and interstitial edema.

B. Laboratory and Histologic Findings

There is no helpful serologic testing. Biopsy should be considered for children with nephrotic syndrome who exhibit unusual features (such as signs of other systemic illness), or who are steroid-resistant or relapse upon withdrawal of corticosteroid therapy; the latter two conditions may indicate an underlying focal and segmental glomerulosclerosis rather than minimal change disease. When kidney biopsy is performed, glomeruli appear normal on light microscopy and immunofluorescence. On electron microscopy, there is a characteristic effacement of podocyte foot processes. Mesangial cell proliferation may be seen in a subgroup of patients; this finding is associated with more hematuria and hypertension and poor response to standard corticosteroid treatment.

► Treatment

Treatment is with prednisone, 60 mg/m²/day orally; remission in steroid-responsive minimal change disease generally occurs within 4–8 weeks. Adults often require longer courses of therapy than children, requiring up to 16 weeks to achieve a response. Treatment should be continued for several weeks after complete remission of proteinuria, and dosing tapers should be individualized. A significant number of patients will relapse and require repeated corticosteroid treatment. Patients with frequent relapses or corticosteroid resistance may require cyclophosphamide, a calcineurin inhibitor (tacrolimus, cyclosporine), or rituximab to induce subsequent remissions. Progression to ESKD is rare. Complications most often arise from prolonged corticosteroid use.

Medjeral-Thomas NR et al. Randomized, controlled trial of tacrolimus and prednisolone monotherapy for adults with *de novo* minimal change disease: a multicenter, randomized, controlled trial. Clin J Am Soc Nephrol. 2020;15:209. [PMID: 31953303]

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

► General Considerations

This relatively common renal pattern of injury results from damage to podocytes; such damage may be a primary/renal-limited disorder or may be secondary to another underlying disease state. Primary causes fall into three categories: (1) heritable abnormalities in any one of several podocyte proteins, or to underlying type 4 collagen mutations; (2) polymorphisms in the *APOL1* gene in those of African ancestry; or (3) increased levels of a circulating permeability factor. Secondary causes include renal overwork injury, obesity, hypertension, chronic urinary reflux, HIV or SARS-CoV-2 infection, or analgesic or bisphosphonate exposure. Genetic testing in primary cases is becoming more common, especially in the pediatric population.

► Clinical Findings

In FSGS caused by a primary kidney disease, 80% of children and 50% of adults have overt nephrotic syndrome; however, when it develops due to a secondary cause, frank nephrotic syndrome is uncommon. Decreased GFR is present in 25–50% of those with FSGS at time of diagnosis.

Diagnosis requires kidney biopsy; there is no helpful serologic test. Light microscopy shows sclerosis of segments of some, but not all, glomeruli. On immunofluorescence, IgM and C3 are seen in the sclerotic lesions, although it is presumed that these immune components are simply trapped in the sclerotic glomeruli and not pathogenic. As in minimal change disease, electron microscopy shows fusion of epithelial foot processes.

► Treatment

Treatment for all forms of FSGS includes diuretics for edema, ACE inhibitors or ARBs to control proteinuria and hypertension, and statins or niacin for hyperlipidemia. Immunosuppression therapy (oral prednisone, 1 mg/kg/day for 4–16 weeks followed by a slow taper) is reserved for nephrotic primary FSGS cases presumed to be due to a circulating permeability factor; in those with steroid-resistance or intolerance, calcineurin inhibitors and mycophenolate mofetil can be considered. Kidney transplantation in this subgroup of FSGS patients is complicated by a relatively high relapse rate and risk of graft loss. Those with *APOL1*-associated and nonhereditary primary renal disease may not benefit from immunosuppression, although robust clinical trials are lacking. Patients with secondary FSGS do not benefit from immunosuppressive therapy; treatment should be directed at the inciting cause.

Ahn W et al. Approach to diagnosis and management of primary glomerular diseases due to podcytopathies in adults: Core Curriculum 2020. Am J Kidney Dis. 2020;75:955. [PMID: 32331832]

Anders HJ et al. SGLT2 inhibition requires reconsideration of fundamental paradigms in chronic kidney disease, 'diabetic nephropathy,' IgA nephropathy and podcytopathies with FSGS lesions. Nephrol Dial Transplant. 2020. [Epub ahead of print] [PMID: 33313878]

Shabaka A et al. Focal segmental glomerulosclerosis: state-of-the-art and clinical perspective. *Nephron*. 2020;144:413. [PMID: 32721952]

MEMBRANOUS NEPHROPATHY



ESSENTIALS OF DIAGNOSIS

- ▶ Varying degrees of proteinuria.
- ▶ Most common cause of primary adult nephrotic syndrome.
- ▶ Significant risk for hypercoagulable state if nephrotic syndrome present.
- ▶ “Spike and dome” pattern on kidney biopsy from subepithelial deposits.
- ▶ Secondary causes include hepatitis B virus and carcinomas.

► General Considerations

Membranous nephropathy is the most common cause of primary nephrotic syndrome in adults, most often presenting in the fifth and sixth decades. Primary membranous nephropathy is an autoimmune disease with reactivity against several possible podocyte antigens. Secondary disease is associated with infections, such as hepatitis B and C, endocarditis, and syphilis; underlying carcinomas (some of these cases may also involve autoimmunity to THSD7A); autoimmune disease, such as SLE, mixed connective tissue disease, and thyroiditis; and certain drugs, such as NSAIDs and captopril. The course of primary disease is highly variable, with spontaneous remission in approximately 30% of patients and progression to ESKD over 3–10 years in 50%. Poorer outcome is associated with concomitant tubulointerstitial fibrosis, male sex, elevated serum creatinine on presentation, hypertension, and proteinuria greater than 10 g/day.

Patients with membranous nephropathy and nephrotic syndrome have a higher risk of hypercoagulable state with thrombosis than nephrosis from other etiologies, including a particular predisposition to renal vein thrombosis.

► Clinical Findings

A. Symptoms and Signs

Patients may be asymptomatic or may have edema or frothy urine. Symptomatic venous thrombosis may be an initial sign. There may be symptoms or signs of an underlying infection or neoplasm (especially lung, stomach, breast, and colon cancers) in secondary membranous nephropathy.

B. Laboratory Findings

Hypoalbuminemia and hyperlipidemia are characteristic laboratory findings in the nephrotic syndrome. Evaluation for secondary causes including serologic testing for SLE, syphilis, and viral hepatitis, and age- and risk-appropriate cancer screening should be performed. Elevated titer of

circulating PLA₂R antibodies is now considered diagnostic for primary membranous nephropathy and may eliminate the need for kidney biopsy. Kidney biopsy findings in membranous nephropathy include increased capillary wall thickness without inflammatory changes or cellular proliferation; when stained with silver methenamine, a “spike and dome” pattern results from projections of excess GBM between the subepithelial immune complex deposits. Immunofluorescence shows IgG and C3 staining along capillary loops. Electron microscopy shows a discontinuous pattern of dense deposits along the subepithelial surface of the basement membrane.

► Treatment

Secondary causes must be considered prior to consideration of treatment. Primary disease treatment depends on the risk of renal disease progression. Roughly 30% of patients present with subnephrotic proteinuria (less than 3 g/day) and most have a good prognosis with conservative management, including antiproteinuric therapy with ACE inhibitor or ARB if blood pressure is greater than 125/75 mm Hg. Spontaneous remission may develop even in those with heavy proteinuria (about 30% of cases). Thus, use of immunosuppressive agents should be limited to those at highest risk for progression and with salvageable renal function. Patients with nephrotic syndrome despite 6 months of conservative management and serum creatinine less than 3.0 mg/dL (265 μmol/L) may elect therapy with rituximab or with corticosteroids and cyclophosphamide for 6 months. Calcineurin inhibitors with or without corticosteroids may be considered as well. Reduction in proteinuria may take up to 6 months, especially with rituximab-based regimens. Patients with primary membranous nephropathy are excellent candidates for transplant.

Fervenza FC et al; MENTOR Investigators. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med*. 2019;381:36. [PMID: 31269364]

Safar-Boueri L et al. Membranous nephropathy: diagnosis, treatment, and monitoring in the post-PLA2R era. *Pediatr Nephrol*. 2021;36:19. [PMID: 31811540]

Trujillo H et al. New ways of understanding membranous nephropathy. *Nephron*. 2020;144:261. [PMID: 32229730]

NEPHROTIC SPECTRUM DISEASE FROM SYSTEMIC DISORDERS

DIABETIC NEPHROPATHY



ESSENTIALS OF DIAGNOSIS

- ▶ Evidence of diabetes mellitus, typically over 10 years.
- ▶ Albuminuria usually precedes decline in GFR.
- ▶ Other end-organ damage, such as retinopathy, is common.

► General Considerations

Diabetic nephropathy is the most common cause of ESKD in the United States. The incidence is approximately 30% in both type 1 and type 2 diabetes mellitus. ESKD is much more likely to develop in persons with type 1 diabetes mellitus, in part due to fewer comorbidities and deaths before ESKD ensues. With the current epidemic of obesity and type 2 diabetes mellitus, rates of diabetic nephropathy will continue to increase. Patients at higher risk include males, African Americans, Native Americans, and those with a family history of kidney disease. Mortality rates are higher for diabetics with kidney disease compared to those without CKD.

► Clinical Findings

Diabetic nephropathy develops about 10 years after the onset of diabetes mellitus. It may be present at the time type 2 diabetes mellitus is diagnosed. The first stage of classic diabetic nephropathy is hyperfiltration with an increase in GFR, followed by the development of microalbuminuria (30–300 mg/day). With progression, albuminuria increases to greater than 300 mg/day and can be detected on a urine dipstick as overt proteinuria; the GFR subsequently declines over time. Yearly screening for microalbuminuria is recommended for all diabetic patients to detect disease at its earliest stage; however, diabetic nephropathy can, less commonly present as nonproteinuric CKD.

The most common lesion in diabetic nephropathy is diffuse glomerulosclerosis, but nodular glomerulosclerosis (Kimmelstiel-Wilson nodules) is pathognomonic. The kidneys are usually enlarged. Kidney biopsy is not required in most patients unless atypical findings are present, such as sudden onset of proteinuria, nephritic spectrum features (see above), massive proteinuria (greater than 10 g/day), urinary cellular casts, or rapid decline in GFR.

Patients with diabetes are prone to other renal diseases. These include papillary necrosis, chronic interstitial nephritis, and type 4 (hyporeninemic hypoaldosteronemic) renal tubular acidosis. Patients are more susceptible to AKI from many insults, including intravenous contrast material and concomitant use of an ACE inhibitor or ARB with NSAID.

► Treatment

With the onset of microalbuminuria, aggressive treatment is necessary. Strict glycemic control should be emphasized early in diabetic nephropathy, with recognition of risk of hypoglycemia as CKD becomes advanced (see CKD section). Recommended blood pressure goals should be tailored to the individual patient: based on the ACCORD trial, those with microalbuminuria (30–300 mg/day) and preserved GFR and those with significant CVD likely derive little benefit from blood pressure lowering much below 140/90 mm Hg, although the 2017 guidelines from the American Heart Association advocate treatment to 130/80 mm Hg or less. Those with overt proteinuria (especially more than 1 g/day) benefit from a goal of less than 130/80 mm Hg. ACE inhibitors and ARBs in those with microalbuminuria lower the rate of progression to overt proteinuria and slow progression to ESKD by reducing intraglomerular pressure and via antifibrotic effects; these

agents are not absolutely indicated in diabetic patients without albuminuria. Diabetic patients, especially with advanced CKD, are at relatively high risk for AKI and hyperkalemia with inhibition of the renin-angiotensin system, so monitoring for hyperkalemia or a decline in GFR more than 30% within ~2 weeks of the initiation or uptitration of this therapy is prudent, with dose reduction or discontinuation of therapy if these complications are encountered. *Combination ARB and ACE inhibitor therapy is not recommended due to lack of efficacy and increased adverse events of hyperkalemia and AKI.* In addition to their cardioprotective effects, the SGLT inhibitors, including canagliflozin, empagliflozin, and dapagliflozin, slow progression of diabetic nephropathy; their use is limited to those with type 2 diabetes mellitus with eGFR greater than 30 mL/min/1.73 m². Use of these agents may require reduction in diuretic dosing in those patients requiring natriuresis. Treatment of other cardiovascular risk factors and obesity is crucial. Many with diabetes have multiple comorbid conditions; therefore, in patients with ESKD who progress to dialysis, mortality over the first 5 years is high. Patients who are relatively healthy, however, benefit from renal transplantation.

Bakris G. Stemming the progression of diabetic kidney disease: the role of the primary care clinician. *J Fam Prac.* 2020;69:S81. [PMID: 33104113]

De Boer IH et al. Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. *Kidney Int.* 2020;98:839. [PMID: 32653403]

Li J et al. Decision algorithm for prescribing SGLT2 inhibitors and GLP-1 receptor agonists for diabetic kidney disease. *Clin J Am Soc Nephrol.* 2020;15:1678. [PMID: 32518100]

Tuttle KR et al. SLGT2 inhibition for CKD and cardiovascular disease in type 2 diabetes: report of a scientific workshop sponsored by the National Kidney Foundation. *Am J Kidney Dis.* 2021;77:94. [PMID: 33121838]

HIV-ASSOCIATED NEPHROPATHY

HIV-associated nephropathy usually presents with nephrotic syndrome and declining GFR in patients with active HIV infection. Most who present with HIV-associated nephropathy are of African descent with *APOL1* risk alleles (see section on Focal Segmental Glomerulosclerosis). HIV-associated nephropathy is usually associated with low CD4 counts and AIDS, but it can also be the initial presentation of HIV disease. Persons living with HIV are at risk for other kidney diseases, such as toxicity from antiretroviral medications (eg, tenofovir disoproxil fumarate), vascular disease, and diabetes, or an immune complex-mediated glomerular disease (HIV-immune complex disease).

Classic HIV-associated nephropathy is characterized by an FSGS pattern of injury with glomerular collapse; severe tubulointerstitial damage may also be present.

HIV-associated nephropathy is less common in the era of HIV screening and more effective antiretroviral therapy. Small, uncontrolled studies have shown that antiretroviral therapy slows progression of disease. ACE inhibitors or ARBs can be used to control blood pressure and proteinuria. Kidney biopsy is necessary for diagnosis and to rule

out other causes of kidney dysfunction. Patients who progress to ESKD and are otherwise healthy are good candidates for kidney transplantation.

Hamzah L et al. Optimizing antiretroviral regimens in chronic kidney disease. *Curr Opin Infect Dis.* 2019;32:1. [PMID: 30461453]
Naicker S. HIV/AIDS and chronic kidney disease. *Clin Nephrol.* 2020;93:87. [PMID: 31397267]

RENAL AMYLOIDOSIS

Amyloidosis is a relatively rare cause of nephrotic syndrome. It is caused by tissue deposition of an overproduced and abnormally folded protein (amyloid). Several different proteins can form amyloid fibrils with renal deposition. Primary amyloidosis, or AL amyloidosis, is the most common form and is due to a plasma cell dyscrasia causing overproduction and deposition of monoclonal Ig light chains (see Chapter 13). Secondary amyloidosis, or AA amyloidosis, can rarely occur in chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, or chronic infection; in these cases, there is deposition of an acute phase reactant, serum amyloid A protein. Other less common forms of amyloidosis may also be encountered.

Proteinuria, decreased GFR, and nephrotic syndrome are presenting symptoms and signs of renal involvement in amyloidosis; evidence of other organ involvement, such as the heart, is common. Serum and urine protein electrophoresis should be done as screening tests; if a monoclonal spike is found on either, serum free light chains should be quantified and the kappa:lambda ratio assessed. Amyloid-affected kidneys are often larger than 10 cm. Pathologically, glomeruli are filled with amorphous deposits that show green birefringence with Congo red staining.

AL amyloidosis progresses to ESKD in an average of 2–3 years. Five-year overall survival is less than 20%, with worse prognosis in those with advanced cardiac involvement. Standard treatment is a combination of melphalan, corticosteroids, and the proteosome inhibitor bortezomib; addition of daratumumab shows promise. Melphalan and autologous stem cell transplantation are associated with a high (45%) mortality rate but can induce remission in 80% of survivors; however, few patients are eligible for this treatment. In AA amyloidosis, remission can occur if the underlying disease is successfully treated. Renal transplantation is an option.

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Mene P et al. Monoclonal gammopathies of renal significance: renal biopsy and beyond. *Cancers (Basel).* 2020;12:1741. [PMID: 32629844]
Palladini G et al. Management of AL amyloidosis in 2020. *Hematology Am Soc Hematol Educ Program.* 2020;2020:363. [PMID: 33275753]

TUBULOINTERSTITIAL DISEASES

Tubulointerstitial disease may be acute or chronic. Acute disease is most commonly associated with medications, infectious agents, and systemic rheumatologic disorders.

Table 22–9. Causes of acute tubulointerstitial nephritis (abbreviated list).

Drug Reactions

Antibiotics

Beta-lactam antibiotics: methicillin, penicillin, ampicillin, cephalosporins
Ciprofloxacin
Erythromycin
Sulfonamides (trimethoprim-sulfamethoxazole, loop and thiazide diuretics)
Tetracycline
Vancomycin
Ethambutol
Rifampin

Nonsteroidal anti-inflammatory drugs

Diuretics

Thiazides
Furosemide

Other

Allopurinol
Cimetidine
Phenytoin
Proton pump inhibitors

Systemic Infections

Bacteria

Streptococcus
Corynebacterium diphtheriae
Legionella

Viruses

Epstein-Barr

Other

Mycoplasma
Rickettsia rickettsii
Leptospira icterohaemorrhagiae
Toxoplasma

Idiopathic

Tubulointerstitial nephritis-uveitis

Interstitial edema, infiltration with polymorphonuclear neutrophils, and accompanying ATN can be seen. (See Acute Kidney Injury, above, and Table 22–9.) Chronic disease is associated with insults from an acute factor or progressive insults without any obvious acute cause. Interstitial fibrosis and tubular atrophy are present, with a mononuclear cell predominance. The chronic disorders are described below.

CHRONIC TUBULOINTERSTITIAL DISEASES



ESSENTIALS OF DIAGNOSIS

- Kidney size is small and contracted.
- Decreased urinary concentrating ability.
- Hyperchloremic metabolic acidosis.
- Reduced GFR.

► General Considerations

The most common cause of *chronic* tubulointerstitial disease is **obstructive uropathy**, which may result from prolonged or recurrent obstruction. The major causes are prostate disease in men; ureteral calculus in a single functioning kidney; bilateral ureteral calculi; carcinoma of the cervix, colon, or bladder; and retroperitoneal tumors or fibrosis.

Reflux nephropathy from **vesicoureteral reflux** is primarily a disorder of childhood and occurs when urine passes retrograde from the bladder to the kidneys during voiding. It is the second most common cause of chronic tubulointerstitial disease. It occurs as a result of an incompetent vesicoureteral sphincter. Urine can extravasate into the interstitium, triggering an inflammatory response that leads to fibrosis over time. The inflammatory response is due to either bacteria or normal urinary components.

Analgesic nephropathy is most commonly seen in patients who ingest large quantities of pain medication. The drugs of concern are phenacetin, paracetamol, aspirin, and other NSAIDs; acetaminophen is a possible but less certain culprit. Ingestion of at least 1 g/day for 3 years of these analgesics is considered necessary for kidney dysfunction to develop, and most patients grossly underestimate their analgesic use. This disorder occurs most frequently in individuals who are using analgesics for chronic headaches, muscular pains, and arthritis; female sex, older age, and malnutrition are risk factors for analgesic nephropathy. Tubulointerstitial inflammation and papillary necrosis are seen on pathologic examination. Papillary tip and inner medullary concentrations of some analgesics are tenfold higher than in the renal cortex. Phenacetin was once a common cause of this disorder but is now rarely available. Aspirin and other NSAIDs can cause damage through intermediate metabolites, which can lead to cell necrosis. These drugs also decrease medullary blood flow (via inhibition of prostaglandin synthesis) and decrease glutathione levels, which are necessary for detoxification.

Environmental exposure to **heavy metals**—such as lead, cadmium, mercury, and bismuth—occurs infrequently now in the United States but can cause tubulointerstitial disease. Individuals at risk for lead-induced tubulointerstitial disease are those with occupational exposure (eg, welders who work with lead-based paint) and drinkers of alcohol distilled in automobile radiators (“moonshine” whiskey users). Lead is filtered by the glomerulus and is transported across the proximal convoluted tubule, where it accumulates and causes cell damage. Fibrosed arterioles and cortical scarring also lead to damaged kidneys.

A form of chronic tubulointerstitial disease disproportionately affecting male agricultural workers in Central America is an important cause of ESKD. While the exact pathophysiology is still unknown, the term **Mesoamerican nephropathy** is applied to reflect the geographic region in which this disease occurs. Affected individuals tend to be 30–50 years of age without diabetes, hypertension, or other causes of kidney disease who work under hot conditions, particularly in sugar cane or cotton fields, and are thus susceptible to dehydration.

► Clinical Findings

A. General Findings

Polyuria is common because tubular damage leads to nephrogenic diabetes insipidus, possibly from vasopressin insensitivity. Volume depletion can also occur as a result of a salt-wasting defect in some individuals.

