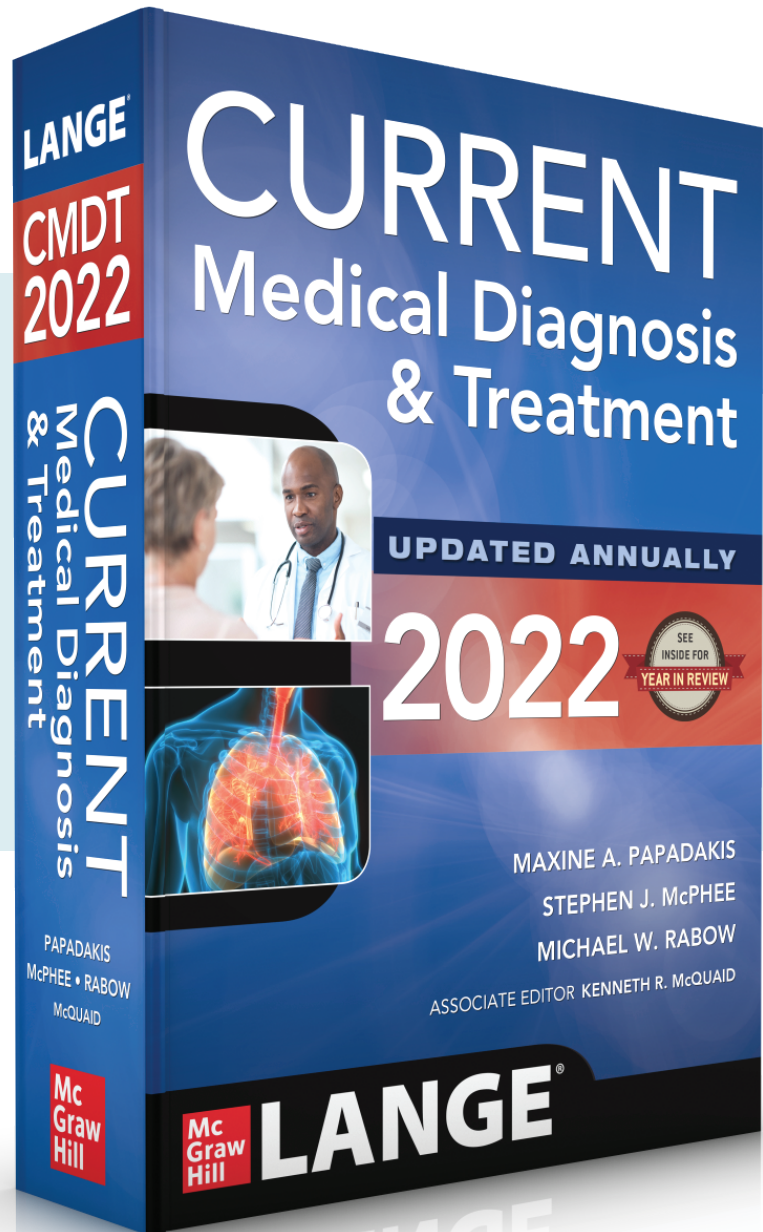


Sample Chapter

CHAPTER 16:
Liver, Biliary Tract, &
Pancreas Disorders



BUY NOW

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 hepatocanalicular 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 asterix may be present, depending on the cause, severity, and chronicity of liver dysfunction.

BUY NOW

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

BUY NOW

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.

BUY NOW

Table 16–4. Causes of serum aminotransferase elevations.¹

Mild Elevations ($< 5 \times$ normal)	Severe Elevations ($> 15 \times$ normal)
Hepatic: ALT-predominant Chronic hepatitis B, C, and D Acute viral hepatitis (A–E, EBV, CMV) Steatosis/steatohepatitis Hemochromatosis Medications/toxins Autoimmune hepatitis Alpha-1-antitrypsin (alpha-1-antitrypsin deficiency) Wilson disease Celiac disease Glycogenic hepatopathy Hepatic: AST-predominant Alcohol-related liver injury (ALT:AST $> 2:1$) Cirrhosis Nonhepatic Strenuous exercise Hemolysis Myopathy Thyroid disease Macro-AST	Acute viral hepatitis (A–E, herpes) Medications/toxins Ischemic hepatitis Autoimmune hepatitis Wilson disease Acute bile duct obstruction Acute Budd-Chiari syndrome Hepatic artery ligation

¹Almost any liver disease can cause moderate aminotransferase elevations ($5\text{--}15 \times$ 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 cholangiopancreatography. 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 $50,000/\text{mL}$ ($50 \times 10^9/\text{mL}$) 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]

BUY NOW

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.

