3 - Hepatic and Biliary Disorders

Chapter 23. Approach to the Patient With Liver Disease

Introduction

The liver is the most metabolically complex organ. Hepatocytes (liver parenchymal cells) perform the liver's metabolic functions:

• Formation and excretion of bile during bilirubin metabolism (see Sidebar 23-1)

• Regulation of carbohydrate homeostasis

• Lipid synthesis and secretion of plasma lipoproteins

• Control of cholesterol metabolism

• Formation of urea, serum albumin, clotting factors, enzymes, and numerous other proteins

• Metabolism or detoxification of drugs and other foreign substances

At the cellular level, portal triads consist of adjacent and parallel terminal branches of bile ducts, portal veins, and hepatic arteries that border the hepatocytes (see Fig. 23-1). Terminal branches of the hepatic veins are in the center of hepatic lobules. Because blood flows from the portal triads past the hepatocytes and drains via vein branches in the center of the lobule, the center of the lobule is the area most susceptible to ischemia.

Pathophysiology

Liver disorders can result from a wide variety of insults, including infections, drugs, toxins, ischemia, and autoimmune disorders. Occasionally, liver disorders occur postoperatively (see p. 223). Most liver disorders cause some degree of hepatocellular injury and necrosis, resulting in various abnormal laboratory test results and, sometimes, symptoms.

[**Fig. 23-1.** Organization of the liver.]

Symptoms may be due to liver disease itself (eg, jaundice due to acute hepatitis) or to complications of liver disease (eg, acute GI bleeding due to cirrhosis and portal hypertension).

Sidebar 23-1 Overview of Bilirubin Metabolism

The breakdown of heme produces bilirubin (an insoluble waste product) and other bile pigments. Bilirubin must be made water soluble to be excreted. This transformation occurs in 5 steps: formation, plasma transport, liver uptake, conjugation, and biliary excretion.

Formation: About 250 to 350 mg of unconjugated bilirubin forms daily; 70 to 80% derives from the breakdown of degenerating RBCs, and 20 to 30% (early-labeled bilirubin) derives primarily from other heme proteins in the bone marrow and liver. Hb is degraded to iron and biliverdin, which is converted to bilirubin.

Plasma transport: Unconjugated (indirect-reacting) bilirubin is not water soluble and so is transported in the plasma bound to albumin. It cannot pass through the glomerular membrane into the urine. Albumin binding weakens under certain conditions (eg, acidosis), and some substances (eg, salicylates, certain antibiotics) compete for the binding sites.

Liver uptake: The liver takes up bilirubin rapidly but does not take up the attached serum albumin.

Conjugation: Unconjugated bilirubin in the liver is conjugated to form mainly bilirubin diglucuronide, or conjugated (direct-reacting) bilirubin. This reaction, catalyzed by the microsomal enzyme glucuronyl transferase, renders the bilirubin water soluble.

Biliary excretion: Tiny canaliculi formed by adjacent hepatocytes progressively coalesce into ductules, interlobular bile ducts, and larger hepatic ducts. Outside the porta hepatis, the main hepatic duct joins the cystic duct from the gallbladder to form the common bile duct, which drains into the duodenum at the ampulla of Vater.

Conjugated bilirubin is secreted into the bile canaliculus with other bile constituents. In the intestine, bacteria metabolize bilirubin to form urobilinogen, much of which is further metabolized to stercobilins, which render the stool brown. In complete biliary obstruction, stools lose their normal color and become light gray (clay-colored stool). Some urobilinogen is reabsorbed, extracted by hepatocytes, and re-excreted in bile (enterohepatic circulation). A small amount is excreted in urine.

Because conjugated bilirubin is excreted in urine and unconjugated bilirubin is not, only conjugated hyperbilirubinemia (eg, due to hepatocellular or cholestatic jaundice) causes bilirubinuria.

Despite necrosis, the liver can regenerate itself. Even extensive patchy necrosis can resolve completely (eg, in acute viral hepatitis). Incomplete regeneration and fibrosis, however, may result from injury that bridges entire lobules or from less pronounced but ongoing damage.

Specific diseases preferentially affect certain hepatobiliary structures or functions (eg, acute viral hepatitis is primarily manifested by damage to hepatocytes or hepatocellular injury; primary biliary cirrhosis, by impairment of biliary secretion; and cryptogenic cirrhosis, by liver fibrosis and resultant portal venous hypertension). The part of the hepatobiliary system affected determines the symptoms, signs, and laboratory abnormalities (see also Ch. 24). Some disorders (eg, severe alcoholic liver disease) affect multiple liver structures, resulting in a combination of patterns of symptoms, signs, and laboratory abnormalities.

The prognosis of serious complications is worse in older adults, who are less able to recover from severe physiologic stresses and to tolerate toxic accumulations.

Evaluation

History: Various symptoms may develop, but few are specific for liver disorders:

- Common nonspecific symptoms include fatigue, anorexia, nausea, and, occasionally, vomiting, particularly in severe disorders.

- Loose, fatty stools (steatorrhea) can occur when cholestasis prevents sufficient bile from reaching the intestines. Patients with steatorrhea are at risk of deficiencies of fat-soluble vitamins (A, D, E, K). Common clinical consequences may include osteoporosis and bleeding.

- Fever can develop in viral or alcoholic hepatitis.

- Jaundice (see p. 212), occurring in both hepatocellular dysfunction and cholestatic disorders, is the most specific symptom. It is often accompanied by dark urine and light stools.

- Right upper quadrant pain due to liver disorders usually results from distention (eg, by passive venous congestion or tumor) or inflammation of the liver capsule.

- Erectile dysfunction and feminization develop; however, these symptoms may reflect the effects of alcohol more than liver disorders.

Family history, social history, and drug and substance use history should note risk factors for liver disorders (see

Table 23-1).

Physical examination: Abnormalities detectable on a physical examination usually do not develop until late in the course of the disease. Some common findings suggest a cause (see Table 23-2).

Ascites

Ascites is free fluid in the peritoneal cavity. The most common cause is portal hypertension. Symptoms usually result from abdominal distention. Diagnosis is based on physical examination and often ultrasonography or CT. Treatments include bed rest, dietary Na restriction, diuretics, and therapeutic paracentesis. Ascitic fluid can become infected (spontaneous bacterial peritonitis), often with pain and fever. Diagnosis of infection involves analysis and culture of ascitic fluid. Infection is treated with antibiotics.

[**Table 23-1.** Risk Factors for Liver Disorders]

Etiology

Ascites can result from chronic, but not acute, liver diseases.

Hepatic causes include the following:

• Portal hypertension (accounts for > 90% of hepatic cases), usually due to cirrhosis

• Chronic hepatitis

• Severe alcoholic hepatitis without cirrhosis

• Hepatic vein obstruction (Budd-Chiari syndrome)

Portal vein thrombosis does not usually cause ascites unless hepatocellular damage is also present.

Nonhepatic causes include the following:

• Generalized fluid retention associated with systemic diseases (eg, heart failure, nephrotic syndrome, severe hypoalbuminemia, constrictive pericarditis)

• Peritoneal disorders (eg, carcinomatous or infectious peritonitis, biliary leak due to surgery or another medical procedure)

• Less common causes, such as renal dialysis, pancreatitis, SLE, and endocrine disorders (eg, myxedema)

Pathophysiology

Mechanisms are complex and incompletely understood. Factors include altered Starling's forces in the portal vessels (low oncotic pressure due to hypoalbuminemia plus increased portal venous pressure), avid renal Na retention (urinary Na concentration is typically < 5 mEq/L), and possibly increased hepatic lymph formation.

Mechanisms that seem to contribute to renal Na retention include activation of the renin-angiotensin-aldosterone system; increased sympathetic tone; intrarenal shunting of blood away from the cortex; increased formation of nitric oxide; and altered formation or metabolism of ADH, kinins, prostaglandins, and atrial natriuretic factor. Vasodilation in the splanchnic arterial circulation may be a trigger, but the specific roles and interrelationships of these abnormalities remain uncertain.

Symptoms and Signs

Small amounts of ascitic fluid cause no symptoms. Moderate amounts cause increased abdominal girth and weight gain. Massive amounts may cause nonspecific diffuse abdominal pressure, but actual pain is uncommon and suggests another cause of acute abdominal pain (see p. 106). If ascites results in elevation of the diaphragm, dyspnea may occur. Symptoms of spontaneous bacterial peritonitis (SBP) may include new abdominal discomfort and fever.

Signs include shifting dullness on abdominal percussion and a fluid wave. Volumes < 1500 mL may not cause physical findings. Massive ascites causes tautness of the abdominal wall and flattening of the umbilicus. In liver diseases or peritoneal disorders, ascites is usually isolated or disproportionate to peripheral edema; in systemic diseases (eg, heart failure), the reverse is usually true.

Diagnosis

• Ultrasonography or CT unless physical findings make diagnosis obvious

• Often tests of ascitic fluid

Diagnosis may be based on physical examination if there is a large amount of fluid, but imaging tests are more sensitive. Ultrasonography and CT reveal much smaller volumes of fluid (100 to 200 mL) than does physical examination. SBP is suspected if a patient with ascites also has abdominal pain, fever, or unexplained deterioration.

Diagnostic paracentesis (see p. 99) should be done if any of the following occur:

• Ascites is newly diagnosed.

• Its cause is unknown.

• SBP is suspected.

[**Table 23-2.** Interpretation of Some Physical Findings]

About 50 to 100 mL of fluid is removed and analyzed for gross appearance, protein content, cell count and differential, cytology, culture, and, as clinically indicated, acid-fast stain, amylase, or both. In contrast to ascites due to inflammation or infection, ascites due to portal hypertension produces fluid that is clear and straw-colored, has a low protein concentration, a low PMN count (< 250 cells/µL), and, most reliably, a high serum-to-ascites albumin concentration gradient, which is the serum albumin concentration minus the ascitic albumin concentration. Gradients > 1.1 g/dL are relatively specific for ascites due to portal hypertension. In ascitic fluid, turbidity and a PMN count > 250 cells/µL indicate SBP, whereas bloody fluid can suggest a tumor or TB. The rare milky (chylous) ascites is most common with lymphoma.

Treatment

• Bed rest and dietary Na restriction

• Sometimes spironolactone, possibly plus furosemide

• Sometimes therapeutic paracentesis

Bed rest and dietary Na restriction (2000 mg/day) are the first and least risky treatments for ascites due to portal hypertension. Diuretics should be used if rigid Na restriction fails to initiate diuresis within a few days. Spironolactone is usually effective (in oral doses ranging from 50 mg once/day to 200 mg bid). A loop diuretic (eg, furosemide 20 to 160 mg po usually once/day or 20 to 80 mg po bid) should be added if spironolactone is insufficient. Because spironolactone can cause K retention and furosemide K depletion, the combination of these drugs often provides optimal diuresis with a lower risk of K abnormalities. Fluid restriction is indicated only for treatment of hyponatremia (serum Na < 120 mEq/L). Changes in body weight and urinary Na determinations reflect response to treatment. Weight loss of about 0.5 kg/day is

optimal because the ascitic compartment cannot be mobilized much more rapidly. More aggressive diuresis depletes fluid from the intravascular compartment, especially when peripheral edema is absent; this depletion may cause renal failure or electrolyte imbalance (eg, hypokalemia) that may precipitate portal-systemic encephalopathy. Inadequate dietary Na restriction is the usual cause of persistent ascites.

Therapeutic paracentesis is an alternative. Removal of 4 L/day is safe; many clinicians infuse IV salt-poor albumin (about 40 g/paracentesis) at about the same time to prevent intravascular volume depletion. Even single total paracentesis may be safe. Therapeutic paracentesis shortens the hospital stay with relatively little risk of electrolyte imbalance or renal failure; nevertheless, patients require ongoing diuretics and tend to reaccumulate fluid more rapidly than those treated without paracentesis.

Techniques for the autologous infusion of ascitic fluid (eg, the LeVeen peritoneovenous shunt) often cause complications and are generally no longer used. Transjugular intrahepatic portosystemic shunting (TIPS) can lower portal pressure and successfully treat ascites resistant to other treatments, but TIPS is invasive and may cause complications, including portal-systemic encephalopathy and worsening hepatocellular function.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is infection of ascitic fluid without an apparent source. Manifestations may include fever, malaise, and symptoms of ascites and worsening hepatic failure. Diagnosis is by examination of ascitic fluid. Treatment is with cefotaxime or another antibiotic.

SBP is particularly common in cirrhotic ascites, especially among alcoholics. This infection can cause serious sequelae or death. The most common bacteria causing SBP are gram-negative *Escherichia coli* and *Klebsiella pneumoniae* and gram-positive *Streptococcus pneumoniae*; usually only a single organism is involved.

Symptoms and Signs

Patients have symptoms and signs of ascites. Discomfort is usually present; it typically is diffuse, constant, and mild to moderate in severity.

Signs of SBP may include fever, malaise, encephalopathy, worsening hepatic failure, and unexplained clinical deterioration. Peritoneal signs (eg, abdominal tenderness and rebound) are present but may be somewhat diminished by the presence of ascitic fluid.

Diagnosis

• Diagnostic paracentesis

Clinical diagnosis of SBP can be difficult; diagnosis requires a high index of suspicion and liberal use of diagnostic paracentesis, including culture. Transferring ascitic fluid to blood culture media before incubation increases the sensitivity of culture to almost 70%. PMN count of > 250 cells/µL is diagnostic of SBP. Blood cultures are also indicated. Because SBP usually results from a single organism, finding mixed flora on culture suggests a perforated abdominal viscus or contaminated specimen.