Patients can become hyperkalemic both because the GFR is lower and the distal tubules become aldosterone resistant. Renal tubular acidosis is common and develops through three possible mechanisms: (1) reduced ammonia production in the proximal tubules, (2) inability to reabsorb bicarbonate in the proximal tubules, and (3) inability to secrete protons in the distal tubules, which is needed for urinary acidification. A type 1 or type 4 renal tubular acidosis is more commonly observed in tubulointerstitial disease, except in the case of heavy metal exposure where direct proximal tubular damage leads to a proximal (type 2) renal tubular acidosis. In contrast to acute interstitial nephritis, the urinalysis in chronic tubulointerstitial disease is often nonspecific; a few cells or broad waxy casts may be seen, but urinalysis often is bland. Proteinuria is typically less than 2 g/day, owing to inability of the proximal tubule to reabsorb freely filterable proteins.

B. Specific Findings

1. Obstructive uropathy—In partial obstruction, patients can exhibit polyuria (from tubular damage) or oliguria (due to decreased GFR). Azotemia and hypertension (due to increased renin-angiotensin production) are usually present. Abdominal, rectal, and genitourinary examinations may be helpful in detecting a distended bladder or large prostate. Urinalysis may show hematuria, pyuria, and bacteriuria but is often bland. Abdominal ultrasound may detect mass lesions, hydronephrosis, and hydronephrosis but may overlook 5% of cases. CT scanning or MRI can be considered if suspicion remains despite a normal ultrasound.

2. Vesicoureteral reflux—Vesicoureteral reflux is typically diagnosed in young children with a history of recurrent urinary tract infections but can also develop after kidney transplantation. Renal ultrasound or IVP can show renal scarring and hydronephrosis. Although most damage occurs before age 5 years, progressive deterioration to ESKD occurs.

3. Analgesics—Patients can exhibit hematuria, mild proteinuria, polyuria (from tubular damage), anemia (from GI bleeding or erythropoietin deficiency), and sterile pyuria. Sloughed papillae can be found in the urine when papillary necrosis occurs and can lead to obstruction. Although classically diagnosed by IVP, papillary necrosis is more commonly detected by CT imaging.

4. Heavy metals—Proximal tubular damage from lead exposure can cause decreased secretion of uric acid, resulting in hyperuricemia and saturnine gout. Patients commonly are hypertensive. Diagnosis is established with a calcium disodium edetate (EDTA) chelation test performed on a timed urine collection. Urine excretion of

greater than 600 mg of lead following 1 g of EDTA indicates excessive lead exposure. The proximal tubular dysfunction from cadmium can cause hypercalciuria and nephrolithiasis.

5. Mesoamerican nephropathy—In addition to low-grade proteinuria, hyperuricemia and hypokalemia are consistently (but not universally) identified among affected individuals. Although not pathognomonic, areas of glomerular ischemia (despite very mild vascular disease) that accompany chronic tubulointerstitial injury on kidney biopsy are highly suggestive of Mesoamerican nephropathy.

6. Balkan nephropathy—Patients commonly develop proteinuria, glycosuria, acidosis, and suffer urinary concentrating defects. Notably, urothelial carcinomas are present in approximately 50% of affected individuals at time of diagnosis.

Treatment

Treatment depends first on identifying the disorder responsible for kidney dysfunction. The degree of interstitial fibrosis on biopsy reflects irreversible damage, which is directly associated with the likelihood of ESKD progression. Treatment is directed at medical management of risk factors for disease progression, such as hypertension and proteinuria. Tubular dysfunction may require bicarbonate supplementation to treat metabolic acidosis or phosphorus and potassium restriction.

If hydronephrosis is present, the obstruction should be promptly relieved. Prolonged obstruction leads to further tubular damage—particularly in the distal nephron—which may become irreversible. Although surgical correction of reflux may be indicated in select circumstances, this will unlikely prevent deterioration toward ESKD if fibrosis is extensive.

Patients in whom lead nephropathy is suspected should continue chelation therapy with EDTA if there is minimal

evidence of irreversible renal damage, and continued exposure should be avoided.

Treatment of analgesic nephropathy requires withdrawal of all analgesics. Stabilization of or improvement in kidney function may occur if significant interstitial fibrosis is not present. Ensuring volume repletion during exposure to analgesics may also have some beneficial effects.

Patients with Mesoamerican nephropathy should be counseled to remain adequately hydrated and, if possible, minimize heat exposure. NSAIDs should be avoided due to their hemodynamic effects (reduced renal blood flow and glomerular filtration), which may exacerbate renal injury in states of volume depletion and hot climates.

When to Refer

- Patients with stage 3–5 CKD should be referred to a nephrologist when tubulointerstitial diseases are suspected. Other select cases of stage 1–2 CKD should also be referred, for example if renal tubular acidosis is present.
- Patients with urologic abnormalities should be referred to a urologist.

Correa-Rotter R et al. Mesoamerican nephropathy. *Semin Nephrol*. 2019;39:263. [PMID: 31054625]

CYSTIC DISEASES OF THE KIDNEY

Renal cysts are epithelium-lined cavities filled with fluid or semisolid material that develop primarily from renal tubular elements. One or more simple cysts are found in 50% of individuals over the age of 50 years. They are rarely symptomatic and have little clinical significance. In contrast, generalized cystic diseases are associated with cysts scattered throughout the cortex and medulla of both kidneys and can progress to ESKD (Table 22–10).

Table 22–10. Clinical features of renal cystic disease.

	Simple Renal Cysts	Acquired Renal Cysts	Autosomal Dominant Polycystic Kidney Disease	Medullary Sponge Kidney	Medullary Cystic Kidney
Prevalence	Common	Dialysis patients	1:1000	1:5000	Rare
Inheritance	None	None	Autosomal dominant	None	Autosomal dominant
Age at onset	20–40 years	40–60 years	Adulthood
Kidney size	Normal	Small	Large	Normal	Small
Cyst location	Cortex and medulla	Cortex and medulla	Cortex and medulla	Collecting ducts	Corticomedullary junction
Hematuria	Occasional	Occasional	Common	Rare	Rare
Hypertension	None	Variable	Common	None	None
Associated complications	None	Adenocarcinoma in cysts	Hepatic cysts, urinary tract infections, renal calculi, cerebral aneurysms	Renal calculi, urinary tract infections	Polyuria, salt wasting
Kidney failure	Never	Always	Frequently	Never	Always

SIMPLE OR SOLITARY CYSTS

Simple cysts account for 65–70% of all renal masses. They are generally found at the outer cortex and contain fluid that is consistent with an ultrafiltrate of plasma. Most are found incidentally on ultrasonographic examination. Simple cysts are typically asymptomatic but can become infected.

The major objective with simple cysts is to differentiate them from malignancy, abscess, or polycystic kidney disease. Cystic disease can develop in dialysis patients and has the potential to progress to malignancy. Ultrasound and CT scanning are recommended to evaluate these masses. Simple cysts must meet three sonographic criteria to be considered benign: (1) echo free, (2) sharply demarcated with smooth walls, and (3) an enhanced back wall (indicating good transmission through the cyst). Complex cysts can have thick walls, calcifications, solid components, and mixed echogenicity. On CT scan, simple cysts should have smooth thin walls that are sharply demarcated and should not enhance with contrast media. Renal cell carcinoma will enhance but typically is of lower density than healthy parenchyma. Arteriography can also be used to evaluate a mass preoperatively. Renal cell carcinoma is hypervasculat in 80%, hypovascular in 15%, and avascular in 5% of cases.

If a cyst has questionable imaging characteristics or is of uncertain significance, periodic reevaluation is recommended. Urologic consultation and surgical exploration may be considered. Benign cysts do not require any specific follow-up, though changes in clinical presentation should prompt repeat imaging.

Smith AD et al. Approach to renal cystic masses and the role of radiology. *Radiol Clin North Am.* 2020;58:897. [PMID: 32792122]

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Multiple cysts in both kidneys; number of cysts depends on patient age.
- ▶ Combination of hypertension and large palpable kidneys suggestive of disease.
- ▶ Autosomal dominant chromosomal abnormalities present in some patients.

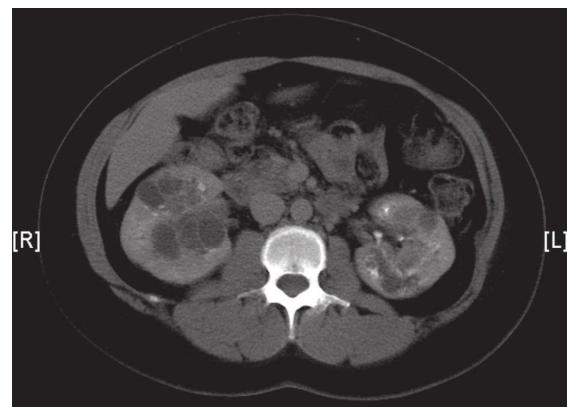
► General Considerations

Autosomal dominant polycystic kidney disease is the most common monogenic kidney disease, affecting 12.5 million individuals worldwide. ESKD develops by age 60 in up to 50% of patients. The disease has variable penetrance but accounts for 5–10% of all ESKD cases globally. At least two genes account for this disorder: *PKD1* on the short arm of chromosome 16 (85–90% of patients) and *PKD2*

on chromosome 4 (10–15%). Patients with the *PKD2* mutation have slower progression of disease and longer life expectancy than those with *PKD1*. Other sporadic cases without these mutations are also recognized.

► Clinical Findings

Abdominal or flank pain and hematuria (either microscopic or gross) are present in most patients. A history of urinary tract infections and nephrolithiasis is common. A family history of autosomal dominant polycystic kidney disease is present in 75% of cases, and more than 50% of patients have hypertension that may precede clinical manifestations. Patients have large kidneys that may be palpable on abdominal examination. The combination of hypertension and an abdominal mass should raise suspicion for the disease. Forty to 50 percent have concurrent hepatic cysts; pancreatic and splenic cysts may occur. Despite development of CKD, hemoglobin is often normal as a result of cystic erythropoietin production. Urinalysis may show hematuria and subnephrotic proteinuria. In patients with an established family history of autosomal dominant polycystic kidney disease, ultrasonography confirms the diagnosis—two or more cysts in patients under age 30 years (sensitivity of 88.5%), two or more cysts in each kidney in patients aged 30–59 years (sensitivity of 100%), and four or more cysts in each kidney in patients aged 60 years or older are diagnostic for autosomal dominant polycystic kidney disease. Importantly, these criteria do *not* apply to individuals without a known family history; patients without a known family history of polycystic kidney disease require additional diagnostic evaluation including CT scanning, which reveals innumerable cysts in cases of polycystic kidney disease (Figure 22–6); the presence of multiple hepatic cysts can aid in establishing the diagnosis. In some cases, genetic testing for *PKD1* and *PKD2* mutations may be required.



► Figure 22–6. Polycystic kidney disease. CT scan showing bilateral polycystic kidneys in a 43-year-old woman who presented with newly diagnosed hypertension and microscopic hematuria. (Used, with permission, from Michael Freckleton, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

► Complications & Treatment

A. Pain

Abdominal or flank pain is caused by infection, bleeding into cysts, and nephrolithiasis. Bed rest and analgesics are recommended. Cyst decompression can help with chronic pain.

B. Hematuria

Gross hematuria is most commonly due to cystic rupture into the renal pelvis, but it can also be caused by a kidney stone or urinary tract infection. Hematuria typically resolves within 7 days with bed rest and hydration.

C. Renal Infection

An infected renal cyst should be suspected in patients who have flank pain, fever, and leukocytosis. Importantly, urinalysis may be normal if the cyst does not communicate directly with the urinary tract. CT scans can be helpful because an infected cyst may have increased wall thickness. Bacterial cyst infections are difficult to treat. Antibiotics with cystic penetration are the agents of choice (eg, fluoroquinolones [ciprofloxacin, 500 mg every 12 hours, or levofloxacin, 500 mg once daily if GFR normal], or trimethoprim-sulfamethoxazole double-strength tablet twice daily).

D. Nephrolithiasis

Up to 20% of patients have kidney stones, primarily calcium oxalate. Hydration (2–3 L/day) is recommended in order to prevent precipitation of stones.

E. Hypertension

At the time of presentation, 50% of patients have hypertension, and it will develop in most patients during the course of the disease. Cyst-induced ischemia appears to cause activation of the renin-angiotensin system, and cyst decompression can lower blood pressure temporarily. Hypertension should be treated with an ACE inhibitor or an ARB as the preferred drug if tolerated. Intensive blood pressure control (goal less than or equal to 110/75 mm Hg) is recommended in adults younger than 50 years of age with eGFR greater than 60 mL/min/1.73m²; for all other affected individuals, goal blood pressure is less than or equal to 130/85 mm Hg.

F. Cerebral Aneurysms

About 10–15% of patients have arterial aneurysms in the circle of Willis. Screening arteriography is not recommended unless the patient has a family history of aneurysms, is employed in a high-risk profession (eg, airline pilot), or is undergoing elective surgery with a high risk of developing moderate to severe perioperative hypertension.

G. Other Complications

Vascular problems include mitral valve prolapse in up to 25% of patients, aortic aneurysms, and aortic valve abnormalities. Colonic diverticula are more common in patients with polycystic kidneys.

► Prognosis

Kidney size, reported as total kidney volume, is the best predictor of kidney function decline in patients with autosomal dominant polycystic kidney disease, and it can be measured via CT or MRI using the Mayo Classification system (www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754). Those at high risk according to this classification system may benefit from treatments that delay cyst growth. Vasopressin receptor antagonists decrease the rate of change in total kidney volume and eGFR decline, and one such medication (tolvaptan) is FDA approved for the treatment of autosomal dominant polycystic kidney disease. Liberal ingestion of water will have the same physiologic effect on vasopressin, and patients should be encouraged to drink at least 2 L of water daily. Other agents such as octreotide, sirolimus, and tyrosine kinase inhibitors decrease the rate of cyst growth but not the decline in kidney function and are thus not routinely used. Avoidance of caffeine may prevent cyst formation due to effects on G-coupled proteins.

Cornec-Le Gall E et al. Autosomal dominant polycystic kidney disease. Lancet. 2019;393:919. [PMID: 30819518]
Nobakht N et al. Advances in autosomal dominant polycystic kidney disease: a clinical review. Kidney Med. 2020;2:196. [PMID: 32734239]

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney is believed to affect less than 1% of the general population. Although present at birth, it is not usually diagnosed until the fourth or fifth decade. It is thought to occur due to disruption of the ureteric bud-metanephric mesenchyme interface, often resulting from autosomal dominant mutations in genes responsible for urogenital development. Kidneys have a marked irregular enlargement of the medullary and interpapillary collecting ducts. This is associated with medullary cysts that are diffuse, giving a “Swiss cheese” appearance in these regions.

► Clinical Findings

Nephrolithiasis is the most common clinical presentation for medullary sponge kidney. Other presentations may include hematuria (either gross or microscopic) or recurrent urinary tract infections. Common abnormalities are a decreased urinary concentrating ability and nephrocalcinosis; less common is incomplete type 1 distal renal tubular acidosis. The diagnosis is established clinically through laboratory data and imaging characteristics. As the preferred imaging test, CT shows cystic dilatation of the distal collecting tubules with a striated appearance, and calcifications in the renal collecting system. Similar findings on ultrasound may also support the diagnosis.

► Treatment

Treatment for medullary sponge kidney is supportive and aimed at underlying abnormalities such as nephrolithiasis and acidosis. Adequate fluid intake (2 L/day) helps reduce risk of stone formation. If hypercalciuria is present,

thiazide diuretics are recommended because they decrease calcium excretion. Alkali therapy is recommended if renal tubular acidosis is present.

► Prognosis

Renal function is well maintained unless there are complications from recurrent urinary tract infections and nephrolithiasis.

Pisani I et al. Ultrasound to address medullary sponge kidney: a retrospective study. *BMC Nephrol.* 2020;21:430. [PMID: 33046028]

MULTISYSTEM DISEASES WITH VARIABLE KIDNEY INVOLVEMENT

PLASMA CELL MYELOMA

Plasma cell myeloma is a malignancy of plasma cells (see Chapter 13) that can cause a variety of renal disorders. Injury is due to the toxic effects of monoclonal immunoglobulins or light chain components produced by plasma cells. "Myeloma kidney" (formally called cast nephropathy) is the most common kidney disease in plasma cell myeloma and occurs when light chains (Bence Jones protein) in the urine cause renal toxicity and tubular obstruction by precipitating in the distal tubules. Plasma cell myeloma may also cause Fanconi syndrome, a type 2 proximal renal tubular acidosis characterized by hypophosphatemia and inappropriate glycosuria. Proteinuria in "myeloma kidney" is exclusively tubular; hence, urine dipstick findings are minimal since glomerular proteinuria is not present. Hypercalcemia and hyperuricemia are frequently seen. Glomerular amyloidosis with nephrotic syndrome can develop in patients with plasma cell myeloma; in these patients, urine dipstick is positive due to glomerular epithelial cell foot process effacement and albumin "spilling" into the Bowman capsule; hematuria may or may not be present. Other conditions resulting in kidney dysfunction include plasma cell infiltration of the renal parenchyma and hyperviscosity syndrome compromising renal blood flow. The presence of myeloma-related kidney disease does not itself preclude use of contrast dye for imaging studies; standard precautions for the use of intravenous contrast and gadolinium in patients with reduced GFR apply to patients with myeloma-related kidney disease. Therapy for AKI (see Acute Kidney Injury, above) attributed to plasma cell myeloma includes correction of hypercalcemia; volume repletion; and chemotherapy for the underlying malignancy, typically with bortezomib-based agents. Plasmapheresis has been proposed to reduce the burden of circulating monoclonal proteins, but results have been equivocal and its use is controversial.

Malyszko J et al. KDIGO Controversies Conference on oncology nephrology: kidney disease in hematological malignancies and the burden of cancer after kidney transplantation. *Kidney Int.* 2020;98:1407. [PMID: 33276867]

SICKLE CELL DISEASE

Kidney dysfunction associated with sickle cell disease is most commonly due to sickling of red blood cells in the renal medulla because of low oxygen tension and hypertonicity. Congestion and stasis lead to hemorrhage, interstitial inflammation, and papillary infarcts with resultant necrosis. Clinically, hematuria is common, and proteinuria can be present as well, portending a poorer prognosis. Damage to renal capillaries also leads to diminished concentrating ability. Isosthenuria (urine osmolality equal to that of serum) is routine, and patients can easily become dehydrated. These abnormalities are also encountered in patients with sickle cell trait. Sickle cell glomerulopathy is less common but inexorably progresses to ESKD. Its primary clinical manifestation is proteinuria. Optimal treatment requires adequate hydration and control of the sickle cell disease.

Liem RI et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. *Blood Adv.* 2019;3:3867. [PMID: 31794601]

Olaniran KO et al. Kidney function decline among black patients with sickle cell trait and sickle cell disease: an observational cohort study. *J Am Soc Nephrol.* 2020;31:393. [PMID: 31810990]

TUBERCULOSIS

Renal tuberculosis usually results from hematogenous spread and is an underdiagnosed entity. Up to 20% of patients with extrapulmonary tuberculosis have urogenital involvement, of which the kidney is most commonly affected. Its classic manifestation is the presence of microscopic pyuria without bacterial growth on urine culture—or "sterile pyuria." More often, other bacteria are also present, and microscopic hematuria may coexist. Urine cultures were once the gold standard for diagnosis, but the advent of urine nucleic acid testing for tuberculosis has increased sensitivity. Characteristic findings on imaging include papillary necrosis and cavitation of the renal parenchyma. Ureteral strictures or calcifications may also be present. Kidney biopsy is not usually needed to confirm the diagnosis but reveals granulomatous inflammation and tubulointerstitial nephritis. Prompt initiation of anti-tuberculosis treatment is indicated, without which progression to ESKD occurs due to chronic inflammation and obstruction.

Kulchavanya E et al. Challenges in urogenital tuberculosis. *World J Urol.* 2020;38:89. [PMID: 30997530]

GOUT & THE KIDNEY

The kidney is the primary organ for excretion of uric acid. Patients with proximal tubular dysfunction have decreased excretion of uric acid and are more prone to gouty arthritis attacks. Depending on the pH and uric acid concentration, deposition can occur in the tubules, the interstitium, or the urinary tract. The more alkaline pH of the interstitium causes urate salt deposition,

whereas the acidic environment of the tubules and urinary tract causes uric acid crystal deposition at high concentrations.

Three disorders are commonly seen: (1) uric acid nephrolithiasis, (2) acute uric acid nephropathy, and (3) chronic urate nephropathy. Kidney dysfunction with uric acid nephrolithiasis stems from obstructive physiology. Acute uric acid nephropathy presents with direct tubulointerstitial toxicity from uric acid crystals and distal tubule obstruction caused by precipitation of uric acid crystals. Chronic urate nephropathy is caused by deposition of urate crystals in the alkaline medium of the interstitium; this can lead to fibrosis and atrophy.

Treatment between gouty attacks involves avoidance of food and drugs causing hyperuricemia (see Chapter 20), aggressive hydration, and urate-lowering therapy (such as with allopurinol and febuxostat). The three disorders mentioned above are seen in both “overproducers” and “underexcretors” of uric acid. The latter situation may seem counterintuitive; however, these patients have acidic urine, which enables precipitation of relatively insoluble uric acid crystals. For those with uric acid nephrolithiasis, fluid intake should exceed 3 L/day, and use of a urinary alkalinizing agent can be considered. Patients with hyperuricemia who do not have a history of gout or uric acid nephrolithiasis have not been shown to benefit from urate-lowering therapy.