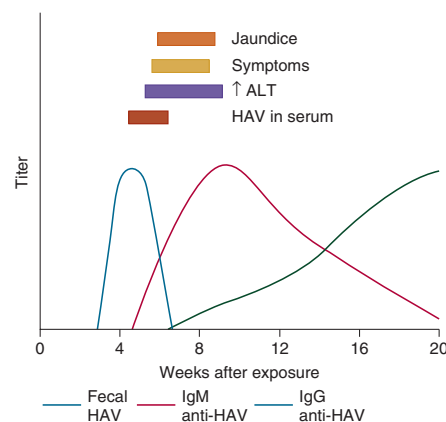
The incubation period averages 30 days. HAV is excreted in feces for up to 2 weeks before clinical illness but rarely after the first week of illness. The mortality rate for hepatitis A is low, and acute liver failure due to hepatitis A is uncommon except for rare instances in which it occurs in a patient 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.)

BUY NOW

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/mL ($0.2 \times 10^9/L$).

► 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

BUY NOW

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 coinfecting 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.

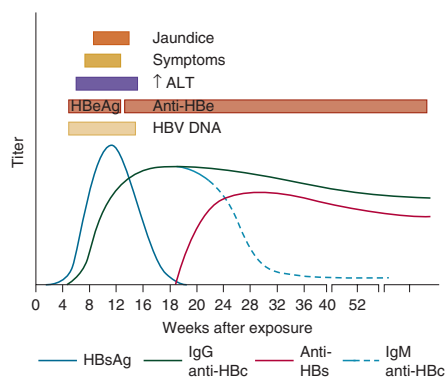
The acute illness usually subsides over 2–3 weeks with complete clinical and laboratory recovery by 16 weeks. In 5–10% of cases, the course may be more protracted, but less than 1% will develop acute liver failure. Hepatitis B may become chronic.

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

BUY NOW



▲ **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 B, 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-HBe	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.

BUY NOW

► 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 log₁₀ 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.

BUY NOW

Chou R et al. Screening for hepatitis B virus infection in non-pregnant adolescents and adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2020;324:2423. [PMID: 33320229]
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]
US Preventive Services Task Force; Krist AH et al. Screening for hepatitis B virus infection in adolescents and adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;324:2415. [PMID: 33320230]
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-ABCD 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

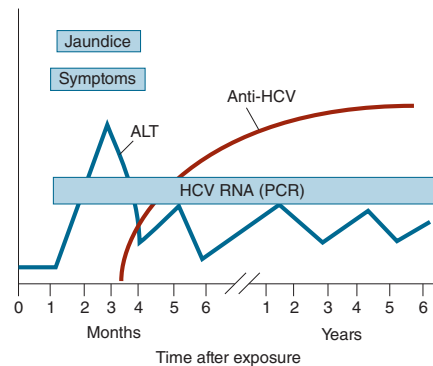
A. Symptoms and Signs

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

BUY NOW



▲ **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 coinfecting 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.

BUY NOW

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

BUY NOW

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 $\mu\text{mol/L}$ and is invariable when it is greater than 200 $\mu\text{mol/L}$. 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 H_2 -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 silybinin (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

BUY NOW

saline to induce hyponatremia (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 (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-antitrypsin 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

BUY NOW

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 coinfecting 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 HBeAg-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 **HBeAg-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-HBe seroconversion, some patients (especially Asian patients) serorevert to HBeAg after discontinuation, have a rise in

BUY NOW

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

BUY NOW

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 (“...asvirs”), 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 (“...buvirs”) 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 coinfecting 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.

BUY NOW

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.

BUY NOW

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 coinfecting 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.

European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol*. 2020;73:1170. [PMID: 32956768]
Gonzalez HC et al. Hepatitis C: does successful treatment alter the natural history and quality of life? *Gastroenterol Clin North Am*. 2020;49:301. [PMID: 32389364]
Rabaan AA et al. Overview of hepatitis C infection, molecular biology, and new treatment. *J Infect Public Health*. 2020;13:773. [PMID: 31870632]

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.

BUY NOW

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 ≥ upper limit of normal or 2 points for level ≥ 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

BUY NOW

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.

Mack CL et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. *Hepatology*. 2020;72:671. [PMID: 31863477]
Pape S et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. *Clin Gastroenterol Hepatol*. 2020;18:1609. [PMID: 31715274]
Trivedi PJ et al. Grand Rounds: Autoimmune hepatitis. *J Hepatol*. 2019;70:773. [PMID: 30465775]

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 mkat/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

BUY NOW

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 mkat/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 μmol/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, polymorphonuclear 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

BUY NOW

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 transferin 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.