Treatment

• Cefotaxime or another antibiotic

If SBP is diagnosed, an antibiotic such as cefotaxime 2 g IV q 4 to 8 h (pending Gram stain and culture results) is given for at least 5 days and until ascitic fluid shows < 250 PMNs/µL. Antibiotics increase the chance of survival. Because SBP recurs within a year in up to 70% of patients, prophylactic antibiotics are indicated; quinolones (eg, norfloxacin 400 mg po once/day) are most widely used.

Antibiotic prophylaxis in ascitic patients with variceal hemorrhage decreases the risk of SBP.

Fatty Liver

(Hepatic Steatosis)

Fatty liver is excessive accumulation of lipid in hepatocytes, the most common liver response to injury.

Fatty liver develops for many reasons, involves many different biochemical mechanisms, and causes different types of liver damage. Clinically, it is most useful to distinguish fatty liver due to pregnancy or alcoholic liver disease (see p. 235) from that occurring in the absence of pregnancy and alcoholism (nonalcoholic fatty liver disease [NAFLD]). NAFLD includes simple fatty infiltration (a benign condition) and nonalcoholic steatohepatitis, a less common but more important variant.

(See also the American Gastroenterological Association's Medical Position Statement and Technical Review on nonalcoholic fatty liver disease.)

Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis (NASH) is a syndrome that develops in patients who are not alcoholics; it causes liver damage that is histologically indistinguishable from alcoholic hepatitis. It develops most often in patients with at least one of the following risk factors: obesity, dyslipidemia, and glucose intolerance. Pathogenesis is poorly understood but seems to be linked to insulin resistance (eg, as in obesity or metabolic syndrome). Most patients are asymptomatic. Laboratory findings include elevations in aminotransferase levels. Biopsy is required to confirm the diagnosis. Treatment includes elimination of causes and risk factors.

NASH (sometimes called steatonecrosis) is diagnosed most often in patients between 40 yr and 60 yr but can occur in all age groups. Many affected patients have obesity, type 2 diabetes mellitus, or dyslipidemia.

Pathophysiology

Pathophysiology involves fat accumulation (steatosis), inflammation, and, variably, fibrosis. Steatosis results from hepatic triglyceride accumulation. Possible mechanisms for steatosis include reduced synthesis of very low density lipoprotein (VLDL) and increased hepatic triglyceride synthesis (possibly due to decreased oxidation of fatty acids or increased free fatty acids being delivered to the liver). Inflammation may result from lipid peroxidative damage to cell membranes. These changes can stimulate hepatic stellate cells, resulting in fibrosis. If advanced, NASH can cause cirrhosis and portal hypertension.

Symptoms and Signs

Most patients are asymptomatic. However, some have fatigue, malaise, or right upper quadrant abdominal discomfort. Hepatomegaly develops in about 75% of patients. Splenomegaly may develop if advanced hepatic fibrosis is present and is usually the first indication that portal hypertension has developed. Patients with cirrhosis due to NASH can be asymptomatic and may lack the usual signs of chronic liver disease.

Diagnosis

• Presence of risk factors

• Absence of hepatitis B and C and excessive alcohol intake

• Liver biopsy

The diagnosis should be suspected in patients with risk factors such as obesity, type 2 diabetes mellitus, or dyslipidemia and in patients with unexplained laboratory abnormalities suggesting liver disease. The

most common laboratory abnormalities are elevations in aminotransferase levels. Unlike in alcoholic liver disease, the ratio of AST/ALT in NASH is usually < 1. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) occasionally increase. Hyperbilirubinemia, prolongation of PT, and hypoalbuminemia are uncommon.

For diagnosis, strong evidence (such as a history corroborated by friends and relatives) that alcohol intake is not excessive (eg, is < 20 g/day) is needed. Serologic tests should show absence of hepatitis B and C infection (ie, hepatitis B surface antigen and hepatitis C virus antibody should be negative). Liver biopsy should reveal damage similar to that seen in alcoholic hepatitis, usually including large fat droplets (macrovesicular fatty infiltration). Indications for biopsy include unexplained signs of portal hypertension (including splenomegaly or cytopenia) and unexplained elevations in aminotransferase levels that persist for > 6 mo in a patient with diabetes, obesity, or dyslipidemia.

Imaging tests, including ultrasonography, CT, and particularly MRI, may identify hepatic steatosis. However, these tests cannot identify the inflammation typical of NASH and cannot differentiate NASH from other causes of hepatic steatosis.

Prognosis

Prognosis is controversial. Probably, most patients do not develop hepatic insufficiency or cirrhosis. However, some drugs (eg, cytotoxic drugs) and metabolic disorders are associated with acceleration of NASH. Prognosis is often good unless complications (eg, variceal hemorrhage) develop.

Treatment

• Elimination of causes and control of risk factors

The only widely accepted treatment goal is to eliminate potential causes and risk factors. Such a goal may include discontinuation of drugs or toxins, weight loss, and treatment for dyslipidemia or hyperglycemia. Preliminary evidence suggests that thiazolidinediones can help correct biochemical and histologic abnormalities in NASH. Many other treatments (eg, ursodeoxycholic acid, vitamin E, metronidazole, metformin, betaine, glucagon, glutamine infusion) have not been proved effective.

Jaundice

Jaundice is a yellowish discoloration of the skin and mucous membranes caused by hyperbilirubinemia. Jaundice becomes visible when the bilirubin level is about 2 to 3 mg/dL (34 to 51 µmol/L).

Pathophysiology

Most bilirubin is produced when Hb is broken down into unconjugated bilirubin (and other substances). Unconjugated bilirubin binds to albumin in the blood for transport to the liver, where it is taken up by hepatocytes and conjugated with glucuronic acid to make it water soluble. Conjugated bilirubin is excreted in bile into the duodenum. In the intestine, bacteria metabolize bilirubin to form urobilinogen. Some urobilinogen is eliminated in the feces, and some is reabsorbed, extracted by hepatocytes, reprocessed, and re-excreted in bile (enterohepatic circulation—see p. 205).

Mechanisms of hyperbilirubinemia: Hyperbilirubinemia may involve predominantly unconjugated or conjugated bilirubin.

Unconjugated hyperbilirubinemia is most often caused by ≥ 1 of the following:

• Increased production

• Decreased hepatic uptake

• Decreased conjugation

Conjugated hyperbilirubinemia is most often caused by ≥ 1 of the following:

• Dysfunction of hepatocytes (hepatocellular dysfunction)

• Slowing of bile egress from the liver (intrahepatic cholestasis)

• Obstruction of extrahepatic bile flow (extra-hepatic cholestasis)

Consequences: Outcome is determined primarily by the cause of jaundice and the presence and severity of hepatic dysfunction. Hepatic dysfunction can result in coagulopathy, encephalopathy, and portal hypertension (which can lead to GI bleeding).

Etiology

Although hyperbilirubinemia can be classified as predominantly unconjugated or conjugated, many hepatobiliary disorders cause both forms.

Many conditions (see
Table 23-3), including use of certain drugs (see
Table 23-4), can cause jaundice, but the most common causes overall are

• Inflammatory hepatitis (viral hepatitis, autoimmune hepatitis, toxic hepatic injury)

• Alcoholic liver disease

• Biliary obstruction

Evaluation

History: History of present illness should include onset and duration of jaundice. Hyperbilirubinemia can cause urine to darken before

[**Table 23-3.** Mechanisms and Some Causes of Jaundice in Adults]

jaundice is visible. Therefore, the onset of dark urine indicates onset of hyperbilirubinemia more accurately than onset of jaundice. Important associated symptoms include fever, prodromal symptoms (eg, fever, malaise, myalgias) before jaundice, urine and stool color, pruritus, steatorrhea, and abdominal pain (including location, severity, duration, and radiation). Important symptoms suggesting severe disease include nausea and vomiting, weight loss, and possible symptoms of coagulopathy (eg, easy bruising or bleeding, tarry or bloody stools).

Review of systems should seek symptoms of possible causes, including weight loss and abdominal pain (cancer); joint pain and swelling

[**Table 23-4.** Some Drugs and Toxins that Can Cause Jaundice]

(autoimmune or viral hepatitis, hemochromatosis, primary sclerosing cholangitis, sarcoidosis); and missed menses (pregnancy).

Past medical history should identify known causative disorders, such as hepatobiliary disease (eg, gallstones, hepatitis, cirrhosis); disorders that can cause hemolysis (eg, hemoglobinopathy, G6PD deficiency); and disorders associated with liver or biliary disease, including inflammatory bowel disease, infiltrative disorders (eg, amyloidosis, lymphoma, sarcoidosis, TB), and HIV infection or AIDS.

Drug history should include questions about use of drugs or exposure to toxins known to affect the liver (see Table 23-4) and about vaccination against hepatitis.

Surgical history should include questions about previous surgery on the biliary tract (a potential cause of strictures).

Social history should include questions about risk factors for hepatitis (see Table 23-5), amount and duration of alcohol use, injection drug use, and sexual history.

Family history should include questions about recurrent, mild jaundice in family members and diagnosed hereditary liver disorders. The patient's history of recreational drug and alcohol use should be corroborated by friends or family members when possible.

Physical examination: Vital signs are reviewed for fever and signs of systemic toxicity (eg, hypotension, tachycardia).

General appearance is noted, particularly for cachexia and lethargy.

Head and neck examination includes inspection of the sclerae and tongue for icterus and the eyes for Kayser-Fleischer rings. Mild jaundice is best seen by examining the sclerae in natural light; it is usually detectable when serum bilirubin reaches 2 to 2.5 mg/dL (34 to 43 µmol/L). Breath odor should be noted (eg, for fetor hepaticus).

The abdomen is inspected for collateral vasculature, ascites, and surgical scars. The liver is palpated for hepatomegaly, masses, nodularity, and tenderness. The spleen is palpated for splenomegaly. The abdomen is examined for umbilical hernia, shifting dullness, fluid wave, masses, and tenderness. The rectum is examined for gross or occult blood.

Men are checked for testicular atrophy and gynecomastia.

The upper extremities are examined for Dupuytren's contractures.

Neurologic examination includes mental status assessment and evaluation for asterixis.

The skin is examined for jaundice, palmar erythema, needle tracks, vascular spiders, excoriations, xanthomas (consistent with primary biliary cirrhosis), paucity of axillary and pubic hair, hyperpigmentation, ecchymoses, petechiae, and purpura.

Red flags: The following findings are of particular concern:

• Marked abdominal pain and tenderness

• Altered mental status

• GI bleeding (occult or gross)

• Ecchymoses, petechiae, or purpura

Interpretation of findings: Severity of illness is indicated mainly by the degree (if any) of hepatic dysfunction. Ascending cholangitis is a concern because it requires emergency treatment.

Severe hepatic dysfunction is indicated by encephalopathy (eg, mental status change, asterixis) or coagulopathy (eg, easy bleeding, purpura, tarry or heme-positive stool), particularly in patients with signs of portal hypertension

[**Table 23-5.** Some Risk Factors for Hepatitis]

(eg, abdominal collateral vasculature, ascites, splenomegaly). Massive upper GI bleeding suggests variceal bleeding due to portal hypertension (and possibly coagulopathy).

Ascending cholangitis is suggested by fever and marked, continuous right upper quadrant abdominal

pain; acute pancreatitis with biliary obstruction (eg, due to a common duct stone or pancreatic pseudocyst) may manifest similarly.

Cause of jaundice may be suggested by the following:

- Acute jaundice in the young and healthy suggests acute viral hepatitis, particularly when a viral prodrome, risk factors, or both are present; however, acetaminophen overdose is also common.
- Acute jaundice after acute drug or toxin exposure in healthy patients is likely due to that substance.
- A long history of heavy alcohol use suggests alcoholic liver disease, particularly when typical stigmata are present.
- A personal or family history of recurrent, mild jaundice without findings of hepatobiliary dysfunction suggests a hereditary disorder, usually Gilbert syndrome.
- Gradual onset of jaundice with pruritus, weight loss, and clay-colored stools suggests intrahepatic or extrahepatic cholestasis.
- Painless jaundice in elderly patients with weight loss and a mass but with minimal pruritus suggests biliary obstruction caused by cancer.

Other examination findings can also be helpful (see Table 23-6).

Testing: The following are done:

- Blood tests (bilirubin, aminotransferase, alkaline phosphatase)
- Usually imaging
- Sometimes biopsy or laparoscopy

Blood tests include measurement of total and direct bilirubin, aminotransferase, and alkaline phosphatase levels in all patients. Results help differentiate cholestasis from hepatocellular dysfunction (important because patients with cholestasis usually require imaging tests):

- Hepatocellular dysfunction: Marked aminotransferase elevation (> 500 U/L) and moderate alkaline phosphatase elevation (< 3 times normal)
- Cholestasis: Moderate aminotransferase elevation (< 200 U/L) and marked alkaline phosphatase elevation (> 3 times normal)
- Hyperbilirubinemia without hepatobiliary dysfunction: Mild hyperbilirubinemia (eg, < 3.5 mg/dL [< 59 µmol/L]) with normal aminotransferase and alkaline phosphatase levels

Also, patients with hepatocellular dysfunction or cholestasis have dark urine due to bilirubinuria because conjugated bilirubin is excreted in urine; unconjugated bilirubin is not. Bilirubin fractionation also differentiates conjugated from unconjugated forms. When aminotransferase and alkaline phosphatase levels are normal, fractionation of bilirubin can help suggest causes, such as Gilbert syndrome or hemolysis (unconjugated) vs Dubin-Johnson syndrome or Rotor's syndrome (conjugated).