Badve SV et al; CKD-FIX Study Investigators. Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med.* 2020;382:2504. [PMID: 32579811]

NEPHROGENIC SYSTEMIC FIBROSIS

Nephrogenic systemic fibrosis is a multisystem disorder seen only in patients with CKD (primarily with an eGFR less than 15 mL/min/1.73 m², but rarely 15–29 mL/min/1.73 m²), AKI, and after kidney transplantation. Histopathologically, there is an increase in dermal spindle cells

positive for CD34 and procollagen I. Collagen bundles with mucin and elastic fibers are also noted.

Nephrogenic systemic fibrosis was first recognized in hemodialysis patients in 1997 and has been strongly linked to use of contrast agents containing gadolinium. Incidence following gadolinium injection is approximately 1–4% in the highest risk (ESKD) population and lower in patients with less severe kidney dysfunction. The incidence has decreased over time due to limiting use of gadolinium in patients with CKD and AKI and modified gadolinium preparations. There is an FDA warning regarding avoidance of this agent for patients with an eGFR less than 30 mL/min/1.73 m².

Clinical Findings

Nephrogenic systemic fibrosis affects several organ systems, including the skin, muscles, lungs, and cardiovascular system. The most common manifestation is a debilitating fibrosing skin disorder that can range from skin-colored to erythematous papules, which coalesce to brawny patches. The skin can be thick and woody in areas and is painful out of proportion to findings on examination.

Treatment

Case reports and series describe benefit of corticosteroids, photopheresis, plasmapheresis, and sodium thiosulfate, but their true efficacy is unknown. CT is preferred to MR imaging with gadolinium when similar diagnostic information can be gleaned. If gadolinium absolutely must be used in patients on dialysis, practice guidelines recommend using no more than the standard dose and hemodialysis immediately after exposure.

Mathur M et al. Gadolinium deposition and nephrogenic systemic fibrosis: a radiologist's primer. *Radiographics.* 2020;40:153. [PMID: 31809230]

Rudnick MR et al. Risks and options with gadolinium-based contrast agents in patients with CKD: a review. *Am J Kidney Dis.* 2021;77:517. [PMID: 32861792]

23

Urologic Disorders

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HEMATURIA



ESSENTIALS OF DIAGNOSIS

- ▶ Gross hematuria requires evaluation: the upper urinary tract should be imaged, and the lower tract evaluated by cystoscopy.
- ▶ In microscopic hematuria, the workup should be risk stratified.

► General Considerations

An **upper tract source** (kidneys and ureters) can be identified in 10% of patients with gross or microscopic hematuria. For upper tract sources, stone disease accounts for 40%, medical kidney disease (medullary sponge kidney, glomerulonephritis, papillary necrosis) for 20%, renal cell carcinoma for 10%, and urothelial cell carcinoma of the ureter or renal pelvis for 5%. Medication ingestion and associated medical problems may provide diagnostic clues. Analgesic use (papillary necrosis), cyclophosphamide (chemical cystitis), antibiotics (interstitial nephritis), diabetes mellitus, sickle cell trait or disease (papillary necrosis), a history of stone disease, or malignancy should all be investigated. The **lower tract source** of gross hematuria (in the absence of infection) is most commonly from bleeding prostatic varices or urothelial carcinoma of the bladder. Microscopic hematuria in the male is most commonly from benign prostatic hyperplasia (13%), kidney stones (6%), or urethral stricture (1.4%). The presence of hematuria in patients receiving antiplatelet or anticoagulation therapy cannot be presumed to be due to the medication; a complete evaluation is warranted consisting of upper tract imaging, cystoscopy, and urine cytology (see Chapter 39 for **Bladder Cancer, Cancers of the Ureter & Renal Pelvis, Renal Cell Carcinoma, and Other Primary Tumors of the Kidney**).

► Clinical Findings

A. Symptoms and Signs

If gross hematuria occurs, a description of the timing (initial, terminal, total) may provide a clue to the localization of

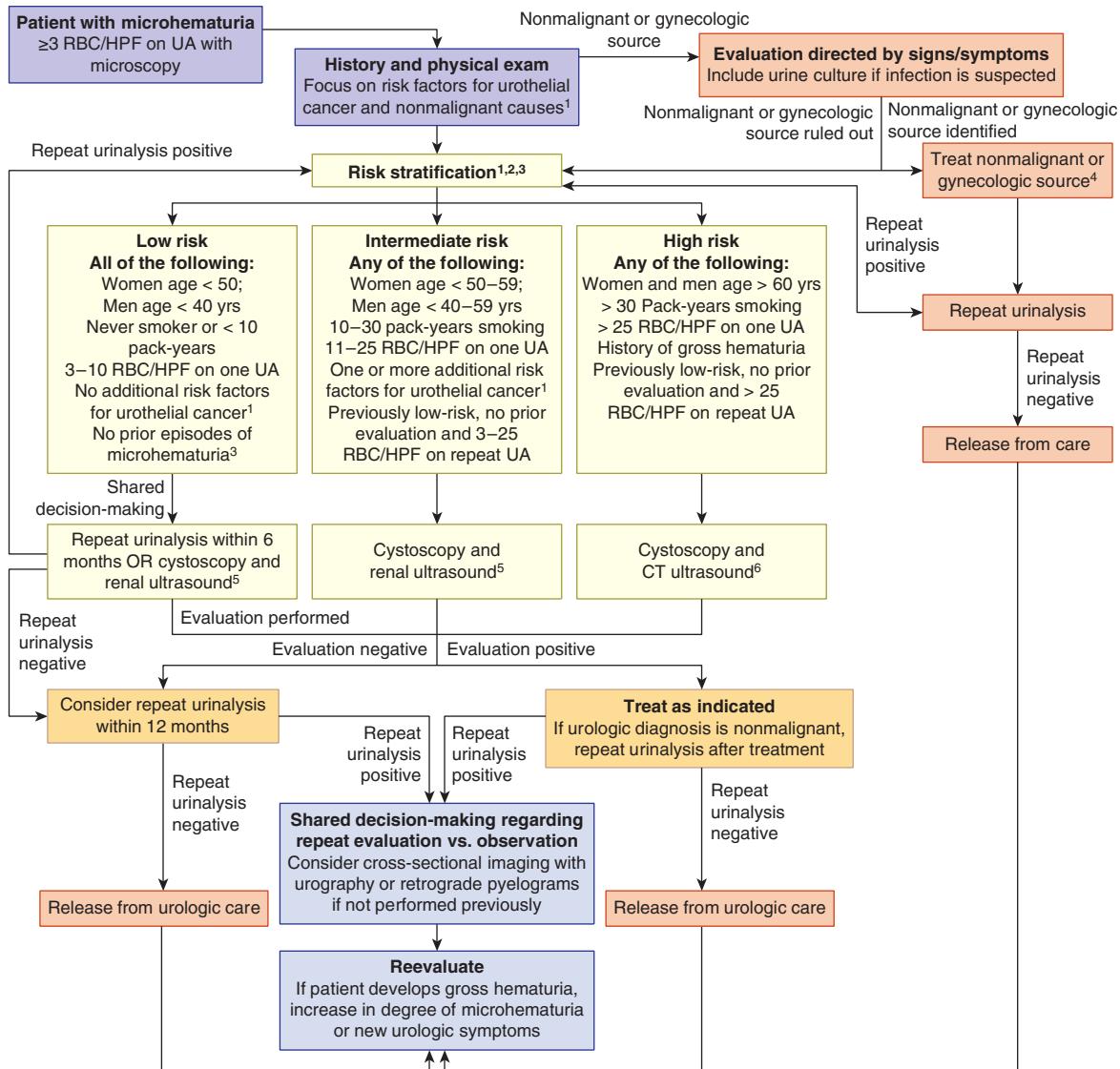
disease. Associated symptoms (ie, renal colic, irritative voiding symptoms, or constitutional symptoms) should be investigated. The history should be focused on risk factors for urothelial cancer (age, male sex, smoking history, history of gross hematuria, irritative lower urinary tract voiding symptoms, history of cyclophosphamide or ifosfamide chemotherapy, family history of urothelial carcinoma or Lynch syndrome, occupational exposure to benzene chemicals or aromatic amines, history of chronic indwelling foreign body in the urinary tract) and on nonmalignant causes. The physical examination should look for signs of systemic disease (fever, rash, lymphadenopathy, abdominal or pelvic masses) as well as signs of medical kidney disease (hypertension, volume overload). The urologic evaluation may demonstrate an enlarged prostate, flank mass, or urethral disease. The evaluation of patients with hematuria and their risk stratification should not be influenced by whether they are taking any antiplatelet or anticoagulant agents.

B. Laboratory Findings

Initial laboratory investigations include a urinalysis and urine culture. Microhematuria is defined as three or more red blood cells per high-power field on a microscopic evaluation of the urine. The degree of microscopic hematuria is important in risk stratification according to the 2020 American Urological Association hematuria guidelines (Figure 23–1). A positive dipstick reading for heme merits microscopic examination to confirm or refute the diagnosis of hematuria but is not enough to warrant workup on its own. If urinalysis and culture is suggestive of a urinary tract infection, follow-up urinalysis after treatment of the infection is important to ensure resolution of the hematuria. An estimate of kidney function should be obtained since renal insufficiency may influence the methods of further evaluation and management (eg, ability to obtain contrast imaging) of patients with hematuria. Urine cytology and other urinary-based markers are not routinely recommended in the evaluation of asymptomatic microscopic hematuria.

C. Risk Stratification

Following initial evaluation, clinicians should categorize patients with microscopic hematuria as low, intermediate, or high risk for a urothelial malignancy (Figure 23–1).



- Main risk factors for urothelial cancer are those in the AUA risk stratification system (age, male sex, smoking, degree of microhematuria and history of gross hematuria). Additional risk factors for urothelial carcinoma include but are not limited to irritative lower urinary tract voiding symptoms, history of cyclophosphamide or ifosfamide chemotherapy, family history of urothelial carcinoma or Lynch syndrome, occupational exposures to benzene chemicals or aromatic amines, history of chronic indwelling foreign body in the urinary tract.
- If medical kidney disease is suspected, consider nephrologic evaluation, but pursue concurrent risk-based urological evaluation.
- Patients may be low-risk at first presentation with microhematuria, but may be considered intermediate- or high-risk if found to have persistent microhematuria.
- There are nonmalignant and gynecologic sources of hematuria that do not require treatment and/or may confound the diagnosis of microhematuria. Clinicians can consider catheterized urine specimen in women with vaginal atrophy or pelvic organ prolapse. Clinicians must use careful judgment and patient engagement to decide whether to pursue microhematuria evaluation in the setting of chronic conditions that do not require treatment, such as the aforementioned gynecologic conditions, nonobstructing stones or BPH.
- Clinician may perform cross-sectional imaging with urography or retrograde pyelograms if hematuria persists after negative renal ultrasound.
- If contraindications to CT urogram, MR urogram or noncontrast imaging plus retrograde pyelograms.

▲ **Figure 23-1.** Microscopic hematuria: algorithmic approach to risk stratification of patients as low risk, intermediate risk, and high risk for urothelial malignancy. HPF, high-powered field; RBC, red blood cell; UA, urinalysis. (Reproduced, with permission, from Barocas D et al; Microhematuria Panel. Microhematuria: AUA/SUFU Guideline. J Urol. 2020;204:778.)

D. Evaluation

Patients with gross hematuria should have both complete evaluation of the upper tract by a CT-intravenous pyelogram (CT-IVP), or a magnetic resonance urogram (MR-urogram) with and without contrast, and evaluation of the

bladder by cystoscopy. No imaging study adequately evaluates the bladder.

Low-risk patients with microscopic hematuria should undertake a shared decision-making approach with their clinician to decide between repeat urinalyses over

the next 6 months or proceeding immediately with cystoscopy and renal ultrasound. If microscopic hematuria persists on a repeat urinalysis, then patients who did not initially undergo cystoscopy should be reclassified as intermediate- or high-risk and undergo both upper tract imaging according to their risk group, and lower tract evaluation by cystoscopy.

Intermediate-risk patients should undergo both upper tract imaging with renal ultrasound and lower tract evaluation by cystoscopy.

High-risk patients should undergo upper tract evaluation with CT-IVP (preferred), MR-urogram (if CT-IVP contraindicated), and cystoscopic evaluation of the bladder. If there are contraindications to CT-IVP and MR-urogram, clinicians may perform noncontrast axial imaging along with retrograde pyelography at the time of cystoscopy.

► Follow-Up

In patients with negative hematuria evaluations, it is typically recommended that a urinalysis with microscopy be repeated at 6–12 months. Patients with a negative follow-up urinalysis require no further evaluation. If microscopic hematuria persists or recurs on follow-up urinalyses, then providers should engage patients with shared decision-making regarding repeat evaluation. However, patients who develop gross hematuria or increased severity of microscopic hematuria should be referred for repeat upper and lower tract evaluation.

► When to Refer

In the absence of a clear benign etiology (such as an infection, menstruation, vigorous exercise, acute stone event, medical renal disease, viral illness, trauma, or recent urologic procedure), hematuria (either gross or microscopic) requires evaluation.

- Barocas DA et al. Microhematuria: AUA/SUFU Guideline. *J Urol.* 2020;204:778. [PMID: 32698717]
Peterson LM. Hematuria. *Prim Care.* 2019;46:265. [PMID: 31030828]
Yecies T et al. Evaluation of the risks and benefits of computed tomography urography for assessment of gross hematuria. *Urology.* 2019;133:40. [PMID: 31255539]

GENITOURINARY TRACT INFECTIONS

Urinary tract infections are among the most common entities encountered in medical practice. In acute infections, a single pathogen is usually found, whereas two or more pathogens are often seen in chronic infections. Coliform bacteria are responsible for most non-nosocomial, uncomplicated urinary tract infections, with *Escherichia coli* being the most common. Such infections typically are sensitive to a wide variety of orally administered antibiotics and respond quickly. Nosocomial infections often are due to more resistant pathogens and may require parenteral antibiotics. Renal infections are of particular concern because if they are inadequately treated, loss of kidney function

may result. A urine culture is recommended for patients with suspected urinary tract infection and ideally should be obtained prior to the initiation of antibiotic therapy. Previously, a colony count greater than 10^5 /mL was considered the criterion for urinary tract infection, though up to 50% of women with symptomatic infections may have lower counts. In addition, the presence of pyuria correlates poorly with the diagnosis of urinary tract infection, and thus urinalysis alone is not adequate for diagnosis. With respect to treatment, tissue infections (pyelonephritis, prostatitis) require therapy for 1–2 weeks, while mucosal infections (cystitis) require only 1–3 days of therapy.

1. Acute Cystitis



ESSENTIALS OF DIAGNOSIS

- ▶ Irritative voiding symptoms.
- ▶ Patient usually afebrile.
- ▶ Positive urine culture; blood cultures may also be positive.

► General Considerations

Acute cystitis is an infection of the bladder, most commonly due to the coliform bacteria (especially *E coli*) and occasionally gram-positive bacteria (enterococci). The route of infection is typically ascending from the urethra. Viral cystitis due to adenovirus is sometimes seen in children but is rare in immunocompetent adults. Uncomplicated cystitis in men is rare and implies a pathologic process such as infected stones, prostatitis, or chronic urinary retention requiring further investigation.

► Clinical Findings

A. Symptoms and Signs

Irritative voiding symptoms (frequency, urgency, dysuria) and suprapubic discomfort are common. Women may experience gross hematuria, and symptoms may often appear following sexual intercourse. Physical examination may elicit suprapubic tenderness, but examination is often unremarkable. Systemic toxicity is absent.

B. Laboratory Findings

Urinalysis shows pyuria, bacteriuria, and varying degrees of hematuria. The degree of pyuria and bacteriuria does not necessarily correlate with the severity of symptoms. Urine culture is positive for the offending organism, but colony counts exceeding 10^5 /mL are not required for the diagnosis. Patients with asymptomatic bacteriuria or colonization are expected to have positive urine cultures but do not require treatment except in pregnant women. Patients with long-term urinary catheters (indwelling urinary [Foley] or suprapubic catheter) or urostomy urinary diversions are expected to be colonized with

bacteria, and thus, urinalysis and urine culture are most helpful in directing therapy rather than determining whether symptomatic infection exists.

C. Imaging

Because uncomplicated cystitis is rare in men, elucidation of the underlying problem with appropriate investigations, such as abdominal ultrasonography, postvoid residual testing, and cystoscopy, is warranted. Follow-up imaging using CT scanning is warranted if pyelonephritis, recurrent infections, or anatomic abnormalities are suspected.

► Differential Diagnosis

In women, infectious processes such as vulvovaginitis and pelvic inflammatory disease can usually be distinguished by pelvic examination and urinalysis. In men, urethritis and prostatitis may be distinguished by physical examination (urethral discharge or prostatic tenderness).

Noninfectious causes of cystitis-like symptoms include pelvic irradiation, chemotherapy (cyclophosphamide), bladder carcinoma, interstitial cystitis, voiding dysfunction disorders, bladder irritants, and psychosomatic disorders.

► Prevention

The risk of developing a urinary tract infection can be reduced by drinking plenty of fluid and completely emptying the bladder frequently. Women in whom urinary tract infections tend to develop after intercourse should be advised to void before, and especially after intercourse, and may benefit from a postcoital single-dose of antibiotic. Postmenopausal women with recurrent urinary tract infections (three or more episodes per year) may benefit from a topical estrogen cream. Daily cranberry tablets may reduce the risk of cystitis, though the data are conflicting. Prophylactic antibiotics are generally discouraged. Prior to institution of antibiotic prophylaxis, a thorough urologic evaluation is warranted to exclude any anatomic abnormality (eg, stones, reflux, fistula). An initial course of 6–12 months of prophylactic antibiotics can be offered, though the benefits of prophylactic antibiotics should be weighed against the risks associated with expected bacterial resistance.

The risk of acquiring a catheter-associated urinary tract infection in hospitalized patients can be minimized by using indwelling catheters only when necessary, implementing systems to ensure removal of catheters when no longer needed, using antimicrobial catheters in high-risk patients, using external collection devices (condom catheters) in select men, identifying significant postvoid residuals by ultrasound, maintaining proper insertion techniques, and utilizing alternatives such as intermittent catheterization.

► Treatment

Uncomplicated cystitis in women can be treated with short-term antimicrobial therapy, which consists of single-dose therapy or 1–7 days of therapy. Fosfomycin, nitrofurantoin, and trimethoprim-sulfamethoxazole are the medications of choice for uncomplicated cystitis (Table 23–1). The US

Food and Drug Administration (FDA) advises restricting fluoroquinolone use for uncomplicated infections. Local patterns of bacterial resistance should be consulted to identify best treatment options. Some antibiotics may be ineffective because of the emergence of resistant organisms. A review of the literature proposed that acute uncomplicated cystitis in women can be diagnosed without office evaluation or urine culture, and that appropriate first-line therapies include trimethoprim-sulfamethoxazole (160/800 mg twice daily for 3 days), nitrofurantoin (100 mg twice daily for 5–7 days), or fosfomycin trometamol (3 g single dose). In men, uncomplicated urinary tract infection is rare; thus, the duration of antibiotic therapy depends on the underlying etiology. Hot sitz baths or urinary analgesics (phenazopyridine, 200 mg orally three times daily) may provide additional symptomatic relief. Postmenopausal women with recurrent cystitis can be treated with vaginal estrogen cream 0.5 g nightly for 2 weeks and then twice weekly thereafter.

► Prognosis

Infections typically respond rapidly to therapy, and failure to respond suggests resistance to the selected medication or anatomic abnormalities requiring further investigation.

► When to Refer

- Suspicion or radiographic evidence of anatomic abnormality.
- Evidence of urolithiasis.
- Recurrent cystitis due to bacterial persistence.

Babikar A et al. Fosfomycin for treatment of multidrug-resistant pathogens causing urinary tract infection: a real-world perspective and review of the literature. *Diagn Microbiol Infect Dis.* 2019;95:114856. [PMID: 31307867]

Gill CM et al. A review of nonantibiotic agents to prevent urinary tract infections in older women. *J Am Med Dir Assoc.* 2020;21:46. [PMID: 31227473]

Kim DK et al. Reappraisal of the treatment duration of antibiotic regimens for acute uncomplicated cystitis in adult women: a systematic review and network meta-analysis of 61 randomised clinical trials. *Lancet Infect Dis.* 2020;20:1080. [PMID: 32446327]

Nicolle LE et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2019;68:1611. [PMID: 31506700]

2. Acute Pyelonephritis

ESSENTIALS OF DIAGNOSIS

- Fever.
- Flank pain.
- Irritative voiding symptoms.
- Positive urine culture.

Table 23–1. Empiric therapy for urinary tract infections.