BUY NOW

Avila MA et al. Recent advances in alcohol-related liver disease (ALD): summary of a Gut round table meeting. *Gut*. 2020;69:764. [PMID: 3187928]
Crabb DW et al. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2020;71:306. [PMID: 31314133]
Sussman NL et al (editors). *Alcoholic liver disease*. *Clin Liver Dis*. 2019;23:1.

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-B*57:01 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, methylphenidate, naltrexone, nevirapine, oxacillin, phenytoin, pyrazinamide, quinidine, rivaroxaban, streptomycin, temozolomide, thiazolidinediones, tolmetamol, 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.

BUY NOW

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 nonhepatic 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), methyl dopa, 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 hepatis (blood-filled cavities)—Peliosis hepatis 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 (hepatic 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.

Gholam PM (editor). Drug hepatotoxicity. Clin Liver Dis 2020;24:1. [Full issue]
Hoofnagle JH et al. Drug-induced liver injury—types and phenotypes. N Engl J Med. 2019;381:264. [PMID: 31314970]
Peeraphatdit TB et al. Hepatotoxicity from immune checkpoint inhibitors: a systematic review and management recommendation. Hepatology. 2020;72:315. [PMID: 32167613]

BUY NOW

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,

BUY NOW

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://naflscore.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.

BUY NOW

► When to Refer

Refer patients with NAFLD who require liver biopsy for diagnosis.

Eslam M et al. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. 2020;158:1999. [PMID: 32044314]
Sanyal AJ et al (editors). Nonalcoholic fatty liver disease. *Gastroenterol Clin N Am*. 2020;49:1. [Full issue]
Sheka AC et al. Nonalcoholic steatohepatitis: a review. *JAMA*. 2020;323:1175. [PMID: 32207804]
Younossi ZM et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019; 394:2184. [PMID: 31813633]

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, asterix, 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

BUY NOW

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 indeterminate 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 ($150 \times 10^9/L$) 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).

BUY NOW

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

BUY NOW

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 ($75 \times 10^9/L$), 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 ($0.5 \times 10^9/L$) with a high polymorphonuclear (PMN) cell count (250/mcL [$0.25 \times 10^9/L$] 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 multidrug-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 ($11 \times 10^9/L$). 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])

BUY NOW

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 µmol/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 µmol/L) and a platelet count greater than 75,000/mL ($75 \times 10^9/L$). 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%), hyponatremia (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 asterix. 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

BUY NOW

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 dilations 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 dilations, 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 hypoxemic patients. The syndrome may reverse with liver transplantation, although postoperative morbidity and mortality from severe hypoxemic 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 treprostinil (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

BUY NOW

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 (mmol/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: $\text{MELD-Na} = \text{MELD} + (140 - \text{Na}) \times (1 - 0.025 \times \text{MELD})$.			

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 mmol/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

BUY NOW

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 nonelective 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.

Aithal GP et al. Guidelines on the management of ascites in cirrhosis. *Gut*. 2021;70:9. [PMID: 33067334]
 Arroyo V et al. Acute-on-chronic liver failure. *N Engl J Med*. 2020;382:2137. [PMID: 32459924]
 Bajaj JS et al. Important unresolved questions in the management of hepatic encephalopathy: an ISHEN consensus. *Am J Gastroenterol*. 2020;115:989. [PMID: 32618647]
 John S, Friedman LS. Portal hypertensive ascites: current status. *Curr Hepatology Rep*. 2020;19:226. <https://doi.org/10.1007/s11901-020-00524-y>
 Zermatten MG et al. Hemostatic alterations in patients with cirrhosis: from primary hemostasis to fibrinolysis. *Hepatology*. 2020;71:2135. [PMID: 32090357]

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, xanthelasmas, 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 *Chlamydia 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

BUY NOW

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 aminopeptide, 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-HT₂) 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-

BUY NOW

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.

Gatselis NK et al. Factors associated with progression and outcomes of early stage primary biliary cholangitis. *Clin Gastroenterol Hepatol.* 2020;18:684. [PMID: 31419573]
Lindor KD et al. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology.* 2019;69:394. [PMID: 30070375]
Murillo Perez CF et al. Goals of treatment for improved survival in primary biliary cholangitis: treatment target should be bilirubin within the normal range and normalization of alkaline phosphatase. *Am J Gastroenterol.* 2020;115:1066. [PMID: 32618657]
Younossi ZM et al. Diagnosis and management of primary biliary cholangitis. *Am J Gastroenterol.* 2019;114:48. [PMID: 30429590]

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

BUY NOW

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

BUY NOW

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, deferiprone, 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]
Prabhu A et al. Systematic review of the clinical outcomes of iron reduction in hereditary hemochromatosis. *Hepatology*. 2020;72:1469. [PMID: 32500577]

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

BUY NOW

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.