Other blood tests are done based on clinical suspicion and initial test findings, as for the following:

- Signs of hepatic insufficiency (eg, encephalopathy, ascites, ecchymoses) or GI bleeding: Coagulation profile (PT/PTT)
- Hepatitis risk factors (see Table 23-5) or a hepatocellular mechanism suggested by blood test results:

Hepatitis viral and autoimmune serologic tests

- Fever, abdominal pain, and tenderness: CBC and, if patients appear ill, blood cultures

[**Table 23-6.** Findings Suggesting a Cause of Jaundice]

Suspicion of hemolysis can be confirmed by a peripheral blood smear.

Imaging is done if pain suggests extrahepatic obstruction or cholangitis or if blood test results suggest cholestasis.

Abdominal ultrasonography usually is done first; usually, it is highly accurate in detecting extrahepatic obstruction. CT and MRI are alternatives. Ultrasonography is usually more accurate for gallstones, and CT is more accurate for pancreatic lesions. All these tests can detect abnormalities in the biliary tree and focal liver lesions but are less accurate in detecting diffuse hepatocellular disorders (eg, hepatitis, cirrhosis).

If ultrasonography shows extrahepatic cholestasis, other tests may be necessary to determine the cause; usually, magnetic resonance cholangiopancreatography (MRCP) or ERCP is used. ERCP is more invasive but allows treatment of some obstructive lesions (eg, stone removal, stenting of strictures).

Liver biopsy is not commonly required but can help diagnose certain disorders (eg, disorders causing intrahepatic cholestasis, some kinds of hepatitis, some infiltrative disorders, Dubin-Johnson syndrome, hemochromatosis, Wilson's disease). Biopsy can also help when liver enzyme abnormalities are unexplained by other tests.

Laparoscopy (peritoneoscopy) allows direct inspection of the liver and gallbladder without the trauma of a full laparotomy. Unexplained cholestatic jaundice warrants laparoscopy occasionally and diagnostic laparotomy rarely.

Treatment

The cause and any complications are treated. Jaundice itself requires no treatment in adults (unlike in neonates—see p. 2788). Itching, if bothersome, may be relieved with cholestyramine 2 to 8 g po bid. However, cholestyramine is ineffective in patients with complete biliary obstruction.

Geriatrics Essentials

Symptoms may be attenuated or missed in the elderly; eg, abdominal pain may be mild or absent in acute viral hepatitis. A sleep disturbance or mild confusion resulting from portosystemic encephalopathy may be misattributed to dementia.

Key Points

- Acute jaundice, particularly with a viral prodrome, in the young and healthy suggests acute viral hepatitis.
- Painless jaundice in elderly patients with weight loss, an abdominal mass, and minimal pruritus suggests biliary obstruction caused by cancer.
- Aminotransferase levels of > 500 U/L and alkaline phosphatase elevation < 3 times normal suggest hepatocellular dysfunction.
- Aminotransferase levels of < 200 U/L and alkaline phosphatase elevation > 3 times normal suggest cholestasis.
- Significant hepatic dysfunction is indicated by altered mental status and coagulopathy.

Inborn Metabolic Disorders Causing Hyperbilirubinemia

Hereditary or inborn metabolic disorders may cause unconjugated or conjugated hyperbilirubinemia.

- Unconjugated hyperbilirubinemia: Gilbert syndrome, Crigler-Najjar syndrome, and primary shunt hyperbilirubinemia

- Conjugated hyperbilirubinemia: Dubin-Johnson syndrome and Rotor's syndrome

Gilbert Syndrome

Gilbert syndrome is a presumably lifelong disorder in which the only significant abnormality is asymptomatic, mild, unconjugated hyperbilirubinemia. It can be mistaken for chronic hepatitis or other liver disorders. Gilbert syndrome may affect as many as 5% of people. Although family members may be affected, a clear genetic pattern is difficult to establish.

Pathogenesis may involve complex defects in the liver's uptake of bilirubin. Glucuronyl transferase activity is low, though not as low as in Crigler-Najjar syndrome type II. In many patients, RBC destruction is also slightly accelerated, but this acceleration does not explain hyperbilirubinemia. Liver histology is normal.

Gilbert syndrome is most often detected in young adults serendipitously by finding an elevated bilirubin level, which usually fluctuates between 2 and 5 mg/dL (34 and 86 µmol/L) and tends to increase with fasting and other stresses.

Gilbert syndrome is differentiated from hepatitis by fractionation that shows predominantly unconjugated bilirubin, otherwise normal liver function test results, and absence of urinary bilirubin. It is differentiated from hemolysis by the absence of anemia and reticulocytosis. Treatment is unnecessary. Patients should be reassured that they do not have liver disease.

Crigler-Najjar Syndrome

This rare inherited disorder is caused by deficiency of the enzyme glucuronyl transferase. Patients with autosomal recessive type I (complete) disease have severe hyperbilirubinemia. They usually die of kernicterus by age 1 yr but may survive into adulthood. Treatment may include phototherapy and liver transplantation. Patients with autosomal dominant type II (partial) disease (which has variable penetrance) often have less severe hyperbilirubinemia (< 20 mg/dL [< 342 µmol/L]) and usually live into adulthood without neurologic damage. Phenobarbital 1.5 to 2 mg/kg po tid, which induces the partially deficient glucuronyl transferase, may be effective.

Primary Shunt Hyperbilirubinemia

This rare, familial, benign condition is characterized by overproduction of early-labeled bilirubin.

Dubin-Johnson Syndrome and Rotor's Syndrome

Dubin-Johnson syndrome and Rotor's syndrome cause conjugated hyperbilirubinemia, but without cholestasis, causing no symptoms or sequelae other than jaundice. In contrast to unconjugated hyperbilirubinemia in Gilbert syndrome (which also causes no other symptoms), bilirubin may appear in the urine. Aminotransferase and alkaline phosphatase levels are usually normal. Treatment is unnecessary.

Dubin-Johnson syndrome: This rare autosomal recessive disorder involves impaired excretion of bilirubin glucuronides. It is usually diagnosed by liver biopsy; the liver is deeply pigmented as a result of an intracellular melanin-like substance but is otherwise histologically normal.

Rotor's syndrome: This rare disorder is clinically similar to Dubin-Johnson syndrome, but the liver is not pigmented, and other subtle metabolic differences are present.

Portal Hypertension

Portal hypertension is caused most often by cirrhosis (in developed countries), schistosomiasis (in endemic areas), or hepatic vascular abnormalities. Consequences include esophageal varices and portal-systemic encephalopathy. Diagnosis is based on clinical criteria, often in conjunction with imaging tests and endoscopy. Treatment involves prevention of GI bleeding with endoscopy, drugs, or both and sometimes with portocaval shunting.

The portal vein, formed by the superior mesenteric and splenic veins, drains blood from the abdominal GI tract, spleen, and pancreas into the liver. Within reticuloendotheliumlined blood channels (sinusoids), blood from the terminal portal venules merges with hepatic arterial blood. Blood flows out of the sinusoids via the hepatic veins into the inferior vena cava.

Normal portal pressure is 5 to 10 mm Hg (7 to 14 cm H_2O), which exceeds inferior vena caval pressure by 4 to 5 mm Hg (portal venous gradient). Higher values are defined as portal hypertension.

Etiology

Portal hypertension results mainly from increased resistance to flow, which commonly arises from disease within the liver itself or uncommonly from blockage of the splenic or portal vein or impaired hepatic venous outflow (see Table 23-7). Increased flow volume is a rare cause, although it often contributes to portal hypertension in cirrhosis and in hematologic disorders that cause massive splenomegaly.

Pathophysiology

In cirrhosis, tissue fibrosis and regeneration increase resistance in the sinusoids and terminal portal venules. However, other potentially reversible factors contribute; they include contractility of sinusoidal lining cells, production of vasoactive substances (eg, endothelins, nitric oxide), various systemic mediators of arteriolar resistance, and possibly swelling of hepatocytes.

Over time, portal hypertension creates portal-systemic venous collaterals. They may slightly decrease portal vein pressure but can cause complications. Engorged serpentine submucosal vessels (varices) in the distal esophagus and sometimes in the gastric fundus can rupture, causing sudden, catastrophic GI bleeding. Bleeding rarely occurs unless the portal pressure gradient is > 12 mm Hg. Gastric mucosal vascular congestion (portal hypertensive gastropathy) can cause acute or chronic bleeding independent of varices. Visible abdominal wall collaterals are common; veins radiating from the umbilicus (caput medusae) are much rarer and indicate extensive flow in the umbilical and periumbilical veins.

[**Table 23-7.** Most Common Causes of Portal Hypertension]

Collaterals around the rectum can cause rectal varices that can bleed.

Portal-systemic collaterals shunt blood away from the liver. Thus, less blood reaches the liver when portal flow increases (diminished hepatic reserve). In addition, toxic substances from the intestine are shunted directly to the systemic circulation, contributing to portal-systemic encephalopathy (see p. 220). Venous congestion within visceral organs due to portal hypertension contributes to ascites via altered Starling's forces. Splenomegaly and hypersplenism (see p. 984) commonly occur as a result of increased splenic vein pressure. Thrombocytopenia, leukopenia, and, less commonly, hemolytic anemia may result.

Portal hypertension is often associated with a hyperdynamic circulation. Mechanisms are complex and seem to involve altered sympathetic tone, production of nitric oxide and other endogenous vasodilators, and enhanced activity of humoral factors (eg, glucagon).

Symptoms and Signs

Portal hypertension is asymptomatic; symptoms and signs result from its complications. The most dangerous is acute variceal bleeding (see p. 103). Patients typically present with sudden painless upper

GI bleeding, often massive. Bleeding from portal hypertensive gastropathy is often subacute or chronic. Ascites, splenomegaly, or portal-systemic encephalopathy may be present.

Diagnosis

• Usually, clinical evaluation

Portal hypertension is inferred in a patient with chronic liver disease by the presence of collateral circulation, splenomegaly, ascites, or portal-systemic encephalopathy. Proof requires direct portal pressure measurement by a transjugular catheter, which is invasive and usually not done. Imaging may help when cirrhosis is suspected. Ultrasonography or CT often reveals dilated intra-abdominal collaterals, and Doppler ultrasonography can determine portal vein patency and flow.

Esophagogastric varices and portal hypertensive gastropathy are best diagnosed by endoscopy, which may also identify predictors of esophagogastric variceal bleeding (eg, red markings on a varix).

Prognosis

Mortality during acute variceal hemorrhage may exceed 50%. Prognosis is predicted by the degree of hepatic reserve and the degree of bleeding. For survivors, the bleeding risk within the next 1 to 2 yr is 50 to 75%. Ongoing endoscopic or drug therapy lowers the bleeding risk but decreases long-term mortality only marginally. For treatment of acute bleeding, see pp. 102 and 104.

Treatment

• Ongoing endoscopic therapy and surveillance

• β-Blockers with or without isosorbide mononitrate

• Sometimes portal vein shunting

When possible, the underlying disorder is treated. Long-term treatment of esophagogastric varices that have bled is a series of endoscopic banding sessions to obliterate residual varices, then periodic surveillance endoscopy for recurrent varices.

Long-term drug therapy for varices that have bled involves β-blockers; these drugs lower portal pressure primarily by diminishing portal flow, although the effects vary. Propranolol (40 to 80 mg po bid) or nadolol (40 to 160 mg po once/day) is preferred, with dosage titrated to decrease heart rate by about 25%. Adding isosorbide mononitrate 10 to 20 mg po bid may further reduce portal pressure. Combined long-term endoscopic and drug therapy may be slightly more effective than either alone. Patients who do not adequately respond to either treatment should be considered for transjugular intrahepatic portosystemic shunting (TIPS) or, less frequently, a surgical portocaval shunt. TIPS creates a stent between the portal and hepatic venous circulation within the liver. Although TIPS may result in fewer immediate deaths than surgical shunting, particularly during acute bleeding, maintenance of patency may require repeat procedures because the stent may become stenosed or occluded over time. Long-term benefits are unknown. Liver transplantation may help some patients.

For patients with varices that have not yet bled, β-blockers lower the risk of bleeding.

For bleeding due to portal hypertensive gastropathy, drugs can be used to decrease portal pressure. A shunt should be considered if drugs are ineffective, but results may be less successful than for esophageal variceal bleeding.

Because it rarely causes clinical problems, hypersplenism requires no specific treatment, and splenectomy should be avoided.

Portal-Systemic Encephalopathy

Portal-systemic encephalopathy is a neuropsychiatric syndrome. It most often results from high gut protein or acute metabolic stress (eg, GI bleeding, infection, electrolyte abnormality) in a patient with portal-systemic shunting. Symptoms are mainly neuropsychiatric (eg, confusion, flapping tremor, coma). Diagnosis is based on clinical findings. Treatment usually is correction of the acute cause, restriction of dietary protein, and oral lactulose.

Portal-systemic encephalopathy better describes the pathophysiology than hepatic encephalopathy or hepatic coma, but all 3 terms are used interchangeably.

Etiology

Portal-systemic encephalopathy may occur in fulminant hepatitis caused by viruses, drugs, or toxins, but it more commonly occurs in cirrhosis or other chronic disorders when extensive portal-systemic collaterals have developed as a result of portal hypertension. Encephalopathy also follows portal-systemic anastomoses, such as surgically created anastomoses connecting the portal vein and vena cava (portacaval shunts, transjugular intrahepatic portosystemic shunting [TIPS]).

Precipitants: In patients with chronic liver disease, acute episodes of encephalopathy are usually precipitated by reversible causes. The most common are the following:

- Metabolic stress (eg, infection; electrolyte imbalance, especially hypokalemia; dehydration; use of diuretic drugs)

- Disorders that increase gut protein (eg, GI bleeding, high-protein diet)

- Nonspecific cerebral depressants (eg, alcohol, sedatives, analgesics)

Pathophysiology

In portal-systemic shunting, absorbed products that would otherwise be detoxified by the liver enter the systemic circulation, where they may be toxic to the brain, particularly the cerebral cortex. The substances causing brain toxicity are not precisely known. Ammonia, a product of protein digestion, is an important cause, but other factors (eg, alterations in cerebral benzodiazepine receptors and neurotransmission by γ-aminobutyric acid [GABA]) may also contribute. Aromatic amino acid levels in serum are usually high and branched-chain levels are low, but these levels probably do not cause encephalopathy.