Diagnosis	Antibiotic	Route	Duration	Cost per Duration Noted ¹
Acute cystitis ^a	First-line: Trimethoprim-sulfamethoxazole, 160/800 mg, (one DS tablet) every 12 hours ² Nitrofurantoin (macrocrystals), 100 mg every 12 hours Fosfomycin, 3 g packet once Second-line: Ciprofloxacin, 250 mg every 12 hours ³ Levofloxacin, 250–500 mg daily ³ Alternative agents: Cephalexin, 500 mg every 6–12 hours Amoxicillin/clavulanate, 500/125 mg every 12 hours Cefpodoxime, 100 mg every 12 hours	Oral	3 days	\$2.25
	Nitrofurantoin (macrocrystals), 100 mg every 12 hours	Oral	5 days	\$31.35
	Fosfomycin, 3 g packet once	Oral	1 day	\$109.52
	Ciprofloxacin, 250 mg every 12 hours ³	Oral	3 days	\$25.28
	Levofloxacin, 250–500 mg daily ³	Oral	3 days	\$46.80
	Cephalexin, 500 mg every 6–12 hours	Oral	7 days	\$33.88
	Amoxicillin/clavulanate, 500/125 mg every 12 hours	Oral	3 days	\$10.16
	Cefpodoxime, 100 mg every 12 hours	Oral	3 days	\$30.66
Acute pyelonephritis ^a	Hospitalized: Ampicillin, 1 g every 6 hours, plus gentamicin, 1 mg/kg every 8 hours Ceftriaxone, 1 g daily Ciprofloxacin, 400 mg every 12 hours ³ Non-hospitalized: Initial intravenous dose⁴: Ceftriaxone, 1 g Ciprofloxacin, 400 mg ³ Gentamicin, 5 mg/kg Followed by one of these oral regimens: Ciprofloxacin, 500 mg every 12 hours ³ Levofloxacin, 750 mg daily ³ Trimethoprim-sulfamethoxazole, 160/800 mg (one DS tablet) every 12 hours ²	Intravenous	14 days	\$264.46, not including intravenous supplies
	Ceftriaxone, 1 g daily	Intravenous	14 days	\$25.34
	Ciprofloxacin, 400 mg every 12 hours ³	Intravenous	14 days	\$99.68
	Ceftriaxone, 1 g	Intravenous	Once	\$1.81
	Ciprofloxacin, 400 mg ³	Intravenous	Once	\$3.56
	Gentamicin, 5 mg/kg	Intravenous	Once	\$3.00
	Ciprofloxacin, 500 mg every 12 hours ³	Oral	7 days	\$4.87
	Levofloxacin, 750 mg daily ³	Oral	5 days	\$123.05
	Trimethoprim-sulfamethoxazole, 160/800 mg (one DS tablet) every 12 hours ²	Oral	14 days	\$10.44
Acute bacterial prostatitis ^b	Hospitalized: Ampicillin, 2 g every 6 hours, plus gentamicin, 1.5 mg/kg every 8 hours Followed by one of these outpatient oral regimens: Trimethoprim-sulfamethoxazole, 160/800 mg (one DS tablet) every 12 hours ² Ciprofloxacin, 250–500 mg every 12 hours ³	Intravenous	Until afebrile	\$37.78/day, not including intravenous supplies
	Trimethoprim-sulfamethoxazole, 160/800 mg (one DS tablet) every 12 hours ²	Oral	3 weeks	\$15.67/3 weeks
	Ciprofloxacin, 250–500 mg every 12 hours ³	Oral	3 weeks	\$14.57/3 weeks

(continued)

Table 23–1. Empiric therapy for urinary tract infections. (continued)

Diagnosis	Antibiotic	Route	Duration	Cost per Duration Noted ¹
Chronic bacterial prostatitis ^b				
	First-line:			
	Ciprofloxacin, 500 mg every 12 hours ³	Oral	1–3 months	\$20.81/month
	Levofloxacin, 750 mg daily ³	Oral	28 days	\$689.08
	Second-line:			
	Doxycycline, 100 mg twice daily	Oral	4–12 weeks	\$118.20/month
	Azithromycin, 500 mg daily	Oral	4–12 weeks	\$81.98/month
	Clarithromycin, 500 mg daily	Oral	4–12 weeks	\$117.00/month
Acute epididymitis ^c				
Sexually transmitted (under age 35)	Ceftriaxone, 250 mg as single dose, plus Doxycycline, 100 mg every 12 hours	Intramuscular Oral	Once 10 days	\$0.90/250 mg \$39.40 (10 days)
Sexually transmitted in men who practice insertive anal sex	Ceftriaxone, 250 mg as single dose plus Levofloxacin, 500 mg daily ³ or Ofloxacin, 300 mg every 12 hours ³	Intramuscular Oral Oral	Once 10 days 10 days	\$0.90/250 mg \$156.00 (10 days) \$113.86 (10 days)
Non-sexually transmitted, usually enteric organisms (over age 35)	Levofloxacin, 500 mg daily ³ Ofloxacin, 300 mg every 12 hours ³	Oral Oral	10 days 10 days	\$156.00 (10 days) \$113.86 (10 days)

¹Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

²Increasing resistance noted (up to 20%).

³FDA advises restricting fluoroquinolone use for some uncomplicated infections, including uncomplicated urinary tract infections, because of mental health side effects including disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium; musculoskeletal side effect risks of tendinitis and tendon rupture; neuromuscular side effect of peripheral neuropathy and worsening of myasthenia gravis; and endocrine side effect of coma from hypoglycemia.

⁴Infectious Diseases Society of America (IDSA) recommends an initial 24-hour intravenous dose of antibiotic when local resistance of the selected oral regimen exceeds 10%. Please refer to local antibiograms.

Sources:

^aTreatment regimens based upon Gupta K et al. Treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103.

^bTreatment regimens based upon Sharp VJ et al. Prostatitis: diagnosis and treatment. Am Fam Physician. 2010;82:397.

^cTreatment regimens based upon Workowski KA et al; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1.

► General Considerations

Acute pyelonephritis is an infectious inflammatory disease involving the kidney parenchyma and renal pelvis. Gram-negative bacteria are the most common causative agents including *E coli*, *Proteus*, *Klebsiella*, *Enterobacter*, and *Pseudomonas*. Gram-positive bacteria are less commonly seen but include *Enterococcus faecalis* and *Staphylococcus aureus*. The infection usually ascends from the lower urinary tract—with the exception of *S aureus*, which usually is spread by a hematogenous route.

► Clinical Findings

A. Symptoms and Signs

Symptoms include fever, flank pain, shaking chills, and irritative voiding symptoms (urgency, frequency, dysuria).

Associated nausea and vomiting and diarrhea are common. Signs include fever and tachycardia. Costovertebral angle tenderness is usually pronounced.

B. Laboratory Findings

Complete blood cell count shows leukocytosis and a left shift. Urinalysis shows pyuria, bacteriuria, and varying degrees of hematuria. White cell casts may be seen. Urine culture demonstrates growth of the offending organism, and blood culture may also be positive.

C. Imaging

In complicated pyelonephritis, renal ultrasound may show hydronephrosis from a stone or other source of obstruction. CT scan may demonstrate decreased perfusion of the

kidney or focal areas within the kidney and nonspecific perinephric fat stranding.

► Differential Diagnosis

The differential diagnosis includes acute cystitis or a lower urinary source. Acute intra-abdominal disease such as appendicitis, cholecystitis, pancreatitis, or diverticulitis must be distinguished from pyelonephritis. A normal urinalysis is usually seen in gastrointestinal disorders; however, on occasion, inflammation from adjacent bowel (appendicitis or diverticulitis) may result in hematuria or sterile pyuria. Abnormal liver biochemical tests or elevated amylase levels may assist in the differentiation. Lower-lobe pneumonia is distinguishable by the abnormal chest radiograph.

In males, the main differential diagnosis for acute pyelonephritis also includes acute epididymitis and acute prostatitis. Physical examination and the location of the pain should permit this distinction.

► Complications

Sepsis with shock can occur with acute pyelonephritis. In diabetic patients, emphysematous pyelonephritis resulting from gas-producing organisms may be life-threatening if not adequately treated. Healthy adults usually recover complete kidney function, yet if coexistent kidney disease is present, scarring or chronic pyelonephritis may result. Inadequate therapy could result in abscess formation.

► Treatment

Urine and blood cultures are obtained to identify the causative agent and to determine antimicrobial sensitivity. In the inpatient setting, intravenous ampicillin and an aminoglycoside are initiated prior to obtaining sensitivity results (Table 23–1). In the outpatient setting, empiric therapy may be initiated (Table 23–1). Antibiotics are adjusted according to sensitivities. If local antibiograms demonstrate local resistance rates for the oral regimen exceed 10%, an initial 24-hour intravenous dose of antibiotic is required. Fevers may persist for up to 72 hours even with appropriate antibiotics; failure to respond within 48 hours warrants imaging (CT or ultrasound) to exclude complicating factors that may require intervention (such as a perinephric abscess or an obstructing stone). Catheter drainage may be necessary in the face of urinary retention and nephrostomy drainage if there is ureteral obstruction. In inpatients, intravenous antibiotics are continued for 24 hours after the fever resolves, and oral antibiotics are then given to complete a 14-day course of therapy.

► Prognosis

With prompt diagnosis and appropriate treatment, acute pyelonephritis carries a good prognosis. Complicating factors, underlying kidney disease, and increasing patient age may lead to a less favorable outcome.

► When to Refer

- Evidence of complicating factors (urolithiasis, obstruction).
- Failure of clinical improvement in 48 hours.

► When to Admit

- Severe infections or complicating factors, evidence of sepsis, or need for parenteral antibiotics.
- Need for radiographic imaging or drainage of urinary tract obstruction.

Bader MS et al. Treatment of urinary tract infections in the era of antimicrobial resistance and new antimicrobial agents. Postgrad Med. 2020;132:234. [PMID: 31608743]

Johnson JR et al. Acute pyelonephritis in adults. N Engl J Med. 2018;378:1162. [PMID: 29562155]

Kolman KB. Cystitis and pyelonephritis: diagnosis, treatment and prevention. Prim Care. 2019;46:191. [PMID: 31030820]

Wagenlehner FME et al; EPIC Study Group. Once-daily plazomicin for complicated urinary tract infections. N Engl J Med. 2019;380:729. [PMID: 30786187]

3. Acute Bacterial Prostatitis

ESSENTIALS OF DIAGNOSIS



- ▶ Fever.
- ▶ Irritative voiding symptoms.
- ▶ Perineal or suprapubic pain; exquisite tenderness common on rectal examination.
- ▶ Positive urine culture.

► General Considerations

Acute bacterial prostatitis is usually caused by gram-negative rods, especially *E coli* and *Pseudomonas* species, and less commonly by gram-positive organisms (eg, enterococci). The most likely routes of infection include ascent up the urethra and reflux of infected urine into the prostatic ducts. Lymphatic and hematogenous routes are probably rare.

► Clinical Findings

A. Symptoms and Signs

Perineal, sacral, or suprapubic pain, fever, and irritative voiding complaints are common. Varying degrees of obstructive symptoms may occur as the acutely inflamed prostate swells, which may lead to urinary retention. High fevers and a warm and often exquisitely tender prostate are detected on examination. Care should be taken to perform a gentle rectal examination, since vigorous manipulations may result in septicemia. Prostatic massage is contraindicated.

B. Laboratory Findings

Complete blood count shows leukocytosis and a left shift. Urinalysis shows pyuria, bacteriuria, and varying degrees of hematuria. Urine or expressed prostatic secretions cultures will demonstrate the offending pathogen (Table 23–2).

Table 23–2. Clinical characteristics of prostatitis and chronic pelvic pain syndrome.

Findings	Acute Bacterial Prostatitis	Chronic Bacterial Prostatitis	Chronic Nonbacterial Prostatitis	Chronic Pelvic Pain Syndrome
Fever	+	–	–	–
Urinalysis	+	–	–	–
Expressed prostate secretions	Contraindicated	+ WBC + Culture	+ WBC – Culture	– WBC – Culture
Postprostatic massage urine specimen	Contraindicated	+ Culture	– Culture	– Culture

WBC, white blood cell.

C. Imaging

Acute prostatitis can progress to prostatic abscess and a pelvic CT or transrectal ultrasound is indicated in patients who do not respond to antibiotics in 24–48 hours.

► Differential Diagnosis

Acute pyelonephritis or acute epididymitis should be distinguishable by the location of pain as well as by physical examination. Acute diverticulitis is occasionally confused with acute prostatitis; however, the history and urinalysis should permit clear distinction. Urinary retention from prostatic enlargement is distinguishable by initial or follow-up rectal examination and postvoid residual bladder scan.

► Treatment

Hospitalization may be required, and parenteral antibiotics (ampicillin and aminoglycoside) should be initiated until organism sensitivities are available (Table 23–1). After the patient is afebrile for 24–48 hours, oral antibiotics (eg, quinolones if organism is sensitive) are used to complete 4–6 weeks of therapy. If urinary retention develops, an in-and-out catheterization to relieve the initial obstruction or short-term (12 hours) small indwelling urinary catheter is appropriate.

► Prognosis

Acute bacterial prostatitis is relatively simple to treat, since bacteria are eradicated with appropriate antibiotic therapy. Progression to chronic bacterial prostatitis is rare.

► When to Refer

- Evidence of urinary retention.
- Evidence of chronic prostatitis.

► When to Admit

- Signs of sepsis.
- Need for surgical drainage of bladder or prostatic abscess.

Kwan ACF et al. Fosfomycin for bacterial prostatitis: a review. *Int J Antimicrob Agents*. 2020;56:106106. [PMID: 32721595]
Lupo F et al. Is bacterial prostatitis a urinary tract infection? *Nat Rev Urol*. 2019;16:203. [PMID: 30700862]

Xiong S et al. Pharmacological interventions for bacterial prostatitis. *Front Pharmacol*. 2020;11:504. [PMID: 32425775]

4. Chronic Bacterial Prostatitis



ESSENTIALS OF DIAGNOSIS

- Irritative voiding symptoms.
- Perineal or suprapubic discomfort, often dull and poorly localized.
- Abnormal expressed prostatic secretions and positive culture.

► General Considerations

Although chronic bacterial prostatitis may evolve from acute bacterial prostatitis or recurrent urinary tract infection, over half of affected men have no history of acute infection. Gram-negative rods are the most common etiologic agents, but only one gram-positive organism (*Enterococcus*) is associated with chronic infection. Routes of infection are the same as discussed for acute infection.

► Clinical Findings

A. Symptoms and Signs

Clinical manifestations are variable. Most patients have varying degrees of irritative voiding symptoms, urethral pain, and obstructive urinary symptoms. Low back and perineal pain are common. Many patients (25–43%) report a history of urinary tract infections. Physical examination is often unremarkable, although the prostate may feel normal, boggy, or indurated. A postvoid residual urine volume should be measured to evaluate for urinary retention.

B. Laboratory Findings

Urinalysis is normal unless a secondary cystitis is present. Expressed prostatic secretions or a postprostatic massage voided urine or both demonstrate increased numbers of leukocytes (greater than 5–10 per high-power field) and

bacterial growth when cultured (Table 23–2). Culture of the secretions and the postprostatic massage urine specimen is necessary to make the diagnosis. Leukocyte and bacterial counts from expressed prostatic secretions do not correlate with severity of symptoms. If no organisms are identified on culture, then nonbacterial prostatitis, chronic pelvic pain, or interstitial cystitis should be suspected.

C. Imaging

Imaging tests are typically not necessary.

Differential Diagnosis

Chronic urethritis may mimic chronic prostatitis, though cultures of the fractionated urine may localize the source of infection to the initial specimen, which comes from the urethra. Cystitis may be secondary to prostatitis, but urine samples after prostatic massage may localize the infection to the prostate. Other chronic prostatic conditions, such as nonbacterial prostatitis, chronic pelvic pain, or interstitial cystitis, are distinguished from chronic bacterial prostatitis by examination and culture of prostatic secretions and postprostatic massage urine sample. Anal disease may share some of the symptoms of prostatitis, but physical examination should distinguish between the two.

Treatment

As in acute prostatitis, if patients are febrile or systemically ill, they may require admission and initial intravenous therapy with broad-spectrum antibiotics, such as ampicillin plus gentamicin, a third-generation cephalosporin, or a fluoroquinolone (Table 23–1). Therapy would then continue with oral trimethoprim-sulfamethoxazole, fluoroquinolone, or extended-spectrum beta-lactamase antibiotic based on culture and sensitivities of expressed prostatic secretion or postprostatic massage urine. The optimal duration of therapy remains controversial, ranging from 4 to 6 weeks. Symptomatic relief may be provided by anti-inflammatory agents (indomethacin, ibuprofen), hot sitz baths, and alpha-blockers (tamsulosin, alfuzosin, silodosin).

Prognosis

Chronic bacterial prostatitis may be recurrent, can be difficult to cure, and often requires repeated courses of therapeutic antibiotics.

When to Refer

- Persistent symptoms.
- Consideration of enrollment in clinical trials.

Su ZT et al. Management of chronic bacterial prostatitis. *Curr Urol Rep*. 2020;21:29. [PMID: 32488742]
Zaidi N et al. Management of chronic prostatitis. *Curr Urol Rep*. 2018;19:88. [PMID: 30167899]

5. Nonbacterial Chronic Prostatitis/Chronic Pelvic Pain Syndrome



ESSENTIALS OF DIAGNOSIS

- Irritative voiding symptoms.
- Perineal or suprapubic discomfort, similar to that of chronic bacterial prostatitis.
- Presence of white blood cells in expressed prostatic secretions but negative culture.

General Considerations

Nonbacterial chronic prostatitis and chronic pelvic pain syndromes are incompletely understood with symptoms due to interrelated cascade of inflammatory, immunologic, endocrine, muscular, neuropathic, and psychologic mechanisms. There are a variety of subtypes based on the most pronounced symptoms. Chronic perineal, suprapubic, or pelvic pain is the most common presenting symptom, though men may complain of pain in the testes, groin, and low back. Pain during or after ejaculation is one of the most prominent and bothersome symptoms in many patients. Psychosocial factors (depression, anxiety, catastrophizing, poor social support, stress) also likely play an important role in the exacerbation of chronic pelvic pain symptoms. Because the cause of nonbacterial prostatitis remains unknown, the diagnosis is usually one of exclusion, and treatment may require multimodal therapy. Quality of life is greatly decreased for many patients with chronic nonbacterial prostatitis and chronic pelvic pain syndrome.

Clinical Findings

A. Symptoms and Signs

The clinical presentation is identical to that of chronic bacterial prostatitis; however, no history of urinary tract infections is typically present. The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) (www.prostatitisclinic.com/graphics/questionnaire2.pdf) has been validated to quantify symptoms of chronic nonbacterial prostatitis or chronic pelvic pain syndrome.

B. Laboratory Findings

Increased numbers of leukocytes are typically seen in expressed prostatic secretions, but cultures of both expressed prostatic secretions and postprostatic urine specimens are negative.

Differential Diagnosis

The major distinction is from chronic bacterial prostatitis. The absence of positive cultures makes the distinction (Table 23–2). In older men with irritative voiding symptoms and negative cultures, bladder cancer must be excluded. Urinary cytologic examination and cystoscopy are warranted.

► Treatment

Multimodal therapy is recommended according to the various modes of patient presentation. Patients with voiding symptoms are treated with alpha-blockers (tamsulosin, alfuzosin, silodosin). Antibiotics are used to treat newly diagnosed, antimicrobial-naïve patients. Psychosocial disorders are treated with cognitive behavioral therapy, anti-depressants, anxiolytics, and, if necessary, referral to mental health specialists. Neuropathic pain is treated with gabapentinoids, amitriptyline, neuromodulation, acupuncture, and if necessary, referral to a pain management specialist (see Chapter 5). Pelvic floor muscle dysfunction may respond to diazepam, biofeedback, physical therapy (kegel exercises), pelvic shock wave lithotripsy, and heat therapy. Sexual dysfunction with pain is treated with sexual therapy and phosphodiesterase-5 inhibitors (avanafil, sildenafil, tadalafil, vardenafil). Surgery is not recommended for chronic prostatitis.

► Prognosis

Annoying, recurrent symptoms are common, but serious sequelae have not been identified.

- Doiron RC et al. Male CP/CPPS: where do we stand? *World J Urol*. 2019;37:1015. [PMID: 30864007]
- Doiron RC et al. Management of chronic prostatitis/chronic pelvic pain syndrome. *Can Urol Assoc J*. 2018;12:S161. [PMID: 29875042]
- Doiron RC et al. The evolving clinical picture of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a look at 1310 patients over 16 years. *Can Urol Assoc J*. 2018;12:196. [PMID: 29485036]
- Franco JVA et al. Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. *Cochrane Database Syst Rev*. 2018;1:CD012551. Update in: *Cochrane Database Syst Rev* 2018;5:CD012551. [PMID: 29372565]
- Franco JVA et al. Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome: a Cochrane systematic review. *BJU Int*. 2020;125:490. [PMID: 31899937]

6. Acute Epididymitis



ESSENTIALS OF DIAGNOSIS

- Fever.
- Irritative voiding symptoms.
- Painful enlargement of epididymis.

► General Considerations

Most cases of acute epididymitis are infectious and can be divided into one of two categories that have different age distributions and etiologic agents. **Sexually transmitted forms** typically occur in men under age 35 years, are associated with urethritis, and result from *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. **Men who practice insertive anal intercourse** may have acute epididymitis from sexually transmitted and enteric organisms. **Non-sexually transmitted**

forms typically occur in men age 35 years and older, are associated with urinary tract infections and prostatitis, and are caused by enteric gram-negative rods. The route of infection is probably via the urethra to the ejaculatory duct and then down the vas deferens to the epididymis. Amiodarone has been associated with self-limited epididymitis in a dose-dependent phenomenon.

► Clinical Findings

A. Symptoms and Signs

Symptoms may follow chronic dysfunctional voiding, urinary retention, sexual activity, or trauma. Associated symptoms of urethritis (pain at the tip of the penis and urethral discharge) or cystitis (irritative voiding symptoms) may occur. Pain develops in the scrotum and may radiate along the spermatic cord or to the flank. Scrotal swelling and tenderness are usually apparent. Severe cases may develop systemic symptoms such as fever. Early in the course, the epididymis may be distinguishable from the testis; however, later the two may appear as one enlarged, tender mass. A reactive hydrocele may develop. The prostate may be tender on rectal examination.