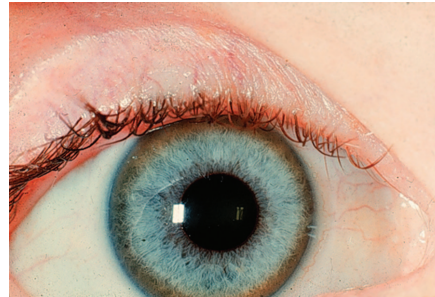
Clinical Findings

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

BUY NOW

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, Behçet 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.

BUY NOW

► 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.

BUY NOW

► 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 μmol/L), due in part to hypoxia of perivenular 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]
Horvath T et al. Liver injury and failure in critical illness. *Hepatology.* 2019;70:2204. [PMID: 31215660]
Kudravalli 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,

BUY NOW

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]

BUY NOW

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 (pyelphlebitis); (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 VV 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]

BUY NOW

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 hepatis, 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.

BUY NOW

CHOLELITHIASIS (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.

BUY NOW

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
Cholesterosis 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

BUY NOW

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 $\mu\text{mol/L}$) 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. $^{99\text{mTc}}$ 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 $\mu\text{mol/L}$) (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,” cholesterosis). 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.

BUY NOW

► 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. Cholelithiasis 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 AYW 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 Heesewijk 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. Cholelithiasis 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

BUY NOW

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]

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 juxtaepapillary 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

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.

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 mkat/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 μmol/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

BUY NOW

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 $\mu\text{mol/L}$], 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 $\mu\text{mol/L}$]), 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),

BUY NOW

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 carbapenem 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]

Iqbal U et al. Emergent versus urgent ERCP in acute cholangitis: a systematic review and meta-analysis. *Gastrointest Endosc.* 2020;91:753. [PMID: 31628955]

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 μmol/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

BUY NOW

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]

Lakhtakia S et al. Long-term outcomes after temporary placement of a self-expanding fully covered metal stent for benign biliary strictures secondary to chronic pancreatitis. *Gastrointest Endosc.* 2020;91:361. [PMID: 31494135]

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 sacular dilations 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,

BUY NOW

anticardiolipin, antithyroperoxidase, 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,

BUY NOW

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).

Chapman MH et al. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. *Gut*. 2019;68:1356. [PMID: 31154395]
Eaton JE et al. Primary sclerosing cholangitis risk estimate tool (PREsTo) predicts outcomes of the disease: a derivation and validation study using machine learning. *Hepatology*. 2020;71:214. [PMID: 29742811]
Trivedi PJ et al. Effects of primary sclerosing cholangitis on risks of cancer and death in people with inflammatory bowel disease, based on sex, race, and age. *Gastroenterology*. 2020;159:915. [PMID: 32445859]

DISEASES OF THE PANCREAS

See Chapter 39 for Carcinoma of the Pancreas and Periapillary 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, methyl dopa, 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

BUY NOW

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 [$149.94 \text{ } \mu\text{mol/L}$]) 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**)

BUY NOW

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.

BUY NOW

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

BUY NOW

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 nasojunal 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 μ mol/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

BUY NOW

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.

Ayoub F et al. Pancreatic cysts—an overview and summary of society guidelines, 2021. *JAMA*. 2021;325:391. [PMID: 33496762]
Baron TH et al. American Gastroenterological Association Clinical Practice Update: management of pancreatic necrosis. *Gastroenterology*. 2020;158:67. [PMID: 31479658]
Boxhoorn L et al. Acute pancreatitis. *Lancet*. 2020;396:726. [PMID: 32891214]
Mederos MA et al. Acute pancreatitis: a review. *JAMA*. 2021;325:382. [PMID: 33496779]
Ricci C et al. Treatment for infected pancreatic necrosis should be delayed, possibly avoiding an open surgical approach. *Ann Surg*. 2021;273:251. [PMID: 31972645]

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 (IgG₄ 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 IgG₄-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 IgG₄ 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 inhibitor gene (*PSTI*, also known as the serine protease inhibitor, *SPINK1*), the

BUY NOW

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 inflammatory 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 pancreatolithiasis 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

BUY NOW

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 H_2 -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 IgG_4 -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 minicapsules</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 minitables</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 of 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

BUY NOW

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]

BUY NOW