Symptoms and Signs

Symptoms and signs of encephalopathy tend to develop in progressive stages (see Table 23-8).

Symptoms usually do not become apparent until brain function is moderately impaired. Constructional apraxia, in which patients cannot reproduce simple designs (eg, a star), develops early. Agitation and mania can develop but are uncommon. A characteristic flapping tremor (asterixis) is elicited when patients hold their arms outstretched with wrists dorsiflexed. Neurologic deficits are symmetric. Neurologic signs in coma usually reflect bilateral diffuse hemispheric dysfunction. Signs of brain stem dysfunction develop only in advanced coma, often during the hours or days before death. A musty, sweet breath odor (fetor hepaticus) can occur regardless of the stage of encephalopathy.

Diagnosis

- Clinical evaluation

- Often adjunctive testing with psychometric evaluation, ammonia level, EEG, or a combination

- Exclusion of other treatable disorders

[Table 23-8. Clinical Stages of Portal-Systemic Encephalopathy]

Diagnosis is ultimately based on clinical findings, but testing may help:

- Psychometric testing may reveal subtle neuropsychiatric deficits, which can help confirm early encephalopathy.
- Ammonia levels are usually done.
- An EEG usually shows diffuse slow-wave activity, even in mild cases, and may be sensitive but is not specific for early encephalopathy.

CSF examination is not routinely necessary; the only usual abnormality is mild protein elevation.

Other potentially reversible disorders that could cause similar manifestations (eg, infection, subdural hematoma, hypoglycemia, intoxication) should be ruled out. If portal-systemic encephalopathy is confirmed, the precipitating cause should be sought.

Prognosis

In chronic liver disease, correction of the precipitating cause usually causes encephalopathy to regress without permanent neurologic sequelae. Some patients, especially those with portacaval shunts or TIPS, require continuous therapy, and irreversible extrapyramidal signs or spastic paraparesis rarely develops. Coma (stage 4 encephalopathy) associated with fulminant hepatitis is fatal in up to 80% of patients despite intensive therapy; the combination of advanced chronic liver failure and portal-systemic encephalopathy is often fatal.

Treatment

- Treatment of the cause
- Bowel cleansing using oral lactulose or enemas
- Dietary protein restriction

Treating the cause usually reverses mild cases. Eliminating toxic enteric products is the other goal and is accomplished using several methods. The bowels should be cleared using enemas or, more often, oral lactulose syrup, which can be tube-fed to comatose patients. This synthetic disaccharide is an osmotic cathartic. It also lowers colonic pH, decreasing fecal ammonia production. The initial dosage, 30 to 45 mL po tid, should be adjusted to produce 2 or 3 soft stools daily. Dietary protein should be about 1.0 mg/kg/day, primarily from vegetable sources. Oral nonabsorbable antibiotics such as neomycin and rifaximin are effective for hepatic encephalopathy. Rifaximin is usually preferred because neomycin is an aminoglycoside, which can precipitate ototoxicity or nephrotoxicity.

Sedation deepens encephalopathy and should be avoided whenever possible. For coma caused by fulminant hepatitis, meticulous supportive and nursing care coupled with prevention and treatment of complications increase the chance of survival. High-dose corticosteroids, exchange transfusion, and other complex procedures designed to remove circulating toxins generally do not improve outcome. Patients deteriorating because of fulminant hepatic failure may be saved by liver transplantation.

Other potential therapies, including levodopa, bromocriptine, flumazenil, Na benzoate, infusions of branched-chain amino acids, keto-analogs of essential amino acids, and prostaglandins, have not proved effective. Complex plasma-filtering systems (artificial liver) show some promise but require much more study.

Systemic Abnormalities in Liver Disease

Liver disease often causes systemic symptoms and abnormalities (see Portal-Systemic Encephalopathy

on p. 220).

Circulatory Abnormalities

Hypotension in advanced liver failure may contribute to renal dysfunction. The pathogenesis of the hyperdynamic circulation (increased cardiac output and heart rate) and hypotension that develop in advanced liver failure or cirrhosis is poorly understood. However, peripheral arterial vasodilation probably contributes to both. Factors that may contribute in cirrhosis may include altered sympathetic tone, production of nitric oxide and other endogenous vasodilators, and enhanced activity of humoral factors (eg, glucagon).

For specific disorders of hepatic circulation (eg, Budd-Chiari syndrome), see Ch. 29.

Endocrine Abnormalities

Glucose intolerance, hyperinsulinism, insulin resistance, and hyperglucagonemia are often present in patients with cirrhosis; the elevated insulin levels reflect decreased hepatic degradation rather than increased secretion, whereas the opposite is true for hyperglucagonemia. Abnormal thyroid function tests may reflect altered hepatic handling of thyroid hormones and changes in plasma binding proteins rather than thyroid abnormalities.

Sexual effects are common. Chronic liver disease commonly impairs menstruation and fertility. Males with cirrhosis, especially alcoholics, often have both hypogonadism (including testicular atrophy, erectile dysfunction, decreased spermatogenesis) and feminization (gynecomastia, female habitus). The biochemical basis is not fully understood. Gonadotropin reserve of the hypothalamicpituitary axis is often blunted. Circulating testosterone levels are low, resulting mainly from decreased synthesis but also from increased peripheral conversion to estrogens. Levels of estrogens other than estradiol are usually increased, but the relationship between estrogens and feminization is complex. These changes are more prevalent in alcoholic liver disease than in cirrhosis of other etiologies, suggesting that alcohol, rather than liver disease, may be the cause. In fact, evidence indicates that alcohol itself is toxic to the testes.

Hematologic Abnormalities

Anemia is common among patients with liver disease. Contributing factors may include blood loss, folate (folic acid) deficiency, hemolysis, marrow suppression by alcohol, and a direct effect of chronic liver disease.

Leukopenia and **thrombocytopenia** often accompany splenomegaly in advanced portal hypertension.

Clotting and coagulation abnormalities are common and complex. Hepatocellular dysfunction and inadequate absorption of vitamin K may impair liver synthesis of clotting factors. An abnormal PT, depending on the severity of hepatocellular dysfunction, may respond to parenteral phytonadione (vitamin K_1) 5 to 10 mg once/day for 2 to 3 days. Thrombocytopenia, disseminated intravascular coagulation, and fibrinogen abnormalities also contribute to clotting disturbances in many patients.

Renal and Electrolyte Abnormalities

Renal and electrolyte abnormalities are common, especially among patients with ascites.

Hypokalemia may result from excess urinary K loss due to increased circulating aldosterone, renal retention of ammonium ion in exchange for K, secondary renal tubular acidosis, or diuretic therapy. Management consists of giving oral KCl supplements and withholding K-wasting diuretics.

Hyponatremia is common even though the kidneys may avidly retain Na (see Ascites on p. 206); it usually occurs with advanced hepatocellular disease and is difficult to correct. Relative water overload is more often responsible than total body Na depletion; K depletion may also contribute. Water restriction and K supplements may help; use of diuretics that increase free water clearance is controversial. Saline solution IV is indicated only if profound hyponatremia causes seizures or if total body Na depletion is

suspected; it should be avoided in patients with cirrhosis and fluid retention because it worsens ascites and only temporarily increases serum Na levels.

Advanced liver failure can alter acid-base balance, usually causing metabolic alkalosis. BUN levels are often low because of impaired liver synthesis; GI bleeding causes elevations because of an increased enteric load rather than renal impairment. When GI bleeding elevates BUN, normal creatinine values tend to confirm normal kidney function.

Renal failure in liver disease may reflect

• Rare disorders that directly affect both the kidneys and the liver (eg, carbon tetrachloride toxicity)

• Circulatory failure with decreased renal perfusion, with or without frank acute tubular necrosis

• Functional renal failure, often called hepatorenal syndrome

Hepatorenal syndrome: This syndrome consists of progressive oliguria and azotemia in the absence of structural damage to the kidney; it usually occurs in patients with fulminant hepatitis or advanced cirrhosis with ascites. Its unknown pathogenesis probably involves extreme vasodilation of the splanchnic arterial circulation, leading to decreased central arterial volume. Neural or humoral reductions in renocortical blood flow follow, resulting in a diminished glomerular filtration rate. Low urinary Na concentration and benign sediment usually distinguish it from tubular necrosis, but prerenal azotemia may be more difficult to distinguish; in equivocal cases, response to a volume load should be assessed.

Once established, renal failure due to hepatorenal syndrome is usually rapidly progressive and fatal (type 1 hepatorenal syndrome), although some cases are less severe, with stable low-grade renal insufficiency (type 2).

Liver transplantation is the only accepted treatment for type 1 hepatorenal syndrome; transjugular intrahepatic portosystemic shunting (TIPS) and vasoconstrictors show some promise, but more study is needed.

The Asymptomatic Patient With Abnormal Laboratory Test Results

Because aminotransferases and alkaline phosphatase are included in commonly done laboratory test panels, abnormalities are often detected in patients without symptoms or signs of liver disease. In such patients, the physician should obtain a history of exposure to possible liver toxins, including alcohol, prescription and nonprescription drugs, herbal teas and remedies, and occupational or other chemical exposures.

Aminotransferases: Mild isolated elevations of ALT or AST (< 2 times normal) may require only repeat testing; they resolve in about one third of cases. If abnormalities are present in other laboratory tests, are severe, or persist on subsequent testing, further evaluation is indicated as follows:

• Fatty liver should be considered; it can often be recognized clinically (see p. 211).

• Patients should be screened for hepatitis B and C (see p. 251).

• Patients > 40 should be screened for hemochromatosis (see p. 1032).

• Patients < 30 should be screened for Wilson's disease (see p. 51).

• Most patients, especially young or middle-aged women, should be screened for autoimmune disorders.

• Patients at risk should be screened for malaria and schistosomiasis.

If at this point the results are negative, screening for α_1-antitrypsin deficiency (see p. 1901) is indicated. If the entire evaluation reveals no cause, liver biopsy may be warranted.

Alkaline phosphatase: Isolated elevation of alkaline phosphatase levels in an asymptomatic patient requires confirmation of hepatic origin by showing elevation of 5´-nucleotidase or γ-glutamyl transpeptidase. If hepatic origin is confirmed, liver imaging, usually with ultrasonography or magnetic resonance cholangiopancreatography, is indicated. If no structural abnormality is found on imaging, intrahepatic cholestasis is possible and may be suggested by a history of exposure to drugs or toxins. Infiltrative diseases and liver metastases (eg, due to colon cancer) should also be considered. In women, antimitochondrial antibody should be obtained. Persistent unexplained elevations or suspicion of intrahepatic cholestasis warrants consideration of liver biopsy.

Postoperative Liver Dysfunction

Mild liver dysfunction sometimes occurs after major surgery even in the absence of preexisting liver disorders. This dysfunction usually results from hepatic ischemia or poorly understood effects of anesthesia. Patients with preexisting well-compensated liver disease (eg, cirrhosis with normal liver function) usually tolerate surgery well. However, surgery can increase the severity of some preexisting liver disorders; eg, laparotomy may precipitate acute liver failure in a patient with viral or alcoholic hepatitis.

Postoperative jaundice: Diagnosis of postoperative jaundice requires liver laboratory tests. Timing of symptoms also aids in diagnosis.

Multifactorial mixed hyperbilirubinemia is the most common reason for postoperative jaundice. It is caused by increased formation of bilirubin and decreased hepatic clearance. This disorder most often occurs after major surgery or trauma requiring multiple transfusions. Hemolysis, sepsis, resorption of hematomas, and blood transfusions can increase the bilirubin load; simultaneously, hypoxemia, hepatic ischemia, and other poorly understood factors impair hepatic function. This condition is usually maximal within a few days of operation. Hepatic insufficiency is rare, and hyperbilirubinemia typically resolves slowly but completely. Liver laboratory tests can often differentiate multifactorial mixed hyperbilirubinemia from hepatitis. In multifactorial mixed hyperbilirubinemia, severe hyperbilirubinemia with mild aminotransferase and alkaline phosphatase elevations are common. In hepatitis, aminotransferase levels are usually very high.

Postoperative hepatitis: Ischemic postoperative "hepatitis" results from insufficient liver perfusion, not inflammation. The cause is transient perioperative hypotension or hypoxia. Typically, aminotransferase levels increase rapidly (often > 1000 units/L), but bilirubin is only mildly elevated. Ischemic hepatitis is usually maximal within a few days of operation and resolves within a few days.

Halothane-related hepatitis can result from use of anesthetics containing halothane or related agents. It usually develops within 2 wk, is often preceded by fever, and is sometimes accompanied by a skin rash and eosinophilia.

True postoperative hepatitis is now rare. It used to result mainly from transmission of hepatitis C virus during blood transfusion.

Postoperative cholestasis: The most common cause of postoperative cholestasis is extrahepatic biliary obstruction due to intra-abdominal complications or drugs given postoperatively. Intrahepatic cholestasis occasionally develops after major surgery, especially after abdominal or cardiovascular procedures (benign postoperative intrahepatic cholestasis). The pathogenesis is unknown, but the condition usually resolves slowly and spontaneously. Occasionally, postoperative cholestasis results from acute acalculous cholecystitis or pancreatitis.