B. Laboratory Findings

A complete blood count shows leukocytosis and a left shift. In the sexually transmitted variety, Gram staining of a smear of urethral discharge may be diagnostic of gram-negative intracellular diplococci (*N gonorrhoeae*). White cells without visible organisms on urethral smear signify nongonococcal urethritis, and *C trachomatis* is the most likely responsible pathogen. In the non-sexually transmitted variety, urinalysis shows pyuria, bacteriuria, and varying degrees of hematuria. Urine cultures will demonstrate the offending pathogen.

C. Imaging

Scrotal ultrasound may aid in the diagnosis if examination is difficult because of the presence of a large hydrocele or because questions exist regarding the diagnosis.

► Differential Diagnosis

Tumors generally cause painless enlargement of the testis. Urinalysis is negative, and examination reveals a normal epididymis. Scrotal ultrasound is helpful to define the pathology. Testicular torsion usually occurs in prepubertal males but is occasionally seen in young adults. Acute onset of symptoms and a negative urinalysis favor testicular torsion or torsion of one of the testicular or epididymal appendages. Prehn sign (elevation of the scrotum improves pain from epididymitis) may be suggestive but is not reliable in its diagnosis. A distal ureteral stone often presents with referred pain into the ipsilateral groin and scrotum, but the scrotum is not tender to palpation and a scrotal ultrasound is normal.

► Treatment

Bed rest, ice, and scrotal elevation are important in the acute phase. Treatment is directed toward the identified

pathogen (Table 23–1). The sexually transmitted variety in patients under age 35 is treated with a single intramuscular injection of ceftriaxone 250 mg plus 10 days of oral doxycycline 100 mg four times daily; in addition, any sexual partners from the preceding 60 days must be evaluated and treated as indicated. Men who practice insertive anal intercourse receive a single intramuscular injection of ceftriaxone 250 mg and 10 days of an oral fluoroquinolone (ciprofloxacin 500 mg twice daily) to cover sexually transmitted and enteric organisms. Non-sexually transmitted forms are treated for 10 days with a fluoroquinolone, at which time evaluation of the urinary tract is warranted to identify underlying disease. Symptoms and signs of epididymitis that do not subside within 3 days require reevaluation of the diagnosis and therapy.

► Prognosis

Prompt treatment usually results in a favorable outcome. If significant scrotal swelling has developed, this may take 4 weeks to resolve. Delayed or inadequate treatment may result in epididymoorchitis, decreased fertility, or abscess formation.

► When to Refer

- Persistent symptoms and infection despite antibiotic therapy.
- Signs of sepsis or abscess formation.

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INTERSTITIAL CYSTITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Pain with bladder filling; urinary urgency and frequency.
- ▶ Submucosal petechiae or ulcers on cystoscopic examination.
- ▶ Diagnosis of exclusion.

► General Considerations

Interstitial cystitis (painful bladder syndrome) is characterized by pain with bladder filling that is relieved by emptying and is often associated with urgency and frequency with a dramatic exaggeration of normal sensations. This is a diagnosis of exclusion, and patients must have a negative urine culture and cytology and no other obvious cause such as radiation cystitis, chemical cystitis (cyclophosphamide), vaginitis, urethral diverticulum, or genital herpes. Up to 40% of patients referred to urologists for interstitial

cystitis may actually be found to have a different diagnosis after careful evaluation. What was once considered a bladder disorder is now considered a chronic pain syndrome.

Population-based studies have demonstrated a prevalence of between 18 and 40 per 100,000 people. Both sexes are involved, but most patients are women, with a mean age of 40 years at onset. Patients with interstitial cystitis are more likely to report bladder problems in childhood, especially women. Up to 50% of patients may experience spontaneous remission of symptoms, with a mean duration of 8 months without treatment.

The etiology of interstitial cystitis is unknown, and it is most likely not a single disease but rather several diseases with similar symptoms. Associated diagnoses include severe allergies, irritable bowel syndrome, or inflammatory bowel disease. Theories regarding the cause of interstitial cystitis include increased epithelial permeability, neurogenic causes (sensory nervous system abnormalities), and autoimmunity.

► Clinical Findings

A. Symptoms and Signs

Pain, pressure, or discomfort with bladder filling that is relieved with urination, and urgency, frequency, and nocturia are the most common symptoms. Patients should be asked about exposure to pelvic radiation or treatment with cyclophosphamide. Examination should exclude genital herpes, vaginitis, or a urethral diverticulum.

B. Laboratory Findings

Urinalysis, urine culture, and urinary cytology are obtained to examine for infectious causes and bladder malignancy; in interstitial cystitis, they are all normal. Urodynamic testing can be done to assess bladder sensation and compliance and to exclude detrusor instability.

C. Cystoscopy

Cystoscopy may reveal glomerulations (submucosal hemorrhage) with hydrodistention of the bladder. Total bladder capacity should be determined. Biopsy of any suspicious lesions should be performed to exclude other causes such as carcinoma, eosinophilic cystitis, and tuberculous cystitis. The presence of submucosal mast cells is *not* needed to make the diagnosis of interstitial cystitis.

► Differential Diagnosis

Exposures to radiation or cyclophosphamide are discovered by the history. Bacterial cystitis, genital herpes, or vaginitis can be excluded by urinalysis, culture, and physical examination. A urethral diverticulum may be suspected if palpation of the urethra demonstrates an indurated mass that results in the expression of pus from the urethral meatus. Urethral carcinoma presents as a firm mass on palpation.

► Treatment

There is no cure for interstitial cystitis, but most patients achieve symptomatic relief from one of several approaches,

including hydrodistention, which is usually done as part of the diagnostic evaluation. Approximately 20–30% of patients notice symptomatic improvement following this maneuver. Patients with very small bladder capacities (less than 200 mL) are unlikely to respond to medical therapy.

Amitriptyline (10–75 mg/day orally) is often used as first-line medical therapy in patients with interstitial cystitis. Both central and peripheral mechanisms may contribute to its activity. Nifedipine (30–60 mg/day orally) and other calcium channel blockers have also demonstrated some activity in patients with interstitial cystitis. Pentosan polysulfate sodium (Elmiron) is an oral synthetic sulfated polysaccharide that helps restore integrity to the epithelium of the bladder in a subset of patients, and it has been evaluated in a placebo-controlled trial. Other options include intravesical instillation of dimethyl sulfoxide (DMSO) and heparin. Intravesical bacillus Calmette-Guérin (BCG) is not beneficial.

Further treatment modalities include transcutaneous electric nerve stimulation (TENS), acupuncture, stress reduction, exercise, biofeedback, massage, and pelvic floor relaxation. Surgical therapy for interstitial cystitis should be considered only as a last resort and may require cystourethrectomy with urinary diversion.

► When to Refer

Persistent and bothersome symptoms in the absence of identifiable cause.

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URINARY STONE DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Severe flank pain.
- ▶ Nausea and vomiting.
- ▶ Identification on noncontrast CT or ultrasonography.

► General Considerations

Urinary stone disease is exceeded in frequency as a urinary tract disorder only by infections and prostatic disease. It is estimated to afflict 240,000–720,000 Americans per year.

The prevalence of kidney stones has increased to 8.8%, or 1 in 11 Americans, representing a 70% increase over the last 15 years. While men are more frequently affected by urolithiasis than women, with a ratio of 1.5:1, the prevalence of stones in women is increasing. Initial presentation usually occurs in the third through fifth decades, and more than 50% of patients will become recurrent stone formers.

Stone formation requires saturated urine that is dependent on solute concentration, ionic strength, pH, and complexation. There are five major types of urinary stones: **calcium oxalate**, **calcium phosphate**, **struvite** (magnesium ammonium phosphate), **uric acid**, and **cystine**. The most common types are those composed of calcium oxalate or phosphate (85%), and for that reason most urinary stones are radiopaque on plain abdominal radiographs. Although pure uric acid stones are radiolucent, uric acid stones are frequently composed of a combination of uric acid and calcium oxalate and thus may be radiopaque. Cystine stones frequently have a smooth-edged ground-glass appearance and are radiolucent.

Geographic factors contribute to the development of stones. High humidity and elevated temperatures appear to be contributing factors, and the incidence of symptomatic ureteral stones is greatest in such areas during hot summer months. Higher incidence rates of stones have also been associated with sedentary lifestyle, obesity, hypertension, insulin resistance and poor glycemic control, carotid calcification, and cardiovascular disease.

Many commonly prescribed medications increase the risk of formation of kidney stones, including carbonic anhydrase inhibitors (topiramate, zonisamide, acetazolamide), systemic corticosteroids (prednisone), antiretroviral protease inhibitors (indinavir), gout medications (probenecid), diuretics (furosemide, bumetanide, torsemide, triamterene), decongestants (guaiifenesin, ephedrine), and laxatives (if abused for weight loss). The risk of stones from calcium supplementation is controversial. Thus, if calcium supplementation is medically necessary, it is recommended that the calcium supplement be taken with meals, and restricted to no more than 2000 mg of total calcium intake daily (including dietary sources).

Inadequate hydration is another very important dietary factor in the development of urinary stones. Stone formers should be encouraged to drink enough fluid to keep their urine clear or light-yellow at all times with a goal of at least 2500 mL of urine produced daily, which typically requires over 3000 mL (100 oz) intake per day. Excess animal protein and salt intake (over 3500 mg daily) as well as restricted dietary calcium intake are other important stone risk factors.

Genetic factors may contribute to urinary stone formation. While approximately 50% of calcium-based stones are thought to have a heritable component, other stone types are better characterized genetically. For example, cystinuria is an autosomal recessive disorder. Homozygous individuals have markedly increased excretion of cystine and frequently have numerous recurrent episodes of urinary stones. Distal renal tubular acidosis may be transmitted as a hereditary trait, and urolithiasis occurs in up to 75% of affected patients.

► Clinical Findings

A. Symptoms and Signs

Obstructing urinary stones usually present with acute, unremitting, and severe colic. Pain most often occurs suddenly and may awaken patients from sleep. It is typically localized to the flank and may be associated with nausea and vomiting. In sharp contrast to patients with an acute abdomen, patients with kidney stones are constantly moving, trying to find a comfortable position. The pain may occur episodically and may radiate anteriorly over the abdomen. As the stone progresses down the ureter, the pain may be referred into the ipsilateral groin. As the stone traverses the ureterovesicular junction, patients may complain of marked urinary urgency and frequency and in men, pain may radiate to the tip of the penis. After the stone passes into the bladder, there typically is immediate relief of symptoms, then the stones pass harmlessly through the urethra. Stone size does not correlate with the severity of the symptoms. If the stone fails to pass and obstruction persists, patients may note a deceptive improvement in symptoms. As many as 25% of patients with resolution of pain will have a persistent stone and thus follow-up imaging is recommended in all patients if the stone has not been witnessed to pass.

B. Laboratory Findings

Regardless of symptom severity, urinalysis usually reveals microscopic or gross hematuria (~90%). However, the absence of microhematuria does not exclude urinary stones. A persistent urinary pH < 5.5 may suggest a uric acid stone, while a persistent urinary pH > 7.2 may suggest a struvite (infection-related) or calcium phosphate stone. Patients with calcium oxalate-based stones typically have a normal urinary pH.

C. Metabolic Evaluation

Stone analysis on recovered stones can facilitate counseling for prevention of recurrence. Patients with uncomplicated first-time stones should undergo dietary counseling as outlined below and can be offered an optional complete metabolic evaluation.

General dietary counseling includes encouraging patients to augment their fluid intake to increase their urine volume (goal urinary output of greater than 2500 mL/day). This typically requires a fluid intake of 3000 mL/day or more. Stone formers should reduce their sodium intake (goal less than 3500 mg/day), and reduce their animal protein intake (eggs, fish, chicken, pork, and beef). Detailed medical and dietary history, serum chemistries, and urinalysis should be obtained for all patients with newly diagnosed nephrolithiasis. A serum parathyroid hormone level should be checked when hyperparathyroidism is suspected as the cause of calcium oxalate or calcium phosphate stones, and a serum uric acid should be obtained to exclude severe hyperuricemia, which can lead to uric acid stones as well as crystal deposition in the kidneys or heart. A 24-hour urine collection to determine urinary volume, creatinine, pH, calcium, uric acid, oxalate, phosphate, sodium, and citrate excretion is recommended for

interested patients with their first stone, for all patients who have recurrent stones, and for patients at high risk for recurrence. Results are used to personalize medical management to individual patient risk factors.

D. Imaging

Noncontrast CT is the most accurate imaging modality for evaluating flank pain given its superior sensitivity and specificity over other tests; however, ultrasonography (which does not use ionizing radiation) is a safe and effective alternative for initial evaluation of renal colic and one that can be used in the emergency department with good accuracy. If the CT scan is used, it should be obtained in the prone position to help differentiate distal ureterovesicular stones from those that have already passed into the urinary bladder. A “low-dose” imaging protocol should be used when available and repeated CT scans should be minimized due to the substantial cumulative radiation exposure that patients with recurrent stones can face. Stone density can be estimated with Hounsfield units (HU) on CT scans to help determine stone type. All stones, whether radiopaque or radiolucent on plain abdominal radiographs, will be visible on noncontrast CT except the rare calculus caused by the protease inhibitor, indinavir. A plain abdominal radiograph (kidney, ureter, and bladder [KUB]) and renal ultrasound examination will diagnose up to 80% of stones. Since more than 60% of patients with acute renal colic will have a stone in the distal 4 cm of the ureter, attention should be directed to that region when examining radiographs and ultrasonographic studies. Pain from a kidney stone is due to the dilatation of the ureter and kidney from the obstruction, and thus small nonobstructing kidney stones are typically not associated with pain.

► Medical Treatment & Prevention

To reduce the recurrence rate of urinary stones, dietary modification is important. Metabolic evaluation often identifies a modifiable risk factor that can further reduce stone recurrence rates. If no medical treatment is provided, stones will generally recur in 50% of patients within 5 years. Some stone types (eg, uric acid, cystine) are more prone to rapid recurrence than others. An increased fluid intake to dilute the urine and prevent dehydration is the most important dietary risk factor to reduce stone recurrence and may diminish the risk by 50%. Increasing fluid intake to ensure a voided volume of 2.5 L/day is recommended (normal average voided volume is 1.6 L/day). Urine should be clear or light yellow at each void. Medical therapy should be tailored to the patient's metabolic workup and the activity of their stone disease. Routine follow-up every 6–8 months and annual imaging (preferably with ultrasonography) will help encourage medical compliance, assess for interval stone formation or growth, and permit adjustments in medical therapy based on repeat metabolic studies.

A. General Dietary Recommendations

A 24-hour urinary sodium level of greater than 150 mmol/day indicates excessive sodium intake. **Sodium intake** should be limited to less than 3500 mg daily. Excessive

sodium intake will increase renal sodium and calcium excretion, increase urinary monosodium urates (that can act as a nidus for stone growth), increase the relative saturation of calcium phosphate, and decrease urinary citrate excretion. All of these factors encourage stone growth.

A urinary sulfate level of greater than 20 mEq/day indicates excessive animal protein intake. **Animal protein intake** should be spread out through the day, not all consumed during any individual meal, and is best limited to 1 g/kg/day. An increased protein load during an individual meal can lead to acidic urine and also increases calcium, oxalate, and uric acid excretion and decrease urinary citrate excretion.

Dietary calcium intake should *not* be restricted in an effort to decrease stone formation because it may paradoxically lead to increased stone formation due to increased oxalate absorption and consequent hyperoxaluria.

B. Calcium Nephrolithiasis

1. Hypercalciuria—Elevated urinary calcium levels (greater than 4 mg/kg/day or greater than 250 mg/day for males and greater than 200 mg/day for females) lead to hypercalciuric calcium nephrolithiasis. Hypercalciuria can be caused by absorptive, resorptive, and renal disorders; however, the categorization system provided below is not routinely used in clinical practice. Thiazide diuretics decrease renal calcium excretion; after primary hyperparathyroidism has been excluded, thiazide diuretics should be offered to patients with high urinary calcium and recurrent calcium stones. Chlorthalidone and indapamide are first-line agents since they can be administered once a day, while hydrochlorothiazide for hypercalciuria should be administered twice a day. All patients respond to thiazide diuretics with decreases in urinary calcium unless they have primary hyperparathyroidism or are nonadherent with taking the medication. Clinicians should periodically test patients taking thiazide diuretics for hypokalemia, since they may require potassium supplementation.

Absorptive hypercalciuria is secondary to increased absorption of calcium at the level of the small bowel, predominantly in the jejunum. Absorptive hypercalciuria can be diet-dependent, independent of calcium intake, or due to renal phosphate leak. Oral calcium load testing is no longer performed.

Resorptive hypercalciuria, or primary hyperparathyroidism, is typically due to a parathyroid adenoma. Hypercalcemia, elevated serum parathyroid hormone level, hypophosphatemia, and elevated urinary calcium level are present. Appropriate surgical resection of the parathyroid adenoma is curative in 75% of patients with kidney stones due to primary hyperparathyroidism. Medical management is typically reserved for patients who are not good surgical candidates.

Renal hypercalciuria is the most common form of hypercalciuria and occurs when the renal tubules are unable to efficiently reabsorb filtered calcium. Spilling calcium in the urine may result in secondary hyperparathyroidism with normal serum calcium. A thiazide diuretic is an effective long-term therapy in patients with this disorder because it corrects the urinary calcium losses and is

associated with an increase in bone mineral density of approximately 1% per year while receiving therapy.

2. Hyperuricosuria—**Hyperuricosuric calcium nephrolithiasis** is defined by elevated urinary uric acid levels (greater than 800 mg/day for males and greater than 750 mg/day for females). It is usually secondary to dietary purine excess or endogenous uric acid metabolic defects. Excess uric acid in the urine can lead to uric acid stones if the urine pH is low, or to calcium stones at higher urine pH due to formation of a monosodium urate crystal that then calcifies in a process known as heterogenous nucleation. Dietary purine restriction can reduce hyperuricosuria in 85% of cases. Patients with hyperuricosuria, normocalciuria, and recurrent calcium oxalate stones can be successfully treated with allopurinol. However, allopurinol is not first-line treatment of uric acid stones; urinary alkalinization is (see below).

3. Hyperoxaluria—**Hyperoxaluric calcium nephrolithiasis** (greater than 40 mg/day of urinary oxalate) is usually due to either an intestinal malabsorption disorder or a mismatch in dietary calcium and oxalate intake. Patients with a history of chronic diarrhea, inflammatory bowel disease, malabsorption, or gastric bypass surgery are at risk for hyperoxaluria. In these disorders, increased intestinal fat or bile (or both) combine with calcium to form a soap-like product. Calcium is therefore unavailable to bind to oxalate, leading to free oxalate absorption. Even a small increase in free oxalate absorption significantly increases risk of stone formation. If the diarrhea or steatorrhea cannot be effectively curtailed, oral calcium should be increased with meals, either by ingesting dairy products or by taking low-dose calcium carbonate supplements (250 mg). When dietary calcium and oxalate intake are consumed concurrently, they are unable to be absorbed systemically since they bind together in the intestinal tract. But if dietary calcium is restricted, or if dietary oxalate is excessive, free oxalate is rapidly absorbed and excreted in the urine, leading to hyperoxaluric calcium nephrolithiasis. Treatment includes adhering to a diet containing moderate calcium intake (1000–1200 mg daily). If dietary calcium increases do not reach 1000 mg daily, low-dose calcium carbonate (250 mg) can be consumed with meals. Treatment also involves avoiding high-oxalate-containing foods (baked potatoes with skins, sweet potatoes, French fries, okra, cocoa powder, grits, beets, spinach, rhubarb, almonds, cashews, miso soup, and Stevia sweetener). NOTE: High-dose ascorbic acid (greater than 2000 mg/day) will substantially increase urinary oxalate levels.

4. Hypocitraturia—Urinary citrate is the most important inhibitor of stone formation. Urinary citrate binds to calcium in solution, thereby decreasing available calcium for precipitation and subsequent stone formation. Low urine citrate levels (less than 450 mg/day) increase the risk of stones. **Hypocitraturic calcium nephrolithiasis** is usually idiopathic. Urinary citrate excretion is influenced by systemic acid-base balance and serum potassium levels, and thus, hypocitraturia occurs secondary to any metabolic acidemia (chronic diarrhea, distal renal tubular acidosis), or with systemic potassium losses (long-term

treatment with thiazide or loop diuretics). Usually effective treatment in these situations is potassium citrate supplementation: a typical dose is 40–60 mEq total daily intake, divided into two or three daily doses. Alternatively, oral lemonade has been shown to modestly increase urinary citrate, but this must be consumed several times every day since oral citrate is cleared from the urine in 6–8 hours.

C. Uric Acid Calculi

Urinary pH is the most important contributor to uric acid stone formation, and thus first-line efforts to prevent hyperuricosuria should focus on alkalinizing the urine with oral potassium citrate or sodium bicarbonate. Efforts to decrease urinary uric acid (with allopurinol 300 mg/day orally) should be reserved for patients continuing to form stones despite adequate urinary alkalinization. In patients who form pure uric acid stones, urine pH is consistently less than 5.5. Increasing the urinary pH dramatically increases uric acid solubility, leading to prevention of stone formation (with urine pH > 6.0) and to even stone dissolution (with urine pH > 6.5). Nitrazine pH test strips (which turn blue with alkaline urine pH > 6.0) are often useful to some patients in reinforcing adherence to urinary alkalinization efforts. Less common contributors to uric acid stone formation include hyperuricemia, myeloproliferative disorders, chemotherapy for malignancies with rapid cell turnover or cell death, abrupt and dramatic weight loss, and uricosuric medications (probenecid).