Chapter 24. Testing for Hepatic and Biliary Disorders

Introduction

Diagnosis of liver and biliary system disorders may include laboratory tests, imaging tests, and liver biopsy. Individual tests, particularly those of liver biochemistry and excretion, often have limited sensitivity and specificity. A combination of tests often best defines the cause and severity of disease. Useful algorithms (eg, Model of End-Stage Liver Disease [MELD], Child-Pugh score) have incorporated clinical and laboratory features to predict survival in patients with decompensated cirrhosis.

Laboratory Tests

Laboratory tests are generally effective for the following:

• Detecting hepatic dysfunction

• Assessing the severity of liver injury

• Monitoring the course of liver diseases and the response to treatment

• Refining the diagnosis

Many tests of liver biochemistry and excretory performance are called liver function tests. However, rather than assessing liver function, several of these tests measure liver enzymes that are released into the bloodstream (eg, release of aminotransferases from injured liver cells or of alkaline phosphatase due to cholestasis). Only certain tests actually assess liver function by evaluating hepatobiliary excretion (eg, bilirubin) or the liver's synthetic capability (eg, PT, usually reported as the INR; albumin).

The most useful laboratory tests to screen for liver disorders are serum aminotransferases (the most commonly used liver function tests), bilirubin, and alkaline phosphatase. Certain patterns of biochemical abnormalities help distinguish hepatocellular injury from impaired bile excretion (cholestasis—see Table 24-1). Tests that detect viral hepatitis, liver inflammation, or altered immunoregulation include hepatitis serologic tests (see p. 251) and measurement of immunoglobulins, antibodies, and autoantibodies.

A few laboratory tests are diagnostic by themselves; they include the following:

• IgM antibody to hepatitis A virus (anti-HAV) for acute hepatitis A

• Hepatitis B surface antigen (HBsAg) for hepatitis B

• Antibody to hepatitis C virus (anti-HCV) and HCV-RNA for hepatitis C

• Antimitochondrial antibody for primary biliary cirrhosis

• Serum ceruloplasmin (reduced) and urinary copper (elevated) for Wilson's disease

• Serum α_1-antitrypsin for α_1-antitrypsin deficiency

• α-Fetoprotein for hepatocellular carcinoma

Tests for Liver Injury

Aminotransferases: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) leak from damaged cells; thus, these enzymes are sensitive indicators of liver injury. Markedly high values (> 500 IU/L; normal, ≤ 40 IU/L), which indicate acute hepatocellular necrosis or injury, usually result from the following:

• Acute viral hepatitis

• Toxin- or drug-induced hepatitis

• Ischemic hepatitis or hepatic infarction

High levels continue usually for days or, in viral hepatitis, for weeks. The degree of elevation may not reflect the extent of liver injury. Serial measurements better reflect severity and prognosis than does a single measurement. A fall to normal indicates recovery unless accompanied by an increase in bilirubin and in PT or INR (which indicates fulminant liver failure). Fulminant liver failure results in fewer liver cells that can leak enzymes.

Aminotransferase levels may also be markedly high in the following:

• Acute exacerbation of autoimmune hepatitis

• Reactivation of chronic hepatitis B

• Acute Budd-Chiari syndrome

• Acute fatty liver of pregnancy

• Passage of a common duct stone

Modest elevations (300 to 500 IU/L) persist in chronic liver disorders (eg, chronic hepatitis, alcoholic hepatitis) and in biliary obstruction, except when passage of a common duct stone can transiently result in markedly high levels, sometimes into the thousands.

Mild increases (< 300 IU/L) are nonspecific and often present in disorders such as

[**Table 24-1.** Common Patterns of Laboratory Test Abnormalities]

• Cirrhosis secondary to viral hepatitis

• Nonalcoholic fatty liver disease (NAFLD)

• Cholestatic liver disorders

• Hepatocellular cancer

Aminotransferases can be normal in certain liver disorders, such as

• Hemochromatosis

• Methotrexate- or amiodarone-induced liver injury

• Chronic hepatitis C

• NAFLD

Elevated ALT is somewhat specific for liver injury. Because AST is present in the heart, skeletal muscle, kidneys, and pancreas, elevated AST may reflect rhabdomyolysis or injury to one of these organs. In most liver disorders, the ratio of AST to ALT is < 1. However, in alcohol-related liver disease, the ratio is characteristically > 2 because pyridoxal-5´-phosphate is deficient in alcoholic patients; it is required for ALT synthesis but is less essential for AST synthesis. This deficiency also explains why elevations of ALT and AST are low (< 300 IU/L) in alcoholic patients.

Lactate dehydrogenase: LDH, commonly included in routine analysis, is present in many other tissues and is insensitive and nonspecific for hepatocellular injury. LDH is typically elevated in ischemic hepatitis and cancers that extensively infiltrate the liver.

Tests for Cholestasis

Bilirubin: Bilirubin, the pigment in bile, is produced from the breakdown of heme proteins, mostly from the heme moiety of hemoglobin in senescent RBCs. Unconjugated (free) bilirubin is insoluble in water and thus cannot be excreted in urine; most unconjugated bilirubin is bound to albumin in plasma. Bilirubin is conjugated in the liver with glucuronic acid to form the more water-soluble bilirubin diglucuronide. Conjugated bilirubin is then excreted through the biliary tract into the duodenum, where it is metabolized into urobilinogens (some of which are reabsorbed and resecreted into bile), then into orange-colored urobilins (most of which are eliminated in feces). These bile pigments give stool its typical color.

Hyperbilirubinemia results from one or more of the following:

• Increased bilirubin production

• Decreased liver uptake or conjugation

• Decreased biliary excretion (see p. 212)

Normally, total bilirubin is mostly unconjugated, with values of < 1.2 mg/dL (< 20 µmol/L). Fractionation measures the proportion of bilirubin that is conjugated (ie, direct, so-called because it is measured directly, without the need for solvents). Fractionation is most helpful for evaluating neonatal jaundice and for evaluating elevated bilirubin when other liver test results are normal, suggesting that hepatobiliary dysfunction is not the cause.

Unconjugated hyperbilirubinemia (indirect bilirubin fraction > 85%) reflects increased bilirubin production (eg, in hemolysis) or defective liver uptake or conjugation (eg, in Gilbert syndrome). Such increases in unconjugated bilirubin are usually < 5 times normal (to < 6 mg/dL [<100 µmol/L]) unless there is concurrent liver injury.

Conjugated hyperbilirubinemia (direct bilirubin fraction > 50%) results from decreased bile formation or excretion (cholestasis). When associated with other liver function test abnormalities, a high serum bilirubin indicates hepatocellular dysfunction. Serum bilirubin is somewhat insensitive for liver dysfunction. However, the development of severe hyperbilirubinemia in primary biliary cirrhosis, alcoholic hepatitis, and acute liver failure suggests a poor prognosis.

Bilirubinuria reflects the presence of conjugated bilirubin in urine; bilirubin spills into urine because blood levels are markedly elevated, indicating severe disease. Unconjugated bilirubin is water insoluble and bound to albumin and so cannot be excreted in urine. Bilirubinuria can be detected at the bedside with commercial urine test strips in acute viral hepatitis or other hepatobiliary disorders, even before jaundice appears. However, the diagnostic accuracy of such urine tests is limited. Results can be falsely negative when the urine specimen has been stored a long time, vitamin C has been ingested, or urine contains nitrates (eg, due to UTIs). Similarly, increases in urobilinogen are neither specific nor sensitive.

Alkaline phosphatase: Increased levels of this hepatocyte enzyme suggest cholestasis. Results may not be specific because alkaline phosphatase consists of several isoenzymes and has a widespread extrahepatic distribution (eg, in the placenta, the small intestine, WBCs, kidneys, and particularly bone).

Alkaline phosphatase levels increase to ≥ 4 times normal 1 to 2 days after onset of biliary obstruction, regardless of the site of obstruction. Levels may remain elevated for several days after the obstruction resolves because the half-life of alkaline phosphatase is about 7 days. Increases of up to 3 times normal occur in many liver disorders, including

• Hepatitis

• Cirrhosis

• Space-occupying lesions (eg, carcinoma)

• Infiltrative disorders (eg, amyloidosis, sarcoidosis, TB, metastases, abscesses)

• Syphilitic hepatitis (alkaline phosphatase may be disproportionately elevated compared with the modest changes in other liver tests)

Isolated elevations (ie, when other liver test results are normal) may accompany

• Focal liver lesions (eg, abscess, tumor)

• Partial or intermittent bile duct obstruction (eg, stone, stricture, cholangiocarcinoma)

• Syphilitic hepatitis

• Occasionally, infiltrative disorders

Isolated elevations also occur in the absence of any apparent liver or biliary disorder, as in the following:

• Some cancers without apparent liver involvement (eg, bronchogenic carcinoma, Hodgkin lymphoma, renal cell carcinoma)

• After ingestion of fatty meals (because of an enzyme produced in the small intestine)

• Pregnancy (because of an enzyme produced in the placenta)

• Children and adolescents who are still growing (because of bone growth)

• Chronic renal failure (because of an enzyme produced in the intestine and bone)

Levels of γ-glutamyl transpeptidase or 5´-nucleotidase, which are more specific to the liver, can differentiate hepatic from extrahepatic sources of alkaline phosphatase better than fractionation of alkaline phosphatase, which is technically difficult. Also, in otherwise asymptomatic elderly people, an increase in alkaline phosphatase usually originates in bone (eg, in Paget's disease) and does not require further investigation for liver injury.

5´-Nucleotidase: Increases in levels of this enzyme are as sensitive as alkaline phosphatase for detecting cholestasis and biliary obstruction but are more specific, almost always indicating hepatobiliary dysfunction. Because levels of alkaline phosphatase and 5´-nucleotidase do not always correlate, one can be normal while the other is increased.

γ-Glutamyl transpeptidase (GGT): Levels of this enzyme increase in hepatobiliary dysfunction, especially cholestasis, and correlate loosely with levels of alkaline phosphatase and 5´-nucleotidase. Levels do not increase because of bone lesions, during childhood, or during pregnancy. However, alcohol and certain drugs (eg, some anticonvulsants, warfarin) can induce hepatic microsomal (cytochrome P-450) enzymes, markedly increasing GGT and thus somewhat limiting its specificity.

Tests of Hepatic Synthetic Capacity

PT and INR: PT may be expressed in time (sec) or, preferably, as a ratio of the patient's measured PT to the laboratory's control value (INR—see p. 971). The INR is more accurate than PT for monitoring anticoagulation. PT or INR is a valuable measure of the liver's ability to synthesize fibrinogen and vitamin K-dependent clotting factors: factors II (prothrombin), V, VII, and X. Changes can occur rapidly because some of the involved clotting factors have short biologic half-lives (eg, 6 h for factor VII). Abnormalities indicate severe hepatocellular dysfunction, an ominous sign in acute liver disorders. In chronic liver disorders, an increasing PT or INR indicates progression to liver failure. The PT or INR does not increase

in mild hepatocellular dysfunction and is often normal in cirrhosis.

A prolonged PT and an abnormal INR can result from coagulation disorders such as a consumptive coagulopathy or vitamin K deficiency. Fat malabsorption, including cholestasis, can cause vitamin K deficiency. In chronic cholestasis, marked hepatocellular dysfunction can be ruled out if vitamin K replacement (10 mg sc) corrects PT by ≥ 30% within 24 h.

Serum proteins: Hepatocytes synthesize most serum proteins, including α- and β-globulins, albumin, and most clotting factors (but not factor VIII, produced by the vascular endothelium, or γ-globulin, produced by B cells). Hepatocytes also make proteins that aid in the diagnosis of specific disorders:

• α_1-Antitrypsin (absent in α_1-antitrypsin deficiency)

• Ceruloplasmin (reduced in Wilson's disease)

• Transferrin (saturated with iron in hemochromatosis)

• Ferritin (greatly increased in hemochromatosis)

These proteins usually increase in response to damage (eg, inflammation) to various tissues, so that elevations may not specifically reflect liver disorders.

Serum albumin commonly decreases in chronic liver disorders because of an increase in volume of distribution (eg, due to ascites), a decrease in hepatic synthesis, or both. Values < 3 g/dL (< 30 g/L) suggest decreased synthesis, caused by one of the following:

• Advanced cirrhosis (the most common cause)

• Alcoholism

• Chronic inflammation

• Protein undernutrition

Hypoalbuminemia can also result from excessive loss of albumin from the kidneys (ie, nephrotic syndrome), gut (eg, due to proteinlosing gastroenteropathies), or skin (eg, due to burns or exfoliative dermatitis).

Because albumin has a half-life of about 20 days, serum levels take weeks to increase or decrease.

Other Laboratory Tests

Ammonia: Nitrogen compounds that enter the colon (eg, ingested protein, secreted urea) are degraded by resident bacteria, liberating ammonia. The ammonia is then absorbed and transported via the portal vein to the liver. The healthy liver readily clears the ammonia from the portal vein and converts it to glutamine, which is metabolized by the kidneys into urea to be excreted. In patients with portal-systemic shunting, the diseased liver does not clear ammonia, which then enters the systemic circulation, possibly contributing to portal-systemic (hepatic) encephalopathy. Elevated ammonia levels occur in hepatic encephalopathy, but levels may be falsely low or high. In advanced liver disorders, the following may increase ammonia levels:

• High-protein meals

• GI bleeding

• Hypokalemia

• Metabolic alkalosis

- Certain drugs (eg, alcohol, barbiturates, diuretics, opioids, valproate)
- High-dose chemotherapy
- Parenteral nutrition
- Renal insufficiency
- Extreme muscle exertion and muscle wasting
- Salicylate intoxication
- Shock
- Ureterosigmoidostomy

UTI with a urease-producing organism (eg, *Proteus mirabilis*)

Because the degree of elevation in the ammonia level correlates poorly with severity of hepatic encephalopathy, this level has limited usefulness in monitoring therapy.