D. Struvite Calculi

Struvite stones are composed of magnesium-ammonium-phosphate and are typically visible on plain radiographs. They are most common in women with recurrent urinary tract infections with urease-producing organisms, including *Proteus*, *Pseudomonas*, *Providencia*, and, less commonly, *Klebsiella*, *Staphylococcus*, and *Mycoplasma* (but not *E coli*). Clinically, they rarely present with colic from a ureteral stone. Instead, a struvite stone is discovered as a large staghorn calculus forming a cast of the renal collecting system. Urinary pH is high, routinely above 7.2. Struvite stones are relatively soft and amenable to percutaneous removal. Appropriate perioperative antibiotics are required. They can recur rapidly, and efforts should be taken to remove all of the stone and then to prevent further urinary tract infections.

E. Cystine Calculi

Cystine stones are caused by a genetic metabolic defect resulting in abnormal excretion of cystine. These stones are exceptionally challenging to manage medically. Prevention involves markedly increasing fluid intake during the day and night to achieve a urinary volume of 3–4 L/day, decreasing sodium and dietary cystine intake, and increasing urinary alkalinization (typically with high-dose potassium citrate) with a goal urinary pH > 7.0. Refractory stone formers may be treated with disulfide inhibitors such as tiopronin (alpha-mercaptopropionylglycine) or penicillamine. There are no known inhibitors of cystine calculi.

► Medical Expulsion & Surgical Treatment

Signs of infection, including associated fever, tachycardia, hypotension, and elevated white blood cell count, may indicate a urinary tract infection behind the obstructing stone. Any obstructing stone with associated infection is a **medical emergency** requiring urology consultation and prompt drainage of the kidney with a ureteral stent or a percutaneous nephrostomy tube. Antibiotics alone are inadequate and only used as an adjunct to drainage of the infected urine behind the obstruction.

In the acute setting, forcing intravenous fluids will not push stones down the ureter. Forced diuresis can actually be counterproductive and exacerbate pain; instead, a euvolemic state should be achieved.

A. Ureteral Stones

Ureteral stones are usually discovered at three sites: the ureteropelvic junction, the crossing of the ureter over the iliac artery, or the ureterovesicular junction. Stones smaller than 5–6 mm in diameter on a plain abdominal radiograph usually pass spontaneously. Medical expulsive therapy with alpha-blockers (eg, tamsulosin, 0.4 mg orally once daily) in combination with an anti-inflammatory agent (eg, ibuprofen 600 mg orally three times per day), with or without a short course of a low-dose oral corticosteroid (eg, prednisone 10 mg orally daily for 5–10 days), may increase the rate of spontaneous stone passage and appears to be most effective for distal stones greater than 5 mm. Attempted medical expulsive therapy with effective pain medications and imaging follow-up is appropriate for a few weeks. If the stone fails to pass within 4 weeks, the patient has fever, intolerable pain, or persistent nausea or vomiting, or the patient must return to work or anticipates travel, then surgical intervention is indicated.

Stones in the mid and distal ureter that require surgical removal are best managed with ureteroscopic stone extraction. Ureteroscopic stone extraction involves placement of a small endoscope through the urethra and bladder and into the ureter. Under direct vision, basket extraction or laser fragmentation followed by fragment extraction is performed. A ureteral stent is often placed temporarily to allow drainage of the kidney while the swelling and inflammation from the stone and procedure resolve.

Extracorporeal shock wave lithotripsy (SWL) can be offered as second-line therapy. SWL utilizes an external energy source focused on the stone with the aid of fluoroscopy or ultrasonography. SWL is typically performed under anesthesia or sedation as an outpatient procedure with the goal of stone fragmentation. Most stone fragments then pass uneventfully within 2 weeks. Occasionally after SWL, stone fragments obstruct the ureter. Conservative management usually results in spontaneous resolution of the obstruction with eventual passage of the stone fragments. Fragments that have not passed within 6 weeks are unlikely to do so without intervention. SWL is strictly contraindicated in pregnant patients as well as in those with untreated urinary tract infection, in those with an

uncorrected coagulopathy, or in those who must continue receiving anticoagulant or antiplatelet therapy. A ureteral stent is typically not necessary with SWL.

Proximal ureteral stones can be treated with SWL or ureteroscopy. SWL is less successful with larger stones and those that are very dense. In cases of SWL failure, ureteroscopic extraction is required.

B. Renal Calculi

Patients with small, asymptomatic, nonobstructing renal calculi, without urinary tract infection, or obstruction may not warrant surgical treatment. If surveillance is undertaken, the patient should be monitored with serial abdominal radiographs or renal ultrasonographic examinations every 3–12 months. If the calculi grow or become symptomatic, intervention is indicated. SWL is most effective for stones less than 1 cm in the lower pole of the kidney or less than 2 cm elsewhere in the kidney. SWL is less effective for stones that are very hard (cystine stones, calcium oxalate stones greater than 1000–1200 Hounsfield units on CT scan) and for obese patients (skin-to-stone distance greater than 10–12 cm). Ureteroscopy and laser lithotripsy are effective for multiple stones and larger stones, though very large stones may require multiple treatment sessions. Stones larger than 15–20 mm and staghorn calculi (large branched stones occupying at least two renal calices) are best treated via percutaneous nephrolithotomy. Percutaneous nephrolithotomy is performed by inserting a needle into the appropriate renal calyx and dilating a tract large enough to allow a nephroscope to pass directly into the kidney. In this fashion, larger and more complex renal stones can be inspected, fragmented, and removed. In unusual cases, laparoscopic, robotic-assisted, or open stone removal may be considered. Perioperative antibiotic coverage should be given for any stone procedure, ideally based on preoperative urine culture results.

► When to Refer

- Evidence of urinary obstruction.
- Urinary stone with associated flank pain.
- Anatomic abnormalities, solitary kidney, or chronic kidney disease.
- Concomitant pyelonephritis or recurrent urinary tract infection.

► When to Admit

- Intractable nausea and vomiting or pain.
- Obstructing stone with fever or other signs of infection.

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MALE SEXUAL DYSFUNCTION & ERECTILE DYSFUNCTION

ESSENTIALS OF DIAGNOSIS

- ▶ Erectile dysfunction is an exceedingly common condition that negatively impacts quality of life when left untreated.
- ▶ Most erectile dysfunction is organic in nature, may be an early sign of cardiovascular disease, and requires evaluation.
- ▶ Peyronie disease is a common, benign fibrotic disorder of the penis that causes pain, penile deformity, and sexual dysfunction.

► General Considerations

Male **sexual dysfunction** is manifested in a variety of ways, and patient history is critical to the proper classification and treatment. A **loss of libido** may indicate androgen deficiency. **Erectile dysfunction** is the consistent inability to attain or maintain a sufficiently rigid penile erection for sexual intercourse. More than half of men aged 40–70 years have erectile dysfunction and its incidence increases with age. **Loss of erections** may result from neurogenic, arterial, venous, hormonal, or psychological causes. Concurrent medical problems may damage one or more of the mechanisms. Normal male erection is a neurovascular event relying on an intact autonomic and somatic nerve supply to the penis, arterial blood flow supplied by the paired cavernosal arteries, and smooth and striated musculature of the corpora cavernosa and pelvic floor. Erection is initiated by nerve impulses in the pelvic plexus leading to an increase in arterial flow, active relaxation of the smooth muscle within the sinusoids of the corpora cavernosa, and an increase in venous resistance. Contraction of the ischiocavernosus muscle causes further rigidity of the penis with intracavernosal pressures exceeding systolic blood pressure. Nitric oxide is the key neurotransmitter that initiates and sustains erections.

The most common cause of erectile dysfunction is a decrease in arterial flow resultant from progressive vascular disease. Endothelial dysfunction results from the decreased bioavailability of nitric oxide with subsequent impairment of arterial vasodilation. Erectile dysfunction may be an early manifestation of endothelial dysfunction, which precedes more severe atherosclerotic cardiovascular disease. Many medications, especially antihypertensive, antidepressant, and opioid agents, are associated with erectile dysfunction.

Anejaculation is the loss of seminal emission and may result from androgen deficiency by decreasing prostate and seminal vesicle secretions, or by sympathetic denervation as a result of spinal cord injury, diabetes mellitus or pelvic or retroperitoneal surgery or radiation. **Retrograde ejaculation** may occur as a result of mechanical disruption of the bladder neck, due to congenital abnormalities, transurethral prostate surgery, pelvic radiation, sympathetic denervation, or treatment with alpha-blockers.

Premature ejaculation is the distressful, recurrent ejaculation with minimal stimulation before a person desires. Primary premature ejaculation may be treated with behavioral modification, sexual health counseling, local anesthetic agents, and systemic medications used alone or in combination. Secondary premature ejaculation is due to erectile dysfunction and responds to treatment of the underlying disorder. **Peyronie disease** is a fibrotic disorder of the tunica albuginea of the penis resulting in varying degrees of penile pain, curvature, or deformity. Peyronie disease affects up to 10% of men and, similar to erectile dysfunction, is more common with increased age. While 10% of men improve spontaneously, 50% will stabilize and the remainder will progress if left untreated. Penile deformity can impair normal sexual function and impact self-esteem.

Priapism is prolonged painful penile erection in the absence of sexual stimulation that results in ischemic injury of the corpora cavernosa from venous congestion, blood coagulation within the cavernous sinuses, and complete cessation of arterial inflow (low flow or “ischemic” priapism). Ischemic priapism is a medical emergency requiring immediate medical or surgical intervention to avoid irreversible penile damage. Ischemic priapism may be caused by red blood cell dyscrasias, drug use, and any of the treatments for erectile dysfunction.

► Clinical Findings

A. Symptoms and Signs

Erectile dysfunction should be distinguished from problems with penile deformity, libido, orgasm, ejaculation, and penile deformity. The severity, intermittency, and timing of erectile dysfunction should be noted. The history should include inquiries about dyslipidemia, hypertension, depression, neurologic disease, diabetes mellitus, kidney disease, endocrine disorders, and cardiac or peripheral vascular disease. Pelvic trauma, surgery, or irradiation increases a man’s likelihood of erectile dysfunction. Histories of prostate cancer treatment or Peyronie disease should be elicited. In the absence of other medical history, the onset of erectile dysfunction may be the first sign of endothelial dysfunction and further cardiovascular risk stratification should be considered. Medication use should be reviewed. Special attention should be given to the use of nitrate-containing medications. Alcohol, tobacco, marijuana, and other recreational drug use are associated with an increased risk of sexual dysfunction. The use of pornography to maintain sexual arousal should be elicited.

During the physical examination, vital signs, body habitus (obesity), and secondary sexual characteristics should be assessed. Basic cardiovascular and neurologic examinations should be performed. The genitalia should be examined, noting the stretched length of the penis, fibrosis of the penile shaft, and any abnormalities in size or consistency of either testicle.

B. Laboratory Findings

Laboratory evaluation should be performed in select cases based on patient history and physical examination findings. Possible testing includes serum lipid profile, glucose, and testosterone. Patients with an abnormal testosterone should have measurement of free testosterone and luteinizing hormone (LH) to distinguish hypothalamic-pituitary dysfunction from primary testicular failure.

► Treatment

Treatment of men suffering from sexual dysfunction should be patient centered and goal oriented. Lifestyle modification and reduction of cardiovascular risk factors are important components of treatment and should include smoking cessation; reduction of alcohol intake; diet; exercise; and treatment of diabetes, dyslipidemia, and hypertension. Men who have a psychogenic component to their erectile dysfunction or who are experiencing emotional distress will benefit from sexual health therapy or psychological counseling.

A. Hormonal Replacement

In men with hypogonadism who have undergone complete endocrinologic evaluation, restoration of normal testosterone levels may improve sexual function (see Male Hypogonadism in Chapter 26.)

B. Vasoactive Therapy

1. Oral agents—Sildenafil, vardenafil, tadalafil, and avanafil inhibit phosphodiesterase type 5 (PDE-5), preventing the degradation of cGMP and increasing blood flow into the penis. These medications are similar but have variable effectiveness in different patients. The medications have variable durations of onset, activity, and side effects. Each medication should be initiated at the lowest dose and titrated to achieve the desired effect. These medications are contraindicated in patients taking nitroglycerin or nitrates, since there may be exaggerated cardiac preload reduction causing hypotension and syncope.

The combination of PDE-5 inhibitors and alpha-receptor blockers (prescribed for lower urinary tract symptoms) may cause a larger reduction in systemic blood pressure than when PDE-5 inhibitors are used alone. However, these two classes of medication may be safely used in combination if they are initiated and titrated in a stepwise fashion.

2. Injectable or suppository medications—Injection of prostaglandin E₂ into the corpora cavernosa is an acceptable form of treatment for erectile dysfunction. Injections are performed using a tuberculin-type syringe or a

metered-dose injection device. The base and lateral aspect of the penis is used as the injection site to avoid injury to the superficial blood and nerve supply located dorsally. Complications include priapism, penile pain, bruising, fibrosis, and infection. Prostaglandin E₂ (alprostadil urethral) can also be delivered via an intraurethral suppository. Prostaglandin E₂ is often compounded with papaverine, phentolamine, or atropine in order to increase effectiveness. Patients using such compounded agents should be cautioned about the risk of priapism and variability of drug effect due to differences in compounding.

C. Vacuum Erection Device

The vacuum erection device creates negative pressure around the penis, drawing blood into the corpora cavernosa. Once tumescence is achieved, an elastic constriction band is placed around the penile base to prevent loss of erection. Such devices are effective but may cause penile discomfort and numbness leading to a high rate of disuse. Serious complications are rare.

D. Penile Prosthetic Surgery

Penile prostheses are surgically implanted into the paired corpora cavernosa and may be semi-rigid (malleable) or inflatable. Inflatable prostheses are self-contained hydraulic devices that result in relatively natural appearance and function. Inflatable prosthetics are used most commonly because they emulate the tumescence and detumescence of the normal erection. This therapy is appropriate for patients who have not achieved a satisfactory response to other therapies.

E. Medical and Surgical Therapy for Peyronie Disease

Injectable collagenase *Clostridium histolyticum* is the only FDA-approved medication for the treatment of Peyronie disease. Collagenase enzymatically severs disordered collagen fibers after injection into the penile plaque. Surgical treatment is an alternative for men with compromised sexual function due to severe curvature, with lesions causing penile instability, or with inadequate results from collagenase. The choice of corrective procedure should be tailored to each patient after a detailed evaluation of disease severity and sexual function.

► When to Refer

- Patients with unsatisfactory response to oral medications.
- Patients with Peyronie disease or other penile deformity.
- Patients with a history of pelvic or perineal trauma, surgery, or radiation.
- Patients with priapism to the emergency department for immediate intervention to allow restoration of penile perfusion.

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MALE INFERTILITY



ESSENTIALS OF DIAGNOSIS

- ▶ Infertility is common, and male factors contribute to 50% of cases.
- ▶ Causes include decreased or absent sperm production or function, or obstruction of the male genital tract.
- ▶ Abnormal semen quality is a risk factor for infertility and may indicate poor health or increased risk of certain health conditions.

► General Considerations

Infertility is the inability of a couple to conceive a child after 1 year of sexual intercourse without contraceptive use. It affects 15–20% of US couples and half of cases result from male factors. The evaluation of both partners is critical for optimizing treatment. Following a detailed history and physical examination, a semen analysis should be performed at least twice, on two separate occasions (Figure 23–2). Because spermatogenesis requires approximately 75 days, it is important to review health events and gonadotoxic exposures from the preceding 3 months. Male infertility is associated with a higher risk of testicular germ cell cancer and with a higher rate of medical comorbidity. These men should be counseled and screened appropriately and taught testicular self-examination.

► Clinical Findings

A. Symptoms and Signs

The history should include prior testicular insults (torsion, cryptorchidism, trauma), infections (mumps orchitis, epididymitis, sexually transmitted infections), environmental factors (excessive heat, radiation, chemotherapy, prolonged pesticide exposure), medications (testosterone, finasteride, cimetidine, selective serotonin reuptake inhibitors, and spironolactone may affect spermatogenesis; phenytoin may lower FSH; sulfasalazine and nitrofurantoin affect sperm motility; tamsulosin causes retrograde ejaculation), and other drugs (alcohol, tobacco, marijuana). Sexual function,

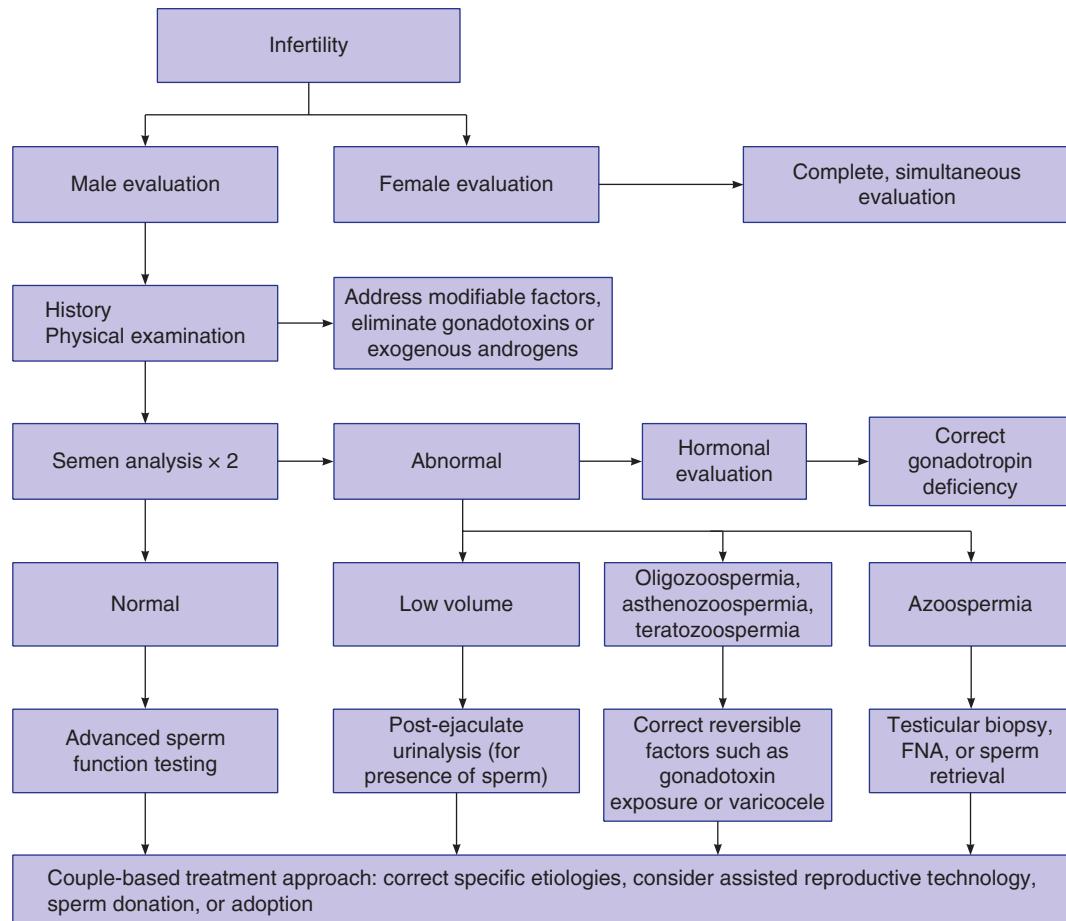


Figure 23–2. Couple-based approach to evaluation and treatment of male factor infertility. FNA, fine-needle aspiration.

frequency and timing of intercourse, use of lubricants, and each partner's previous fertility are important. Past medical and surgical history should be surveyed for chronic disease, including obesity, cardiovascular, thyroid, or liver disease (decreased spermatogenesis); diabetes mellitus (decreased spermatogenesis, retrograde or anejaculation); or radical pelvic or retroperitoneal surgery (absent seminal emission secondary to sympathetic nerve injury).

Physical examination should assess features of hypogonadism: underdeveloped sexual characteristics, diminished male pattern hair distribution (axillary, body, facial, pubic), body habitus, gynecomastia, and obesity. Testicular size should be noted (normal size approximately 4.5 × 2.5 cm, volume 18 mL). **Varicoceles** are abnormally dilated, refluxing veins of the pampiniform plexus that can be identified in the standing position by gentle palpation of the spermatic cord and, on occasion, may only be appreciated with the Valsalva maneuver. The vasa deferentia and epididymides should be palpated (absence of all or part of one or both of the vasa deferentia may indicate the presence of a cystic fibrosis variant, congenital bilateral or unilateral absence of the vasa deferentia).

B. Laboratory Findings

Semen analysis should be performed after 2–5 days of ejaculatory abstinence. The specimen should be analyzed within 1 hour after collection. Abnormal sperm concentrations are less than 15 million/mL (**oligozoospermia** is the presence of less than 15 million sperm/mL in the ejaculate; **azoospermia** is the complete absence of sperm). Normal semen volume should be equal to or greater than 1.5 mL (lesser volumes may be due to retrograde ejaculation, ejaculatory duct obstruction, congenital bilateral absence of the vasa deferentia, or hypogonadism). Normal sperm motility and morphology demonstrate greater than 39% motile cells and greater than 3% normal morphology. Abnormal motility (asthenozoospermia) may result from varicocele, antisperm antibodies, infection, abnormalities of the sperm flagella, or ejaculatory duct obstruction. Abnormal morphology may result from a varicocele, infection, or exposure to gonadotoxins (eg, tobacco, marijuana).

Endocrine evaluation is warranted if sperm concentration is below 10 million sperm/mL or if the history and physical examination suggest an endocrinologic origin.