Serum immunoglobulins: In chronic liver disorders, serum immunoglobulins often increase. However, elevations are not specific and are usually not helpful clinically. Levels increase slightly in acute hepatitis, moderately in chronic active hepatitis, and markedly in autoimmune hepatitis. The pattern of immunoglobulin elevation adds little information, although different immunoglobulins are usually very high in different disorders:

- IgM in primary biliary cirrhosis
- IgA in alcoholic liver disease
- IgG in autoimmune hepatitis

Antimitochondrial antibodies: These heterogeneous antibodies are positive, usually in high titers, in > 95% of patients with primary biliary cirrhosis. They are also occasionally present in the following:

- Autoimmune hepatitis
- Drug-induced hepatitis
- Other autoimmune disorders, such as connective tissue disorders, myasthenia gravis, autoimmune thyroiditis, Addison's disease, and autoimmune hemolytic anemia

Antimitochondrial antibodies can help determine the cause of cholestasis because they are usually absent in extrahepatic biliary obstruction and primary sclerosing cholangitis.

Other antibodies: Other antibodies may help in diagnosis of the following:

- Autoimmune hepatitis: Smooth muscle antibodies against actin, antinuclear antibodies (ANA) that provide a homogeneous (diffuse) fluorescence, and antibodies to liver-kidney microsome type 1 (anti-LKM1) are often present.
- Primary biliary cirrhosis: Antimitochondrial antibody is key to the diagnosis.
- Primary sclerosing cholangitis: Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) can help raise the index of suspicion.

Isolated abnormalities of any of these antibodies are never diagnostic and do not elucidate pathogenesis.

α-Fetoprotein (AFP): AFP, a glycoprotein normally synthesized by the yolk sac in the embryo and then by the fetal liver, is elevated in neonates and hence the pregnant mother. AFP decreases rapidly during the first year of life, reaching adult values (normally, < 10 to 20 ng/mL or < 10 to 20 mg/L depending on the laboratory) by the age of 1 yr. An increase in AFP, no matter how small, should prompt consideration of primary hepatocellular carcinoma (HCC). Serum AFP generally correlates with tumor size, differentiation and metastatic involvement. Because small tumors may produce low levels of AFP, increasing values suggest the presence of HCC, especially when tumors are > 3 cm diameter. AFP also helps predict prognosis.

Mild AFP elevations also occur in acute and chronic hepatitis, probably reflecting liver regeneration; AFP can occasionally increase to 500 ng/mL in fulminant hepatitis. High AFP levels can occur in a few other disorders (eg, embryonic teratocarcinomas, hepatoblastomas in children, some hepatic metastases from GI tract cancers, some cholangiocarcinomas), but these circumstances are not common and usually can be differentiated based on clinical and histopathologic grounds.

Sensitivity, specificity, and peak levels of AFP in patients with HCC vary by population, reflecting differences in factors such as hepatitis prevalence and ethnicity. In areas with a relatively low prevalence of hepatitis (eg, North America and western Europe), AFP cutoff values of 20 ng/mL have a sensitivity of 39 to 64% and a specificity of 76 to 91%. However, not all HCCs produce AFP. Thus, AFP is not an ideal screening test but does have a role in detecting HCC. Levels exceeding normal (> 20 ng/mL), especially when increasing, strongly suggest HCC. In cirrhotic patients with a mass and a high value (eg, > 200 ng/mL), the predictive value is high. The combined use of AFP and ultrasonography currently provides the best surveillance.

Imaging Tests

Imaging is essential for accurately diagnosing biliary tract disorders and is important for detecting focal liver lesions (eg, abscess, tumor). It is limited in detecting and diagnosing diffuse hepatocellular disease (eg, hepatitis, cirrhosis).

Ultrasonography: Ultrasonography, traditionally done transabdominally and requiring a period of fasting, provides structural, but not functional, information. It is the least expensive, safest, and most sensitive technique for imaging the biliary system, especially the gallbladder. Ultrasonography is the procedure of choice for

• Screening for biliary tract abnormalities

• Evaluating the hepatobiliary tract in patients with right upper quadrant abdominal pain

• Differentiating intrahepatic from extrahepatic causes of jaundice

• Detecting liver masses

The kidneys, pancreas, and blood vessels are also often visible on hepatobiliary ultrasounds. Ultrasonography can measure spleen size and thus help diagnose splenomegaly, which suggests portal hypertension.

Use of endoscopic ultrasonography may further refine the approaches to hepatobiliary abnormalities.

Ultrasonography can be difficult in patients with intestinal gas or obesity and is operator-dependent. Endoscopic ultrasonography incorporates an ultrasound transducer into the tip of an endoscope and thus provides greater image resolution even when intestinal gas is present.

Gallstones cast intense echoes with distal acoustic shadowing that move with gravity. Transabdominal ultrasonography is extremely accurate (sensitivity > 95%) for gallstones > 2 mm in diameter. Endoscopic ultrasonography can detect stones as small as 0.5 mm (microlithiasis) in the gallbladder or biliary system.

Transabdominal and endoscopic ultrasonography can also identify biliary sludge (a mixture of particulate material and bile) as low-level echoes that layer in the dependent portion of the gallbladder without acoustic shadowing.

Cholecystitis typically causes

• A thickened gallbladder wall (> 3 mm)

• Pericholecystic fluid

• An impacted stone in the gallbladder neck

• Tenderness on palpation of the gallbladder with the ultrasound probe (ultrasonographic Murphy's sign)

Extrahepatic obstruction is indicated by dilated bile ducts. On transabdominal and endoscopic ultrasounds, bile ducts stand out as echo-free tubular structures. The diameter of the common duct is normally < 6 mm, increases slightly with age, and can reach 10 mm after cholecystectomy. Dilated ducts are virtually pathognomonic for extrahepatic obstruction in the appropriate clinical setting. Ultrasonography can miss early or intermittent obstruction that does not dilate the ducts. Transabdominal ultrasonography may not reveal the level or cause of biliary obstruction (eg, sensitivity for common duct stones is < 40%). Endoscopic ultrasonography has a better yield.

Focal liver lesions > 1 cm in diameter can usually be detected by transabdominal ultrasonography. In general, cysts are echo-free; solid lesions (eg, tumors, abscesses) tend to be echogenic. Carcinoma appears as a nonspecific solid mass. Ultrasonography has been used to screen for hepatocellular carcinoma in patients at high risk (eg, with chronic hepatitis B, cirrhosis, or hemochromatosis). Because ultrasonography can localize focal lesions, it can be used to guide aspiration and biopsy.

Diffuse disorders (eg, cirrhosis, sometimes fatty liver) can be detected with ultrasonography. Ultrasound elastography can measure liver stiffness as an index of hepatic fibrosis. In this procedure, the transducer emits a vibration that induces an elastic shear wave. The rate at which the wave is propagated through the liver is measured; liver stiffness speeds this propagation.

Doppler ultrasonography: This noninvasive method is used to assess direction of blood flow and patency of blood vessels around the liver, particularly the portal vein. Clinical uses include

• Detecting portal hypertension, (eg, indicated by significant collateral flow and the direction of flow)

• Assessing the patency of liver shunts (eg, surgical portocaval, percutaneous transhepatic)

• Evaluating portal vein patency before liver transplantation and detecting hepatic artery thrombosis after transplantation

• Detecting unusual vascular structures (eg, cavernous transformation of the portal vein)

• Assessing tumor vascularity before surgery

CT: CT is commonly used to identify hepatic masses, particularly small metastases, with an accuracy of about 80%. It is considered the most accurate imaging technique. CT with IV contrast is accurate for diagnosing cavernous hemangiomas of the liver as well as differentiating them from other abdominal masses. Neither obesity nor intestinal gas obscures CT images. CT can detect fatty liver and the increased hepatic density that occurs with iron overload. CT is less helpful than ultrasonography in identifying biliary obstruction but often provides the best assessment of the pancreas.

Cholescintigraphy: After patients fast, an IV technetium-labeled iminodiacetic compound (eg, hydroxy or diisopropyl iminodiacetic acid [HIDA or DISIDA]) is injected; these substances are taken up by the liver and excreted in bile, then enter the gallbladder.

In acute calculous cholecystitis, which is usually caused by impaction of a stone in the cystic duct, the gallbladder does not appear on a scintigraphic scan because the radionuclide cannot enter the gallbladder. Such nonvisualization is diagnostically quite accurate (except for false-positive results in some critically ill patients). However, cholescintigraphy is rarely needed clinically to diagnose acute cholecystitis.

If acalculous cholecystitis is suspected, the gallbladder is scanned before and after administration of cholecystokinin (used to initiate gallbladder contraction). The decrease in scintigraphic counts indicates the gallbladder ejection fraction. Reduced emptying, measured as the ejection fraction, suggests acalculous cholecystitis.

Cholescintigraphy also detects bile leaks (eg, after surgery or trauma) and anatomic abnormalities (eg, congenital choledochal cysts, choledochoenteric anastomoses). After cholecystectomy, cholescintigraphy can quantitate biliary drainage; biliary drainage helps identify sphincter of Oddi dysfunction.

Radionuclide liver scanning: Ultrasonography and CT have largely supplanted radionuclide scanning, which had been used to diagnose diffuse liver disorders and mass lesions of the liver. Radionuclide scanning shows the distribution of an injected radioactive tracer, usually technetium (^{99m}Tc sulfur colloid), which distributes uniformly within the normal liver. Space-occupying lesions > 4 cm, such as liver cysts, abscesses, metastases, and tumors, appear as defects. Diffuse liver disorders (eg, cirrhosis, hepatitis) decrease liver uptake of the tracer, with more appearing in the spleen and bone marrow. In hepatic vein obstruction (Budd-Chiari syndrome), liver uptake is decreased except in the caudate lobe because its drainage into the inferior vena cava is preserved.

Plain x-ray of the abdomen: Plain x-rays are not usually useful for diagnosis of hepatobiliary disorders. They are insensitive for gallstones unless the gallstones are calcified and large. Plain x-rays can detect a calcified (porcelain) gallbladder. Rarely, in gravely ill patients, x-rays show air in the biliary tree, which suggests emphysematous cholangitis.

MRI: MRI images blood vessels (without using contrast), ducts, and hepatic tissues. Its clinical uses are still evolving. MRI is superior to CT and ultrasonography for diagnosing diffuse liver disorders (eg, fatty liver, hemochromatosis) and for clarifying some focal defects (eg, hemangiomas). MRI also shows blood flow and therefore complements Doppler ultrasonography and CT angiography in the diagnosis of vascular abnormalities and in vascular mapping before liver transplantation.

Magnetic resonance cholangiopancreatography (MRCP) is more sensitive than CT or ultrasonography in diagnosing common bile duct abnormalities, particularly stones. Its images of the biliary system and pancreatic ducts are comparable to those obtained with ERCP and percutaneous transhepatic cholangiography, which are more invasive. Thus, MRCP is a useful screening tool when biliary obstruction is suspected and before therapeutic ERCP (eg, for simultaneous imaging and stone removal) is done.

ERCP: ERCP combines endoscopy through the second portion of the duodenum with contrast imaging of the biliary and pancreatic ducts. The papilla of Vater is cannulated through an endoscope placed in the descending duodenum, and the pancreatic and biliary ducts are then injected with a contrast agent.

ERCP provides detailed images of much of the upper GI tract and the periampullary area, biliary tract, and pancreas. ERCP can also be used to obtain tissue for biopsy. ERCP is the best test for diagnosis of ampullary cancers. ERCP is as accurate as endoscopic ultrasonography for diagnosis of common duct stones. Because it is invasive, ERCP is used more for treatment (including simultaneous diagnosis and treatment) than for diagnosis alone. ERCP is the procedure of choice for treating biliary and pancreatic obstructing lesions, as for

- Removal of bile duct stones
- Stenting of strictures (inflammatory or malignant)
- Sphincterotomy (eg, for sphincter of Oddi dysfunction)

Morbidity from a diagnostic ERCP with only injection of contrast material is about 1%. Adding sphincterotomy raises morbidity to 4 to 9% (mainly due to pancreatitis and bleeding). ERCP with manometry to measure sphincter of Oddi pressure causes pancreatitis in up to 25% of patients.

Percutaneous transhepatic cholangiography (PTC): With fluoroscopic or ultrasound guidance, the liver is punctured with a needle, the peripheral intrahepatic bile duct system is cannulated above the common hepatic duct, and a contrast agent is injected.

PTC is highly accurate in diagnosing biliary disorders and can be therapeutic (eg, decompression of the biliary system, insertion of an endoprosthesis). However, ERCP is usually preferred because PTC causes more complications (eg, sepsis, bleeding, bile leaks).

Operative cholangiography: A contrast agent is directly injected during laparotomy to image the bile duct system.

Operative cholangiography is indicated when jaundice occurs and noninvasive procedures are equivocal, suggesting common duct stones. The procedure can be followed by common duct exploration for removal of biliary stones. Technical difficulties have limited its use, particularly during laparoscopic cholecystectomy.

Liver Biopsy

Liver biopsy provides histologic information about liver structure and evidence of liver injury (type and degree, any fibrosis); this information can be essential not only to diagnosis but also to staging, prognosis, and management. Although only a small core of tissue is obtained, it is usually representative, even for focal lesions.

Liver biopsy is usually done percutaneously at the bedside or with ultrasound guidance. Ultrasound guidance is preferred because its complication rate is slightly lower and it provides opportunity to visualize the liver and target focal lesions.

Indications: Generally, biopsy is indicated for suspected liver abnormalities that are not identified by less invasive methods or that require histopathology for staging (see Table 24-2). Biopsy is especially valuable

[**Table 24-2.** Indications for Liver Biopsy*]

for detecting TB or other granulomatous infiltrations and for clarifying graft problems (ischemic injury, rejection, biliary tract disorders, viral hepatitis) after liver transplantation. Serial biopsies, commonly done over years, may be necessary to monitor disease progression.

Gross examination and histopathology are often definitive. Cytology (fine-needle aspiration), frozen section, and culture may be useful for selected patients. Metal content (eg, copper in suspected Wilson's disease, iron in hemochromatosis) can be measured in the biopsy specimen.

Limitations of liver biopsy include

• Sampling error

• Occasional errors or uncertainty in cases of cholestasis

• Need for a skilled histopathologist (some pathologists have little experience with needle specimens)

Contraindications: Absolute contraindications to liver biopsy include

• Patient's inability to remain still and to maintain brief expiration for the procedure

- Suspected vascular lesion (eg, hemangioma)

- Bleeding tendency (eg, INR > 1.2 despite receiving vitamin K, bleeding time > 10 min)

- Severe thrombocytopenia (< 50,000/mL)

Relative contraindications include profound anemia, peritonitis, marked ascites, high-grade biliary obstruction, and a subphrenic or right pleural infection or effusion. Nonetheless, percutaneous liver biopsy is sufficiently safe to be done on an outpatient basis. Mortality is 0.01%. Major complications (eg, intra-abdominal hemorrhage, bile peritonitis, lacerated liver) develop in about 2% of patients. Complications usually become evident within 3 to 4 h—the recommended period for monitoring patients.

Other routes: Transjugular venous biopsy of the liver is more invasive than the percutaneous route; it is reserved for patients with a severe coagulopathy. The procedure involves cannulating the right internal jugular vein and passing a catheter through the inferior vena cava into the hepatic vein. A fine needle is then advanced through the hepatic vein into the liver. Biopsy is successful in > 95% of patients. Complication rate is low; 0.2% bleed from puncture of the liver capsule.

Occasionally, liver biopsy is done during surgery (eg, laparoscopy); a larger, more targeted tissue sample can then be obtained.

Chapter 25. Drugs and the Liver

Introduction

Interaction between drugs and the liver can be categorized as follows:

• Effects of liver disease on drug metabolism

• Liver injury caused by drugs

• Effects of hepatic drug metabolism (eg, induction of hepatic enzymes, see p. 3177)

The number of possible interactions is vast.

Effects of Liver Disease on Drug Metabolism

Liver disease may have complex effects on drug clearance, biotransformation, and pharmacokinetics. Pathogenetic factors include alterations in intestinal absorption, plasma protein binding, hepatic extraction ratio, liver blood flow, portal-systemic shunting, biliary excretion, enterohepatic circulation, and renal clearance. Sometimes alterations increase levels of bioavailable drug, causing normal drug doses to have toxic effects. However, levels and effects for an individual drug are unpredictable and do not correlate well with the type of liver injury, its severity, or liver function test results. Thus, no general rules are available for modifying drug dosage in patients with liver disease.

Clinical effects can vary independent of drug bioavailability, especially in chronic liver disease; eg, cerebral sensitivity to opioids and sedatives is often enhanced in patients with chronic liver disease. Thus, seemingly small doses of these drugs given to cirrhotic patients may precipitate encephalopathy. The mechanism of this effect probably involves alterations in cerebral drug receptors.

Adverse drug reactions do not appear to be more likely in patients with advanced liver disease; however, such patients may tolerate any hepatic adverse effects of drugs less well.

Liver Injury Caused by Drugs

Many drugs (eg, statins) commonly cause asymptomatic elevation of hepatic enzymes (ALT, AST, alkaline phosphatase). However, clinically significant liver injury (eg, with jaundice, abdominal pain, or pruritus) or impaired liver function—ie, resulting in deficient protein synthesis (eg, with prolonged PT or with hypoalbuminemia)—is rare.

The term drug-induced liver injury (DILI) may be used to mean clinically significant liver injury or all (including asymptomatic) liver injury. DILI includes injury caused by medicinal herbs, plants, and nutritional supplements as well as drugs.

Pathophysiology

The pathophysiology of DILI varies depending on the drug (or other hepatotoxin) and, in many cases, is not entirely understood. Drug-induced injury mechanisms include covalent binding of the drug to cellular proteins resulting in immune injury, inhibition of cell metabolic pathways, blockage of cellular transport pumps, induction of apoptosis, and interference with mitochondrial function.

In general, the following are thought to increase risk of DILI:

• Age ≥ 18 yr

• Obesity

• Pregnancy

• Concomitant alcohol consumption

• Genetic polymorphisms (increasingly recognized)

Patterns of liver injury: DILI can be predictable (when injury usually occurs shortly after exposure and is dose-related) or unpredictable (when injury develops after a period of latency and has no relation to dose). Predictable DILI (commonly, acetaminophen-induced) is a common cause of acute jaundice and acute liver failure in the US. Unpredictable DILI is a rare cause of severe liver disease. Subclinical DILI may be underreported.

Biochemically, 3 types of liver injury are generally noted (see Table 25-1):

• **Hepatocellular:** Hepatocellular hepatotoxicity generally manifests as malaise and

[**Table 25-1.** Potentially Hepatotoxic Drugs]

right upper quadrant abdominal pain, associated with marked elevation in aminotransferase levels (ALT, AST, or both), which may be followed by hyperbilirubinemia in severe cases. Hyperbilirubinemia in this setting is known as hepatocellular jaundice and, according to Hy's law, is associated with mortality rates as high as 50%. If hepatocellular liver injury is accompanied by jaundice, impaired hepatic synthesis, and encephalopathy, chance of spontaneous recovery is low, and liver transplantation should be considered. This type of injury can result from drugs such as acetaminophen and isoniazid.

• **Cholestatic:** Cholestatic hepatotoxicity is characterized by development of pruritus and jaundice accompanied by marked elevation of serum alkaline phosphatase levels. Usually, this type of injury is less serious than severe hepatocellular syndromes, but recovery may be protracted. Substances known to lead to this type of injury include amoxicillin/clavulanate and chlorpromazine. Rarely, cholestatic hepatotoxicity leads to chronic liver disease and vanishing bile duct syndrome (progressive destruction of intrahepatic bile ducts).

• **Mixed:** In these clinical syndromes, neither aminotransferase nor alkaline phosphatase elevations are clearly predominant. Symptoms may also be mixed. Drugs such as phenytoin can cause this type of injury.

Diagnosis

• Identification of characteristic patterns of laboratory abnormalities

• Exclusion of other causes

Presentation varies widely, ranging from absent or nonspecific symptoms (eg, malaise, nausea, anorexia) to jaundice, impaired hepatic synthesis, and encephalopathy. Early recognition of DILI improves prognosis.

Identification of a potential hepatotoxin and a pattern of liver test abnormalities that is characteristic of the substance (its signature) make the diagnosis likely.

Because there is no confirmatory diagnostic test, other causes of liver disease, especially viral, biliary, alcoholic, autoimmune, and metabolic causes, need to be excluded. Drug rechallenge, although it can strengthen evidence for the diagnosis, should usually be avoided. Suspected cases of DILI should be reported to MedWatch (the FDA's adverse drug reaction monitoring program).

Treatment

• Early drug withdrawal

Management emphasizes drug withdrawal, which, if done early, usually results in recovery. In severe

cases, consultation with a specialist is indicated, especially if patients have hepatocellular jaundice and impaired liver function, because liver transplantation may be required. Antidotes for DILI are available for only a few hepatotoxins; such antidotes include *N*-acetylcysteine for acetaminophen toxicity and silymarin or penicillin for *Amanita phalloides* toxicity.

Prevention

Efforts to avoid DILI begin during the drug development process, although apparent safety in small preclinical trials does not ensure eventual safety of the drug after it is in widespread use. Postmarketing surveillance, although often voluntary in the US, can call attention to potentially hepatotoxic drugs. Routine monitoring of liver enzymes has not been shown to decrease the incidence of hepatotoxicity. Use of pharmacogenomics may allow tailoring of drug use and avoidance of potential toxicities in susceptible patients.

Chapter 26. Alcoholic Liver Disease

Alcohol consumption is high in most Western countries. In the US, > 10% of people abuse or are dependent on alcohol. The male:female ratio is about 2:1. Disorders that occur in alcohol abusers, often in sequence, include

• Fatty liver (in > 90%)

• Alcoholic hepatitis (in 10 to 35%)

• Cirrhosis (in 10 to 20%)

Hepatocellular carcinoma may also develop, especially in association with iron accumulation.

Risk Factors

The main causative factors in alcoholic liver disease are

• Quantity and duration of alcohol use (usually > 8 yr)

• Sex

• Genetic and metabolic traits

• Nutritional status

Quantity of alcohol: Among susceptible people, a linear correlation generally exists between the amount and duration of alcohol use and the development of liver disease.

Alcohol content is estimated to be the beverage volume (in mL) multiplied by its percentage of alcohol. For example, the alcohol content of 40 mL of an 80-proof (40% alcohol) beverage is 16 mL by volume. Each mL contains about 0.79 g of alcohol. Although values can vary, the percentage of alcohol averages 2 to 7% for most beers and 10 to 15% for most wines. Thus, a 12-oz glass of beer contains about 3 to 10 g of alcohol, and an 8-oz glass of wine contains about 10 to 15 g.

Risk increases markedly for men who drink > 40 g, particularly > 80 g, of alcohol/day for > 10 yr (eg, 3 to 6 cans of beer, 3 to 6 shots of hard liquor, 4 to 8 glasses of wine). For cirrhosis to develop, consumption must usually be > 80 g/day for > 10 yr. If consumption exceeds 230 g/day for 20 yr, risk of cirrhosis is about 50%. But only some chronic alcohol abusers develop liver disease. Thus, variations in alcohol intake do not fully explain variations in susceptibility, indicating that other factors are involved.

Sex: Women are more susceptible to alcoholic liver disease, even after adjustment for body size. Women require only 20 to 40 g of alcohol to be at risk—half of that for men. Risk in women may be increased because they have less alcohol dehydrogenase in their gastric mucosa; thus, first-pass oxidation of alcohol is decreased.

Genetic factors: Alcoholic liver disease often runs in families, suggesting genetic factors (eg, deficiency of cytoplasmic enzymes that eliminate alcohol).

Nutritional status: Undernutrition, particularly protein-energy undernutrition, increases susceptibility, as does a diet high in unsaturated fat and obesity.

Other factors: Other risk factors include iron accumulation in the liver (not necessarily related to iron intake) and concomitant hepatitis C.

Pathophysiology

Alcohol absorption and metabolism: Alcohol (ethanol) is readily absorbed from the stomach, but most

is absorbed from the small intestine. Alcohol cannot be stored. A small amount is degraded in transit through the gastric mucosa, but most is catabolized in the liver, primarily by alcohol dehydrogenase (ADH) but also by cytochrome P-450 2E1 (CYP2E1) and the microsomal enzyme oxidation system (MEOS).

Metabolism via the ADH pathway involves the following:

- ADH, a cytoplasmic enzyme, oxidizes alcohol into acetaldehyde. Genetic polymorphisms in ADH account for some individual differences in blood alcohol levels after the same alcohol intake but not in susceptibility to alcoholic liver disease.

- Acetaldehyde dehydrogenase (ALDH), a mitochondrial enzyme, then oxidizes acetaldehyde to acetate. Chronic alcohol consumption enhances acetate formation. Asians, who have lower levels of ALDH, are more susceptible to toxic acetaldehyde effects (eg, flushing); the effects are similar to those of disulfiram, which inhibits ALDH.

- These oxidative reactions generate hydrogen, which converts nicotinamide-adenine dinucleotide (NAD) to its reduced form (NADH), increasing the redox potential (NADH/NAD) in the liver.

- The increased redox potential inhibits fatty acid oxidation and gluconeogenesis, promoting fat accumulation in the liver.

Chronic alcoholism induces the MEOS (mainly in endoplasmic reticulum), increasing its activity. The main enzyme involved is CYP2E1. When induced, the MEOS pathway can account for 20% of alcohol metabolism. This pathway generates harmful reactive O_2 species, increasing oxidative stress and formation of O_2-free radicals.

Hepatic fat accumulation: Fat (triglycerides) accumulates throughout the hepatocytes for the following reasons:

- Export of fat from the liver is decreased because hepatic fatty acid oxidation and lipoprotein production decrease.

- Input of fat is increased because the decrease in hepatic fat export increases peripheral lipolysis and triglyceride synthesis, resulting in hyperlipidemia.

Hepatic fat accumulation may predispose to subsequent oxidative damage.

Endotoxins in the gut: Alcohol changes gut permeability, increasing absorption of endotoxins released by bacteria in the gut. In response to the endotoxins (which the impaired liver can no longer detoxify), liver macrophages (Kupffer cells) release free radicals, increasing oxidative damage.

Oxidative damage: Oxidative stress is increased by

- Liver hypermetabolism, caused by alcohol consumption

- Free radical-induced lipid peroxidative damage

- Reduction in protective antioxidants (eg, glutathione, vitamins A and E), caused by alcohol-related undernutrition

- Binding of alcohol oxidation products, such as acetaldehyde, to liver cell proteins, forming neoantigens and resulting in inflammation

- Accumulation of neutrophils and other WBCs, which are attracted by lipid peroxidative damage and neoantigens

- Inflammatory cytokines secreted by WBCs

Accumulation of hepatic iron, if present, aggravates oxidative damage. Iron can accumulate in alcoholic liver disease through ingestion of iron-containing fortified wines; most often, the iron accumulation is modest. This condition must be differentiated from hereditary hemochromatosis.