Initial testing should include serum testosterone and FSH. Specific abnormalities in these hormones should prompt additional testing, including serum LH and prolactin. Elevated FSH and LH levels and low testosterone levels (**hypergonadotropic** or **primary hypogonadism**) are associated with primary testicular failure. Low FSH and LH associated with low testosterone (**hypogonadotropic** or **secondary hypogonadism**) may be of hypothalamic or pituitary origin. Elevation of serum prolactin may indicate the presence of prolactinoma.

C. Genetic Testing

Men with sperm concentrations less than 1 million/mL should consider testing for Y chromosome microdeletions and karyotypic abnormalities. Gene deletions from the long arm of the Y chromosome may cause azoospermia or oligozoospermia with age-related decline in spermatogenesis that is transmissible to male offspring. When small (5 mL), firm testes are identified, karyotyping may reveal Klinefelter syndrome. Partial or complete absence of the vasa deferentia should prompt testing for gene mutations associated with cystic fibrosis.

D. Imaging

Scrotal ultrasound aids in characterizing the testes and may detect a testicular mass or varicocele. Men with low ejaculate volume and no evidence of retrograde ejaculation may undergo transrectal ultrasound to evaluate the prostate and seminal vesicles. MRI of the sella turcica should be performed in men with elevated prolactin or hypogonadotropic hypogonadism to evaluate the anterior pituitary gland. MRI of the pelvis and scrotum should be considered in men for whom the testes cannot be identified in the scrotum by physical examination or ultrasound. Men with unilateral absence of the vas deferens should have abdominal ultrasound or CT to exclude absence of the ipsilateral kidney.

► Treatment

A. General Measures

Education about intercourse timing in relation to the woman's ovulatory cycle as well as the avoidance of spermicidal lubricants should be discussed. In cases of gonadotoxic exposure or medication-related factors, the offending agent should be removed whenever feasible. Patients with active genitourinary tract infections should be treated with appropriate antibiotics. Healthy lifestyle habits, including diet, exercise, and avoidance of gonadotoxins (tobacco, excessive alcohol, and marijuana), should be reinforced.

B. Varicocele

Varicocelectomy is performed to prevent retrograde blood flow in abnormal spermatic cord veins. Surgical ligation, which is accomplished via a subinguinal incision with the aid of a surgical microscope and Doppler ultrasound, is the gold standard approach given its high success and low complication rates. Percutaneous venographic embolization of varicoceles is another approach but incurs both

radiation and intravenous contrast exposure. Embolization may be the best approach for recurrence of varicocele after surgery.

C. Endocrine Therapy

Hypogonadotropic hypogonadism may be treated with human chorionic gonadotropin (2000 international units intramuscularly three times a week) once primary pituitary disease has been excluded or treated. If sperm concentration fails to rise after 12 months, recombinant FSH therapy should be initiated (150 international units subcutaneously three times a week). Clomiphene citrate is a nonsteroidal anti-estrogen that stimulates a functioning pituitary gland to increase gonadotropin production. Anastrazole inhibits aromatization of testosterone to estradiol, thereby enhancing gonadotropin production. While studied extensively in men, neither clomiphene nor anastrazole are approved by the US FDA for treatment of male infertility. Therefore, men should be counseled appropriately before using either medication.

D. Ejaculatory Dysfunction Therapy

Patients with retrograde ejaculation may benefit from alpha-adrenergic agonists (pseudoephedrine, 60 mg orally three times a day) or imipramine (25 mg orally three times a day). Medical failures may require the collection of post-ejaculation urine for intrauterine insemination. Anejaculation can be treated with vibratory stimulation or electroejaculation in select cases.

E. Ductal Obstruction

Obstruction of the vas deferens after vasectomy may be treated by microsurgical vasectomy reversal or by surgical sperm retrieval in combination with in vitro fertilization. While somewhat dependent on the duration of vasectomy, overall, microsurgical vasectomy reversal is highly successful in returning sperm to the ejaculate.

F. Assisted Reproductive Techniques

Intrauterine insemination and in vitro fertilization (with or without intracytoplasmic sperm injection) are alternatives for patients in whom other means of treating reduced sperm concentration, motility, or functionality have failed. Intrauterine insemination should be performed only when adequate numbers of motile sperm are noted in an ejaculate sample. With the use of intracytoplasmic sperm injection, some men with azoospermia may still initiate a pregnancy by surgical retrieval of sperm from the testicle, epididymis, or vas deferens.

► When to Refer

- Couples with infertility or who are concerned about their fertility potential.
- Men with known genital insults, genetic diagnoses, or syndromes that preclude natural fertility.
- Reproductive-aged men with newly diagnosed cancer or other disease that may require cytotoxic therapies with interest in fertility preservation.

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BENIGN PROSTATIC HYPERPLASIA



ESSENTIALS OF DIAGNOSIS

- ▶ Obstructive or irritative voiding symptoms.
- ▶ Enlarged prostate size on rectal examination.
- ▶ Absence of urinary tract infection, neurologic disorder, stricture disease, prostatic or bladder malignancy.

► General Considerations

Benign prostatic hyperplasia (BPH) is the most common benign tumor in men, and its incidence is age related. The prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41–50 years, to 50% in men aged 51–60, and to greater than 90% in men over 80 years of age. Although clinical evidence of disease occurs less commonly, symptoms of prostatic obstruction are also age related. At age 55 years, approximately 25% of men report obstructive voiding symptoms. At age 75 years, 50% of men report a decrease in the force and caliber of the urinary stream.

Risk factors for the development of BPH are poorly understood. Some studies have suggested a genetic predisposition and some have noted racial differences. Approximately 50% of men under age 60 years who undergo surgery for BPH may have a heritable form of the disease. This form is most likely an autosomal dominant trait, and first-degree male relatives of such patients carry an increased relative risk of approximately fourfold.

► Clinical Findings

A. Symptoms

The symptoms of BPH can be divided into obstructive and irritative complaints. **Obstructive symptoms** include hesitancy, decreased force and caliber of the stream, sensation of incomplete bladder emptying, double voiding (urinating a second time within 2 hours), straining to urinate, and postvoid dribbling. **Irritative symptoms** include urgency, frequency, and nocturia.

The American Urological Association (AUA) symptom index (Table 23–3) is an important tool used in the evaluation of patients with this disorder and should be calculated for all patients before starting therapy. The answers to seven questions quantitate the severity of obstructive or irritative complaints on a scale of 0–5. Thus, the score can range from 0 to 35 with increasing severity of symptoms. An estimation of postvoid residual can provide important information on bladder emptying and the need for more urgent intervention.

A detailed history focusing on the urinary tract should be obtained to exclude other possible causes of symptoms such as prostate cancer, urinary tract infection, neurogenic bladder, or urethral stricture. A focused medical history may also reveal other comorbidities that can directly affect urinary symptoms such as diabetes mellitus, heart failure, Parkinson disease, and obstructive sleep apnea.

B. Signs

A physical examination, digital rectal examination (DRE), and a focused neurologic examination should be performed on all patients. The size and consistency of the prostate should be noted, but prostate size does not correlate with the severity of symptoms or the degree of obstruction. BPH usually results in a smooth, firm, elastic enlargement of the prostate. Induration, if detected, must alert the clinician to the possibility of cancer, and further evaluation is needed (ie, prostate-specific antigen [PSA] testing, transrectal ultrasound, and biopsy). Examination of the lower abdomen should be performed to assess for a distended bladder.

C. Laboratory Findings

Urinalysis should be performed to exclude infection or hematuria. Clinicians should consider obtaining a serum PSA test, particularly in patients whose life expectancy is longer than 10 years. PSA certainly increases the ability to detect prostate cancer over DRE alone; however, because there is much overlap between levels seen in BPH and prostate cancer, its use remains controversial (see Chapter 39).

D. Imaging

Urologists are advised to consider prostate volume assessment prior to surgical intervention to determine the most appropriate approach (eg, TURP vs simple prostatectomy for a very large gland). This assessment can be done with cystoscopy; transrectal or abdominal ultrasound; or cross-sectional imaging of the pelvis, if it is available.

E. Cystoscopy

Cystoscopy is not required to determine the need for treatment but may assist in determining the surgical approach in patients opting for invasive therapy.

F. Additional Tests

Uroflowmetry and postvoid residual should be assessed prior to surgical treatment of the prostate and can be useful in tracking response to treatments. Cystometrograms and

Table 23–3. American Urological Association symptom index for benign prostatic hyperplasia.¹

Questions to Be Answered	Not at All	Less Than One Time in Five	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

¹Sum of seven circled numbers equals the symptom score. See text for explanation.

Reproduced, with permission, from Barry MJ et al; Measurement Committee of the American Urological Association. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol. 2017;197:S189. © American Urological Association Education and Research, Inc.

urodynamic profiles should be reserved for patients with unclear etiology of symptoms, suspected neurologic disease, or those who have not responded to prostate surgery.

Differential Diagnosis

A history of prior urethral instrumentation, urethritis, sexually transmitted infections, or trauma should be elucidated to exclude urethral stricture or bladder neck contracture. Hematuria and pain are commonly associated with bladder stones. Carcinoma of the prostate may be detected by abnormalities on DRE or an elevated PSA (see Chapter 39). A urinary tract infection can mimic the irritative symptoms of BPH and can be readily identified by urinalysis and culture; however, a urinary tract infection can also be a complication of BPH. Carcinoma of the bladder, especially carcinoma in situ, may also present with irritative voiding complaints; however, urinalysis usually shows evidence of hematuria (see Chapter 39). Patients with a neurogenic bladder may also have many of the same symptoms and signs as those with BPH; however, a history of neurologic disease, stroke, diabetes mellitus, or back injury may be obtained, and diminished perineal or lower extremity sensation or alterations in rectal sphincter tone or in the bulbocavernosus reflex might be observed on examination. Simultaneous alterations in bowel function (constipation) might also suggest the possibility of a neurologic disorder.

Treatment

Clinical practice guidelines exist for the evaluation and treatment of patients with BPH. Following evaluation as outlined above, patients may be offered various forms of

therapy for BPH. Patients are advised to consult with their primary care clinicians and make an educated decision on the basis of the relative efficacy and side effects of the treatment options (Table 23–4).

Patients with mild symptoms (AUA scores 0–7) and relatively low bother scores may be managed by watchful waiting only. Medical therapy is appropriate for those with significant bother attributed to their symptoms. Absolute surgical indications include any of the following sequelae of BPH: recurrent urinary tract infection, problematic gross hematuria, bladder stones, refractory urinary retention (failing at least one attempt at catheter removal), or obstructive nephropathy.

A. Watchful Waiting

The risk of progression or complications is uncertain. However, men with progressive symptoms and large prostates do have a higher chance of developing urinary retention or requiring surgical intervention in the future.

Retrospective studies on the natural history of BPH are inherently subject to bias, relating in part to patient selection and to the type and extent of follow-up. Very few prospective studies addressing its natural history have been reported. One small series demonstrated that approximately 10% of symptomatic men may progress to urinary retention while 50% of patients demonstrate improvement or even resolution of symptoms. A large randomized study compared finasteride with placebo in men with moderate to severely symptomatic disease and enlarged prostates on DRE. Patients in the placebo arm demonstrated a 7% risk of developing urinary retention over 4 years.

Table 23–4. Summary of benign prostatic hyperplasia treatment outcomes.¹

Outcome	Rezūm	TUIP	Open Surgery	TURP	Watchful Waiting	Alpha-Blockers	Finasteride ²
Chance for improvement ¹	—	78–83%	94–99.8%	75–96%	31–55%	59–86%	54–78%
Degree of symptom improvement (% reduction in symptom score)	47%	73%	79%	85%	Unknown	51%	31%
Morbidity and complications ¹	3.7–16.9%	2.2–33.3%	7–42.7%	5.2–30.7%	1–5%	2.9–43.3%	8.8–13.6
Death within 30–90 days ¹	0%	0.2–1.5%	1–4.6%	0.5–3.3%	0.8%	0.8%	0.8%
Total incontinence ¹	0%	0.1–1.1%	0.3–0.7%	0.7–1.4%	2%	2%	2%
Need for operative treatment for surgical complications ¹	< 2%	1.3–2.7%	0.6–14.1%	0.7–10.1%	0	0	0
Erectile dysfunction ¹	0%	3.9–24.5%	4.7–39.2%	3.3–34.8%	3%	3%	2.5–5.3%
Retrograde ejaculation	3–6%	6–55%	36–95%	25–99%	0	4–11%	0
Loss of work in days	—	7–21	21–28	7–21	1	3.5	1.5
Hospital stay in days	0%	1–3	5–10	3–5	0	0	0

¹90% confidence interval.²Most of the data reviewed for finasteride are derived from three trials that have required an enlarged prostate for entry. The chance of improvement in men with symptoms yet minimally enlarged prostates may be much less, as noted from the VA Cooperative Trial. TUIP, transurethral incision of the prostate; TURP, transurethral resection of the prostate.

Men with moderate or severe symptoms can also be observed if they so choose. The optimal interval for follow-up is not defined, nor are the specific end points for intervention.

B. Medical Therapy

1. Alpha-blockers—The human prostate and bladder base contains alpha-1-adrenoceptors, which show a contractile response to agonists. Blocking these receptors leads to smooth muscle relaxation and reduced resistance at the bladder outlet. Alpha-blockade has been shown to result in both objective and subjective degrees of improvement in the symptoms and signs of BPH in some patients. Alpha-blockers can be classified according to their receptor selectivity (Table 23–5) as well as their half-life.

Prazosin is a short-acting, nonselective alpha-blocker. Due to its short half-life and high side-effect profile (orthostatic hypotension, dizziness, tiredness, retrograde ejaculation, rhinitis, and headache), it is not typically used in the treatment of BPH.

Table 23–5. Alpha-blockade for benign prostatic hyperplasia.

Agent	Action	Oral Dose
Prazosin	Alpha-1-blockade	1–5 mg twice daily
Terazosin	Alpha-1-blockade	1–10 mg daily
Doxazosin	Alpha-1-blockade	1–8 mg daily
Tamsulosin	Alpha-1a-blockade	0.4 or 0.8 mg daily
Alfuzosin	Alpha-1a-blockade	10 mg daily
Silodosin	Alpha-1a-blockade	4 or 8 mg daily
Tadalafil	Phosphodiesterase type 5 inhibitor	5 mg daily

Long-acting, nonselective alpha-blockers allow for once-a-day dosing, but dose titration is still necessary because side effects similar to those seen with prazosin may occur. Terazosin improves symptoms and in numerous studies it is superior to placebo or finasteride. Terazosin is started at a dosage of 1 mg orally daily for 3 days, increased to 2 mg orally daily for 11 days, then 5 mg orally daily. Additional dose escalation to 10 mg orally daily can be performed if necessary. Doxazosin is started at a dosage of 1 mg orally daily for 7 days, increased to 2 mg orally daily for 7 days, then 4 mg orally daily. Additional dose escalation to 8 mg orally daily can be performed if necessary.

Alpha-1a-receptors are localized to the prostate and bladder neck. Selective blockade of these receptors results in fewer systemic side effects than nonselective alpha-blocker therapy thus obviating the need for dose titration. The typical dose of tamsulosin is 0.4 mg orally daily taken 30 minutes after a meal. Alfuzosin is a long-acting alpha-1a-blocker; its dose is 10 mg orally once daily with food, and it does not require titration. Several randomized, double-blind, placebo-controlled trials have been performed comparing terazosin, doxazosin, tamsulosin, and alfuzosin with placebo. All agents have demonstrated safety and efficacy. Floppy iris syndrome, a complication of cataract surgery, can occur in patients taking both nonselective alpha-blockers and alpha-1a-blockers.

2. 5-Alpha-reductase inhibitors—Finasteride and dutasteride block the conversion of testosterone to dihydrotestosterone. These medications impact the epithelial component of the prostate, resulting in reduction in size of the gland and improvement in symptoms. Six months of therapy are required for maximum effects on prostate size (20–30% reduction) and symptomatic improvement.

Several randomized, double-blind, placebo-controlled trials have been performed comparing finasteride with placebo. Efficacy, safety, and durability are well established.

However, symptomatic improvement is seen only in men with enlarged prostates (greater than 40 mL by ultrasonographic examination). Side effects include decreased libido, decrease in volume of ejaculate, and erectile dysfunction. Serum PSA is reduced by approximately 50% in patients receiving finasteride therapy, but the % free PSA is unchanged. Therefore, in order to compare with pre-finasteride PSA levels, the serum PSA of a patient taking finasteride should be doubled.

A report suggests that finasteride therapy may decrease the incidence of urinary retention and the need for operative treatment in men with enlarged prostates and moderate to severe symptoms. The larger the prostate over 40 mL, the greater the relative-risk reduction. However, optimal identification of appropriate patients for prophylactic therapy remains to be determined. Dutasteride is a dual 5-alpha-reductase inhibitor (inhibiting both 5-alpha-reductase types 1 and 2) that appears to be similar to finasteride in its effectiveness; its dose is 0.5 mg orally daily.

Both finasteride and dutasteride have been shown to be effective chemopreventive agents for prostate cancer in large, randomized clinical trials. A 25% risk reduction was observed in men with both low and high risk for prostate cancer. However, despite the strength of the evidence for 5-alpha-reductase inhibitors in reducing the risk of prostate cancer, an FDA advisory committee recommended against labeling these agents for prostate cancer chemoprevention, citing the potential increased risk of high-grade tumors in these studies (1.8% vs 1.0% for finasteride and 1% vs 0.5% for dutasteride), isolated risk reduction in low-grade tumors, and inability to apply the findings to the general population. Moreover, the FDA has included the increased risk of being diagnosed with high-grade prostate cancer in the labels of all 5-alpha-reductase inhibitors.

3. Phosphodiesterase-5 inhibitor—Tadalafil is approved by the FDA to treat the symptoms and signs of BPH (Table 23–5); it is also approved for use in men with both urinary symptoms and erectile dysfunction. The data from two randomized, double-blind, placebo-controlled trials demonstrated significant improvements in standardized measurements of urinary function between 2 and 4 weeks after initiating treatment at 5 mg once daily, with minimal adverse effects.

4. Combination therapy—The Medical Therapy of Prostatic Symptoms (MTOPS) trial was a large, randomized, placebo-controlled trial comparing finasteride, doxazosin, the combination of the two, and placebo in 3047 men observed for a mean of 4.5 years. Long-term combination therapy with doxazosin and finasteride was safe and reduced the risk of overall clinical progression of BPH significantly more than did treatment with either medication alone. Combination therapy and finasteride alone reduced the long-term risk of acute urinary retention and the need for invasive therapy. Combination therapy had the risks of additional side effects and the cost of two medications.

C. Transurethral Surgical Therapy

Most cases of BPH requiring surgery can be managed with transurethral or minimally invasive techniques. This

remains an area of active research and innovation with several new technologies available. An overview of all the surgical options and decision making was published by the American Urological Association (Figure 23–3). Studies have shown decreased cost with surgical compared to medical therapies in as short as 6 months (or as long as 8 years).

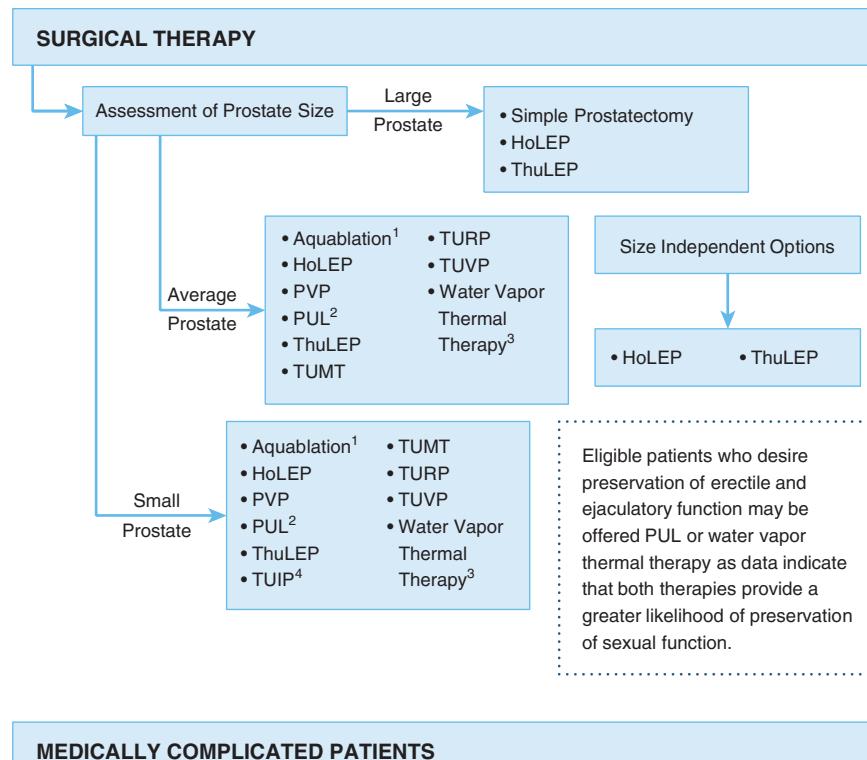
1. Transurethral resection of the prostate (TURP)—Over 95% of prostate surgeries can be performed endoscopically (through the urethra). TURP is the gold standard treatment for surgical treatment of BPH, and it often requires a 1- to 2-day hospital stay. Most head-to-head surgical studies comparing TURP to minimally invasive therapies show symptom scores and flow rate improvements are superior following TURP compared to any minimally invasive therapy. The risks of TURP include retrograde ejaculation (75%), erectile dysfunction (less than 5%), and urinary incontinence (less than 1%). Potential complications include (1) bleeding; (2) urethral stricture or bladder neck contracture; (3) perforation of the prostate capsule with extravasation; and (4) transurethral resection syndrome, a hypervolemic, hyponatremic state resulting from absorption of the hypotonic irrigating solution. Clinical manifestations of the syndrome include nausea, vomiting, confusion, hypertension, bradycardia, and visual disturbances. The risk of transurethral resection syndrome increases with monopolar resection times over 90 minutes. Treatment includes diuresis and, in severe cases, hypertonic saline administration (see Hyponatremia, Chapter 21). This syndrome was much more prevalent when TURPs were most often performed with monopolar electrocautery but, with the increased use of bi-polar TURPs (using saline irrigation), it is now very rare.

2. Transurethral incision of the prostate (TUIP)—Men with moderate to severe symptoms and small prostates (less than 30 g) often have posterior commissure hyperplasia or an “elevated bladder neck.” These patients will often benefit from incision of the prostate. The procedure is more rapid and less morbid than TURP. Outcomes in well-selected patients are comparable, though a lower rate of retrograde ejaculation has been reported (25%).

3. Transurethral electrovaporization of the prostate (TUVP)—TUVP is a technical electrosurgical modification of the standard TURP. A variety of energy delivery surfaces including a spherical rolling electrode (rollerball), grooved roller electrode (vaportrode), or hemi-spherical mushroom electrode (button) are used to deliver high current densities resulting in heat vaporization of prostatic tissue. For larger prostates, this procedure usually takes longer than a standard TURP, but it has comparable efficacy with lower transfusion requirements.

D. Minimally Invasive Therapies

1. Laser therapy—Various laser technologies now exist; they vary based on the wavelength and energy produced and the technique of tissue removal. Initial laser technologies relying on tissue coagulation have essentially been abandoned in favor of lasers that result in vaporization of tissue. The laser fiber is placed in direct contact with the



MEDICALLY COMPLICATED PATIENTS

In patients who are at higher risk for bleeding, such as those taking anticoagulation drugs, therapies with a lower need for blood transfusion, such as HoLEP, PVP and ThuLEP, should be considered. For additional information on the use of anticoagulation and antiplatelet therapy in surgical patients, refer to the ICUD/AUA review on Anticoagulation and Antiplatelet Therapy in Urologic Practice.

¹Eligibility for an aquablation procedure is dependent upon prostate volume > 30/< 80 g.

²Eligibility for a PUL procedure is dependent upon absence of obstructing midline prostate tissue and prostate volume < 80 g.

³Eligibility for a Water Vapor Thermal Therapy procedure is dependent upon prostate volume < 80 g.

⁴Eligibility for a TUIP procedure is dependent upon prostate volume < 30 g.

Figure 23-3. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia. HoLEP, holmium laser enucleation of the prostate; PUL, prostatic urethral lift; PVP, photoselective vaporization of the prostate; ThuLEP, thulium laser enucleation of the prostate; TUIP, transurethral incision of the prostate; TUMT, transurethral microwave therapy; TURP, transurethral resection of the prostate; TUVP, transurethral vaporization of the prostate. (Reproduced, with permission, from Foster HE et al; Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline Amendment 2019. J Urol. 2019;202:592.)

prostate tissue, which is then vaporized. An immediate defect is obtained in the prostatic urethra, similar to that seen during TURP. Advantages to such laser therapy include minimal blood loss, rare occurrence of transurethral resection syndrome, ability to treat patients during anticoagulant therapy, and ability to operate on outpatients. Disadvantages are the lack of tissue for pathologic examination, variable effectiveness, more frequent irritative voiding complaints, and expense of laser fibers and generators.

Holmium laser enucleation of the prostate (HoLEP) is a technique of enucleating the adenomatous lobes intact and morcellating the tissue within the bladder. Advantages of HoLEP compared with other methods include ability to

treat all prostate sizes, low re-treatment rates, few complications, and shorter duration of catheterization. This technique is an attractive alternative to open simple prostatectomy for very large glands (> 100 mL) with comparable outcomes. However, due to the steep learning curve for operators, it is not as widely available as other techniques.

Photovaporization of the prostate (PVP) is a more widely adopted technique that can be performed with a number of different lasers depending on surgeon preference. The original KTP greenlight laser used a 532-nm wavelength that is selectively absorbed by hemoglobin, leading to improved hemostasis. Advantages include combined vaporization and coagulation with significant

reduction in tissue volume, making this an ideal choice for anticoagulated patients. Disadvantages include limitations on prostate volume that can be efficiently treated (less than 80 mL) and difficulty controlling bleeding from larger venous channels.

The thulium laser is a continuous wave of 2013-nm energy that undergoes absorption in the irrigant but without the intermittent nature of holmium. This results in cleaner incisions, more efficient tissue absorption, and similar hemostatic advantages. It has been used for both resection-type and enucleation techniques with success. Advantages and disadvantages are similar to greenlight PVP, though the cleaner incisions make it more appealing for surgeons.

2. Transurethral microwave therapy (TUMT)—Microwave hyperthermia is most commonly delivered with a transurethral catheter. Some devices cool the urethral mucosa to decrease the risk of injury. However, if temperatures do not go above 45°C, cooling is unnecessary. Symptom score and flow rate improvement are obtained, but (as with laser surgery) large randomized studies with long-term follow-up are needed to assess durability and cost-effectiveness. Re-treatment rates are reported to be 9–21% at 5 years.

3. Implant to open prostatic urethra (UroLift)—The UroLift system uses permanent nitinol and stainless steel implants placed under cystoscopic guidance to retract the lateral lobes of the prostate and mechanically open the prostatic urethra. The procedure is FDA approved and can be performed under local anesthesia in the clinic. The ideal candidate has primarily lateral lobe hyperplasia and a prostate volume under 80 mL. Short-term data show improved symptoms and voiding flows with no de novo erectile dysfunction. Re-treatment rates within 5 years have been reported to be as high as 13.6%.

4. Water vapor thermal therapy (Rezūm)—This minimally invasive, FDA-approved technique uses a transurethral device to deliver water vapor into the prostatic tissue. As the steam condenses back into water, it releases large amounts of stored thermal energy leading to tissue necrosis and resorption of tissue within about 3 months. This procedure is done in the clinic or ambulatory surgery setting with local anesthesia; it requires 3–7 days of catheterization. In contrast to the UroLift procedure, there is a significant reduction in prostate volume over time, between 30% and 40% by 6 months, which relieves lower urinary tract symptoms in the process. Results from a 4-year randomized, controlled trial reported significant objective improvement in lower urinary tract symptoms as early as 2 weeks postprocedure, improvement that remained durable throughout the 4-year period. Recommended prostate volume for Rezūm treatment is 30–80 mL. Advantages include the minimally invasive, outpatient nature of the procedure with no significant bleeding risk even for anticoagulated patients, ability to treat the median lobe, and no reports of de novo erectile dysfunction or urinary incontinence. Disadvantages include slower recovery and longer catheterization times compared to TURP and laser procedures. Re-treatment rate at 4 years was reported to be 4.4%, a rate far lower than other minimally invasive options.

5. Aquablation—This ultrasound-guided, robot-assisted waterjet ablation of the prostate is designed to relieve prostatic obstruction with limited bleeding, shorter operative time, and lower sexual side effect profile. It is now offered as a treatment option by the American Urological Association for prostates between 30 mL and 80 mL in volume. Pre-treatment transrectal ultrasound is used to map out the specific region of the prostate to be resected and real-time transrectal ultrasound is used to monitor tissue resection during the procedure. The resection is performed under general or spinal anesthesia using a water jet from a transurethrally placed robotic handpiece. Following the resection, electrocautery or traction from a 3-way catheter is used to obtain hemostasis. Short-term data show improvements in urinary flow rate, postvoid residual volume, and quality-of-life, but long-term data on durability are still pending.

E. Simple Prostatectomy

When the prostate is very large, a simple prostatectomy by an open or robotic enucleation approach may be considered. What size is “too large” depends on the surgeon’s experience with TURP. Glands over 100 g are usually considered for enucleation. In addition to size, other relative indications for open prostatectomy include when there is a concomitant bladder diverticulum or stone, and when dorsal lithotomy positioning of the patient is not possible.

Simple prostatectomy can be performed with either a suprapubic or retropubic approach. Simple suprapubic prostatectomy is performed transvesically and is the operation of choice if there is concomitant bladder pathology (eg, bladder stones). These operations can also be performed via robotic-assisted laparoscopic techniques with shorter hospital stays, less blood loss, and decreased need for a suprapubic catheter.

► When to Refer

- Urinary retention.
- Patient dissatisfaction with medical therapy.
- Need for further evaluation (cystoscopy) or surgical intervention.

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CANCERS OF THE GENITOURINARY TRACT

(See Chapter 39 for Cancers of the Genitourinary Tract: Prostate Cancer, Bladder Cancer, Cancers of the Ureter & Renal Pelvis, Renal Cell Carcinoma, & Testicular Cancers.)

24

Nervous System Disorders

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HEADACHE

Headache is such a common complaint and can occur for so many different reasons that its proper evaluation may be difficult. New, severe, or acute headaches are more likely than chronic headaches to relate to an intracranial disorder; the approach to such headaches is discussed in Chapter 2. **Chronic headaches** may be primary or secondary to another disorder. Common **primary** headache syndromes include migraine, tension-type headache, and cluster headache. Important **secondary** causes to consider include intracranial lesions, head injury, cervical spondylosis, dental or ocular disease, temporomandibular joint dysfunction, sinusitis, hypertension, depression, and a wide variety of general medical disorders. Although underlying structural lesions are not present in most patients presenting with headache, it is nevertheless important to bear this possibility in mind. About one-third of patients with brain tumors, for example, present with a primary complaint of headache.

1. Migraine



ESSENTIALS OF DIAGNOSIS

- ▶ Headache, usually pulsatile, lasting 4–72 hours.
- ▶ Pain is typically, but not always, unilateral.
- ▶ Nausea, vomiting, photophobia, and phonophobia are common accompaniments.
- ▶ Pain is aggravated with routine physical activity.
- ▶ An aura of transient neurologic symptoms (commonly visual) may precede head pain.
- ▶ Commonly, head pain occurs with no aura.

► General Considerations

The pathophysiology of migraine probably relates to neuronal dysfunction in the trigeminal system resulting in release of vasoactive neuropeptides such as calcitonin gene-related peptide leading to neurogenic inflammation,

sensitization, and headache. Migraine aura is hypothesized to result from cortical spreading depression, a wave of neuronal and glial depolarization that moves slowly across the cerebral cortex corresponding to the clinical symptoms (ie, occipital cortex and visual aura). Migraine often exhibits a complex, polygenic pattern of inheritance. Sometimes, an autosomal dominant inheritance pattern is apparent, as in **familial hemiplegic migraine (FHM)**, in which attacks of lateralized weakness represent the aura.

► Clinical Findings

Typical migrainous headache is a lateralized throbbing headache that occurs episodically following its onset in adolescence or early adult life. In many cases, the headaches do not conform to this pattern, although their associated features and response to antimigrainous preparations nevertheless suggest a similar basis. In this broader sense, migrainous headaches may be lateralized or generalized, may be dull or throbbing, and are sometimes associated with anorexia, nausea, vomiting, photophobia, phonophobia, osmophobia, cognitive impairment, and blurring of vision. They usually build up gradually and last several hours or longer. Focal disturbances of neurologic function (**migraine aura**) may precede or accompany the headaches. Visual disturbances occur commonly and may consist of field defects (**scotoma**); of luminous visual hallucinations such as stars, sparks, unformed light flashes (**photopsia**), geometric patterns, or zigzags of light; or of some combination of field defects and luminous hallucinations (**scintillating scotomas**). Other focal disturbances such as aphasia or numbness, paresthesias, clumsiness, dysarthria, dysequilibrium, or weakness in a circumscribed distribution may also occur.

In rare instances, the neurologic or somatic disturbance accompanying typical migrainous headaches becomes the sole manifestation of an attack ("**migraine aura without headache**"). Very rarely, the patient may be left with a permanent neurologic deficit following a migrainous attack, and migraine with aura may be a risk factor for stroke.

Patients often give a family history of migraine. Attacks may be triggered by emotional or physical stress, lack or excess of sleep, missed meals, specific foods (eg, chocolate),

alcoholic beverages, bright lights, loud noise, menstruation, or use of oral contraceptives.

An uncommon variant is **migraine with brainstem aura**, in which blindness or visual disturbances throughout both visual fields are accompanied or followed by dysarthria, dysequilibrium, tinnitus, and perioral and distal paresthesias and are sometimes followed by transient loss or impairment of consciousness or by a confusional state. This, in turn, is followed by a throbbing (usually occipital) headache, often with nausea and vomiting.

In **recurrent painful ophthalmoplegic neuropathy** (previously ophthalmoplegic migraine), lateralized pain—often about the eye—is accompanied by nausea, vomiting, and diplopia due to transient external ophthalmoplegia. The ophthalmoplegia is due to third nerve palsy, sometimes with accompanying sixth nerve involvement, and may outlast the orbital pain by several days or even weeks. The ophthalmic division of the fifth nerve has also been affected in some patients. The condition is rare and a diagnosis of exclusion; more common causes of a painful ophthalmoplegia are internal carotid artery aneurysms and diabetes.

Treatment

Management of migraine consists of avoidance of any precipitating factors, together with prophylactic or symptomatic pharmacologic treatment if necessary.

A. Symptomatic Therapy

During acute attacks, rest in a quiet, darkened room may be helpful until symptoms subside. A simple analgesic (eg, aspirin, acetaminophen, ibuprofen, or naproxen) taken immediately often provides relief, but prescription medication is sometimes necessary. *To prevent medication overuse, use of simple analgesics should be limited to 15 days or less per month, and combination analgesics should be limited to no more than 10 days per month.*

1. Ergotamines—Cafergot, a combination of ergotamine tartrate (1 mg) and caffeine (100 mg), is often particularly helpful; one or two tablets are taken at the onset of headache or warning symptoms, followed by one tablet every 30 minutes, if necessary, up to six tablets per attack and no more than 10 days per month. Cafergot given rectally (one-half to one suppository containing 2 mg of ergotamine) or dihydroergotamine mesylate (0.5–1 mg intravenously or 1–2 mg subcutaneously or intramuscularly) may be useful when vomiting precludes use of oral medications. Ergotamine-containing preparations should be avoided during pregnancy, in patients with cardiovascular disease or its risk factors, and in patients taking potent CYP 3A4 inhibitors.

2. Serotonin agonists—Triptans are 5-HT_{1B/1D} receptor agonists that inhibit release of vasoactive neuropeptides. Sumatriptan is a rapidly effective agent for aborting attacks when given subcutaneously by an autoinjection device (4–6 mg once subcutaneously, may repeat once after 2 hours if needed; maximum dose 12 mg/24 h). Nasal and oral preparations are available but may be less effective due to slower absorption. Zolmitriptan is available in oral and nasal formulations. The dose is 5 mg orally or in one nostril

once; this may be repeated once after 2 hours. The maximum dose for both formulations is 10 mg/24 h. Other triptans are available, including rizatriptan (5–10 mg orally at onset, may repeat every 2 hours twice [maximum dose 30 mg/24 h]); naratriptan (1–2.5 mg orally at onset, may repeat once after 4 hours [maximum dose 5 mg/24 h]); almotriptan (6.25–12.5 mg orally at onset, may repeat dose once after 2 hours [maximum dose 25 mg/24 h]); frovatriptan (2.5 mg orally at onset, may repeat after 2 hours once [maximum dose 7.5 mg/24 h]); and eletriptan (20–40 mg orally at onset; may repeat after 2 hours once [maximum dose 80 mg/24 h]). Eletriptan is useful for immediate therapy, and frovatriptan, which has a longer half-life, may be worthwhile for patients with prolonged attacks or attacks provoked by menstrual periods. Patients often experience greater benefit when the triptan is combined with naproxen (500 mg orally).

Triptans may cause nausea and vomiting. They should probably be avoided in women who are pregnant, and in patients with hemiplegic or basilar migraine, a history of stroke or transient ischemic attack (TIA), or uncontrolled hypertension. In patients whose hypertension is controlled, triptans are commonly used safely, although caution is advised. Triptans are contraindicated in patients with coronary or peripheral vascular disease and Prinzmetal angina.

Lasmiditan (50–200 mg taken once at headache onset; no more than one dose in 24 hours) is a 5-HT_{1F} receptor agonist approved for use in the United States that lacks the vasoconstrictive properties of triptans and can be given safely to patients with cardiovascular risk factors. Dizziness and somnolence are common side effects, and patients should not drive within 8 hours of administration.

3. Calcitonin gene-related peptide antagonists—

Rimegepant sulfate (75 mg orally dissolved tablet taken once at headache onset; maximum dose 75 mg/24 h) and ubrogepant (50 or 100 mg orally at headache onset, may repeat after 2 hours once [maximum dose 200 mg/24 h]) are both calcitonin gene-related peptide antagonists that achieve pain freedom in 20% and pain relief in 60% of patients within 2 hours. Hypersensitivity reactions may occur immediately or several days after administration with rimegepant.

4. Other agents—Prochlorperazine is effective and may be administered rectally (25 mg suppository), intravenously or intramuscularly (5–10 mg), or orally (5–10 mg). Intravenous metoclopramide (10–20 mg) is also particularly useful in the emergency department setting. Various butalbital-containing combination oral analgesics risk overuse and dependence and should only be used as a last resort. Opioid analgesics should be *avoided* because of high rates of rebound headache and the tendency to develop medication overuse headache.

5. Neuromodulation—Sham-controlled trials show that single-pulse transcranial magnetic stimulation aborts migraine with aura, and noninvasive vagus nerve stimulation, transcutaneous trigeminal nerve stimulation, and remote electrical stimulation applied to the upper arm abort migraine with or without aura. Transcranial magnetic stimulation is contraindicated in patients with epilepsy.

B. Preventive Therapy

Preventive treatment may be necessary if migraine headaches occur *more frequently than two or three times a month* or significant disability is associated with attacks. Avoidance of triggers and maintenance of homeostasis with regular sleep, meals, and hydration should not be neglected; a headache diary may be useful to identify triggers. Some more common agents used for prophylaxis are listed in Table 24–1. The medication chosen first will vary with the

individual patient, depending on factors such as comorbid obesity, depression, anxiety, hypertension, and patient preference. Several medications may have to be tried in turn before headaches are brought under control. Once a medication has been found to help, it should be continued for several months. If the patient remains headache-free, the dose may be tapered and the medication eventually withdrawn. Transcutaneous supraorbital neurostimulation reduced the number of migraine days per month in a

Table 24–1. Pharmacologic prophylaxis of migraine (listed in alphabetical order within classes).

Medication	Usual Adult Oral Daily Dose	Selected Side Effects and Comments
Antiepileptic¹		
Topiramate	100 mg (divided twice daily)	Somnolence, nausea, dyspepsia, irritability, dizziness, ataxia, nystagmus, diplopia, glaucoma, renal calculi, weight loss, hypohidrosis, hyperthermia.
Valproic acid ^{2,3}	500–1000 mg (divided twice daily)	Nausea, vomiting, diarrhea, drowsiness, alopecia, weight gain, hepatotoxicity, thrombocytopenia, tremor, pancreatitis.
Cardiovascular		
Candesartan ³	8–32 mg once daily	Dizziness, cough, diarrhea, fatigue.
Guanfacine	1 mg once daily	Dry mouth, somnolence, dizziness, constipation, erectile dysfunction.
Propranolol ⁴	80–240 mg (divided twice to four times daily)	Fatigue, dizziness, hypotension, bradycardia, depression, insomnia, nausea, vomiting, constipation.
Verapamil ⁵	120–240 mg (divided three times daily)	Headache, hypotension, flushing, edema, constipation. May aggravate atrioventricular nodal heart block and heart failure.
Antidepressant⁶		
Amitriptyline ⁷	10–150 mg at bedtime	Sedation, dry mouth, constipation, weight gain, blurred vision, edema, hypotension, urinary retention.
Venlafaxine	37.5–150 mg extended release once daily	Nausea, somnolence, dry mouth, dizziness, diaphoresis, sexual dysfunction, anxiety, weight loss.
Monoclonal antibodies against calcitonin gene-related peptide		
Eptinezumab	100 mg intravenously every 3 months	Hypersensitivity reaction during infusion, nasopharyngitis.
Erenumab	70–140 mg subcutaneously once monthly	Injection site reactions, constipation, muscle cramps, antibody development.
Fremanezumab	225 mg subcutaneously once monthly	Injection site reactions, antibody development.
Galcanezumab	120 mg subcutaneously daily × 2 doses, followed by 120 mg monthly	Injection site reactions, antibody development.
Other		
Acupuncture		More rapid pain relief and fewer side effects than pharmacologic treatment.
Botulinum toxin A	Intramuscular injection	Injection site reaction, hypersensitivity, muscle weakness.
Riboflavin	400 mg once daily	Yellow-orange discoloration of urine.
Transcutaneous supraorbital neurostimulation	20 minutes daily	Transient paresthesia at site of stimulation.

¹Gabapentin and possibly other antiepileptics have also been used successfully.

²Avoid during pregnancy.

³Not FDA-approved for this indication.

⁴Other beta-adrenergic antagonists such as atenolol, metoprolol, nadolol, and timolol are similarly effective.

⁵Other calcium channel antagonists (eg, nimodipine, nicardipine, and diltiazem) may also help.

⁶Depression is commonly comorbid with migraine disorder and may warrant separate treatment.

⁷Other tricyclic antidepressants (eg, nortriptyline and imipramine) may help similarly.