Resultant inflammation, cell death, and fibrosis: A vicious circle of worsening inflammation occurs: Cell necrosis and apoptosis result in hepatocyte loss, and subsequent attempts at regeneration result in fibrosis. Stellate (Ito) cells, which line blood channels (sinusoids) in the liver, proliferate and transform into myofibroblasts, producing an excess of type I collagen and extracellular matrix. As a result, the sinusoids narrow, limiting blood flow. Fibrosis narrows the terminal hepatic venules, compromising hepatic perfusion and thus contributing to portal hypertension. Extensive fibrosis is associated with an attempt at regeneration, resulting in liver nodules. This process culminates in cirrhosis.

Pathology

Fatty liver, alcoholic hepatitis, and cirrhosis are often considered separate, progressive manifestations of alcoholic liver disease. However, their features often overlap.

Fatty liver (steatosis) is the initial and most common consequence of excessive alcohol consumption. Fatty liver is potentially reversible. Macrovesicular fat accumulates as large droplets of triglyceride and displaces the hepatocyte nucleus, most markedly in perivenular hepatocytes. The liver enlarges.

Alcoholic hepatitis (steatohepatitis) is a combination of fatty liver, diffuse liver inflammation, and liver necrosis (often focal)—all in various degrees of severity. The damaged hepatocytes are swollen with a granular cytoplasm (balloon degeneration) or contain fibrillar protein in the cytoplasm (Mallory or alcoholic hyaline bodies). Severely damaged hepatocytes become necrotic. Sinusoids and terminal hepatic venules are narrowed. Cirrhosis may also be present.

Alcoholic cirrhosis is advanced liver disease characterized by extensive fibrosis that disrupts the normal liver architecture. The amount of fat present varies. Alcoholic hepatitis may coexist. The feeble compensatory attempt at hepatic regeneration produces relatively small nodules (micronodular cirrhosis). As a result, the liver usually shrinks. In time, even with abstinence, fibrosis forms broad bands, separating liver tissue into large nodules (macronodular cirrhosis—see p. 241).

Symptoms and Signs

Symptoms usually become apparent in patients during their 30s or 40s; severe problems appear about a decade later.

Fatty liver is often asymptomatic. In one third of patients, the liver is enlarged and smooth, but it is not usually tender.

Alcoholic hepatitis ranges from mild and reversible to life threatening. Most patients with moderate disease are undernourished and present with fatigue, fever, jaundice, right upper quadrant pain, tender hepatomegaly, and sometimes a hepatic bruit. About 40% deteriorate soon after hospitalization, with consequences ranging from mild (eg, increasing jaundice) to severe (eg, ascites, portal-systemic encephalopathy, variceal bleeding, liver failure with hypoglycemia, coagulopathy). Other manifestations of cirrhosis may be present.

Cirrhosis, if compensated, may be asymptomatic. The liver is usually small; when the liver is enlarged, fatty liver or hepatoma should be considered. Symptoms range from those of alcoholic hepatitis to the complications of end-stage liver disease, such as portal hypertension (often with esophageal varices and upper GI bleeding, splenomegaly, ascites, and portal-systemic encephalopathy). Portal hypertension may lead to intrapulmonary arteriovenous shunting with hypoxemia (hepatopulmonary syndrome), which may cause cyanosis and nail clubbing. Acute renal failure secondary to progressively decreasing renal blood flow (hepatorenal syndrome) may develop. Hepatocellular carcinoma develops in 10 to 15% of patients with alcoholic cirrhosis.

Chronic alcoholism, rather than liver disease, causes Dupuytren's contracture of the palmar fascia,

vascular spiders, and peripheral neuropathy. In men, chronic alcoholism causes signs of hypogonadism and feminization (eg, smooth skin, lack of male-pattern baldness, gynecomastia, testicular atrophy, changes in pubic hair). Undernutrition may lead to multiple vitamin deficiencies (eg, of folate and thiamin), enlarged parotid glands, and white nails. In alcoholics, Wernicke's encephalopathy and Korsakoff's psychosis result mainly from thiamin deficiency. Hepatitis C occurs in > 25% of alcoholics; this combination markedly worsens the progression of liver disease.

Rarely, patients with fatty liver or cirrhosis present with Zieve's syndrome (hyperlipidemia, hemolytic anemia, and jaundice).

Diagnosis

• Confirmed history of alcohol use

• Liver function tests and CBC

• Sometimes liver biopsy

Alcohol is suspected as the cause of liver disease in any patient who chronically consumes excess alcohol, particularly > 80 g/day. History should be confirmed by family members. Patients can be screened for alcoholism using the CAGE questionnaire (need to *C*ut down, *A*nnoyed by criticism, *G*uilty about drinking, and need for a morning *E*ye-opener). There is no specific test for alcoholic liver disease, but if the diagnosis is suspected, liver function tests (PT; serum bilirubin, aminotransferase, and albumin levels) and CBC are done to detect signs of liver injury and anemia.

Elevations of aminotransferases are moderate (< 300 IU/L) and do not reflect the extent of liver damage. The ratio of AST to ALT is ≥ 2. The basis for low ALT is a dietary deficiency of pyridoxal phosphate (vitamin B_6), which is needed for ALT to function. Its effect on AST is less pronounced. Serum γ-glutamyl transpeptidase (GGT) increases, more because ethanol induces this enzyme than because patients have cholestasis or liver injury or use other drugs. Serum albumin may be low, usually reflecting undernutrition but occasionally reflecting otherwise obvious liver failure with deficient synthesis. Macrocytosis with an MCV > 100 fL reflects the direct effect of alcohol on bone marrow as well as macrocytic anemia resulting from folate deficiency, which is common among undernourished alcoholics. Indexes of the severity of liver disease are

• Serum bilirubin, which represents secretory function

• PT or INR, which reflects synthetic ability

Thrombocytopenia can result from the direct toxic effects of alcohol on bone marrow or from splenomegaly, which accompanies portal hypertension. Neutrophilic leukocytosis may result from alcoholic hepatitis, although coexisting infection (particularly pneumonia and spontaneous bacterial peritonitis) should also be suspected.

Imaging tests are not routinely needed for diagnosis. If done for other reasons, abdominal ultrasonography or CT may suggest fatty liver or show evidence of splenomegaly, portal hypertension, or ascites. Ultrasound elastrography measures liver stiffness and thus detects advanced fibrosis. This valuable adjunct can obviate the need for liver biopsy to check for cirrhosis and help assess prognosis. Its exact role is under study.

If abnormalities suggest alcoholic liver disease, screening tests for other treatable forms of liver disease, especially viral hepatitis, should be done. Because features of fatty liver, alcoholic hepatitis, and cirrhosis overlap, describing the precise findings is more useful than assigning patients to a specific category, which can only be determined by liver biopsy.

Not all experts agree on the indications for liver biopsy. Proposed indications include the following:

• Unclear clinical diagnosis (eg, equivocal clinical and laboratory findings, unexplained persistent

elevations of aminotransferase levels)

• Clinical suspicion of > 1 cause of liver disease (eg, alcohol plus viral hepatitis)

• Desire for a precise prediction of prognosis

Liver biopsy confirms liver disease, helps identify excessive alcohol use as the likely cause, and establishes the stage of liver injury. If iron accumulation is observed, measurement of the iron content and genetic testing can eliminate hereditary hemochromatosis (see p. 1032) as the cause.

For stable patients with cirrhosis, α-fetoprotein measurement and liver ultrasonography should be done to screen for hepatocellular carcinoma (see p. 265).

Prognosis

Prognosis is determined by the degree of hepatic fibrosis and inflammation. Fatty liver and alcoholic hepatitis without fibrosis are reversible if alcohol is avoided. With abstinence, fatty liver completely resolves within 6 wk. Fibrosis and cirrhosis are irreversible.

Certain biopsy findings (eg, neutrophils, perivenular fibrosis) indicate a worse prognosis. Proposed quantitative indexes to predict severity and mortality use primarily laboratory features of liver failure such as prothrombin time, creatinine (for hepatorenal syndrome) and bilirubin levels. The Maddrey discriminant function is calculated from the formula:

$$4.6 \times (\text{PT} - \text{control PT}) + \text{serum bilirubin}$$

For this formula, bilirubin level is measured in mg/dL (converted from bilirubin in µmol/L by dividing by 17). A value of > 32 is associated with a high short-term mortality rate (eg, after 1 mo, 35% without encephalopathy and 45% with encephalopathy). Other indexes include the Model for End-Stage Liver Disease (MELD), Glasgow alcoholic hepatitis score, and Lille model.

Once cirrhosis and its complications (eg, ascites, bleeding) develop, the 5-yr survival rate is about 50%; survival is higher in patients who abstain and lower in patients who continue drinking.

Coexisting iron accumulation or chronic hepatitis C increases risk of hepatocellular carcinoma.

Treatment

• Abstinence

• Supportive care

• Corticosteroids and enteral nutrition for severe alcoholic hepatitis

• Sometimes transplantation

Restricting alcohol intake: Abstinence is the mainstay of treatment; it prevents further damage from alcoholic liver disease and thus prolongs life. Because compliance is problematic, a compassionate team approach is essential. Behavioral and psychosocial interventions can help motivated patients; they include rehabilitation programs and support groups (see p. 1521), brief interventions by primary care physicians, and therapies that explore and clarify the motivation to abstain (motivational enhancement therapy).

Drugs, if used, should only supplement other interventions. Opioid antagonists (naltrexone or nalmefene) and drugs that modulate γ-aminobutyric acid receptors (baclofen or acamprosate) appear to have a short-

term benefit by reducing the craving and withdrawal symptoms. Disulfiram inhibits aldehyde dehydrogenase, allowing acetaldehyde to accumulate; thus, drinking alcohol within 12 h of taking disulfiram causes flushing and has other unpleasant effects. However, disulfiram has not been shown to promote abstinence and consequently is recommended only for certain patients.

Supportive care: General management emphasizes supportive care. A nutritious diet and vitamin supplements (especially B vitamins) are important during the first few days of abstinence. Alcohol withdrawal requires use of benzodiazepines (eg, diazepam). In patients with advanced alcoholic liver disease, excessive sedation can precipitate hepatic encephalopathy and thus must be avoided.

Severe acute alcoholic hepatitis commonly requires hospitalization, often in an intensive care unit, to facilitate enteral feeding (which can help manage nutritional deficiencies) and to manage specific complications (eg, infection, bleeding from esophageal varices, specific nutritional deficiencies, Wernicke's encephalopathy, Korsakoff's psychosis, electrolyte abnormalities, portal hypertension, ascites, portal-systemic encephalopathy—see elsewhere in THE MANUAL).

Specific treatment: Corticosteroids (eg, prednisolone 40 mg/day po for 4 wk, followed by tapered doses improve outcome in patients who have severe acute alcoholic hepatitis and who do not have infection, GI bleeding, renal failure, or pancreatitis.

Other than corticosteroids and enteral feeding, few specific treatments are clearly established. Antioxidants (eg, *S*-adenosyl-L-methionine, phosphatidylcholine, metadoxine) show promise in ameliorating liver injury during early cirrhosis but require further study. Therapies directed at cytokines, particularly tumor necrosis factor-α (TNF-α), and aiming to reduce inflammation have had mixed results in small trials. Pentoxifylline, a phosphodiesterase inhibitor that inhibits TNF-α synthesis, has some benefit. In contrast, when biologic agents that inhibit TNF-α (eg, infliximab, etanercept) are used, risk of infection outweighs benefit. Drugs given to decrease fibrosis (eg, colchicine, penicillamine) and drugs given to normalize the hypermetabolic state of the alcoholic liver (eg, propylthiouracil) have no proven benefit. Antioxidant remedies, such as silymarin (milk thistle) and vitamins A and E, are ineffective.

Liver transplantation can be considered if disease is severe. With transplantation, 5-yr survival rates are comparable to those for nonalcoholic liver disease—as high as 80% in patients without active liver disease and 50% in those with acute alcoholic hepatitis. Because up to 50% of patients resume drinking after transplantation, most programs require 6 mo of abstinence before transplantation is done.

Chapter 27. Fibrosis and Cirrhosis

Introduction

In hepatic fibrosis, excessive connective tissue accumulates in the liver; this tissue represents scarring in response to chronic, repeated liver cell injury. Commonly, fibrosis progresses, disrupting hepatic architecture and eventually function, as regenerating hepatocytes attempt to replace and repair damaged tissue. When such disruption is widespread, cirrhosis is diagnosed. To develop, cirrhosis usually requires > 6 mo of liver disease but can occur more rapidly (eg, during infancy with biliary atresia, after liver transplantation for severe liver disease secondary to chronic hepatitis B or C).

Fibrosis

Hepatic fibrosis is overly exuberant wound healing in which excessive connective tissue builds up in the liver. The extracellular matrix is overproduced, degraded deficiently, or both. The trigger is chronic injury, especially if there is an inflammatory component. Fibrosis itself causes no symptoms but can lead to portal hypertension (the scarring distorts blood flow through the liver) or cirrhosis (the scarring results in disruption of normal hepatic architecture and liver dysfunction). Diagnosis is based on liver biopsy. Treatment involves correcting the underlying condition when possible.

Various types of chronic liver injury can cause fibrosis (see Table 27-1). Self-limited, acute liver injury (eg, acute viral hepatitis A), even when fulminant, does not necessarily distort the scaffolding architecture and hence does not cause fibrosis, despite loss of hepatocytes. In its initial stages, hepatic fibrosis can regress if the cause is reversible (eg, with viral clearance). After months or years of chronic or repeated injury, fibrosis becomes permanent. Fibrosis develops even more rapidly in mechanical biliary obstruction.

Pathophysiology

Activation of the hepatic perivascular stellate cells (Ito cells, which store fat) initiates fibrosis. These and adjacent cells proliferate, becoming contractile cells termed myofibroblasts. These cells produce excessive amounts of abnormal matrix (consisting of collagen, other glycoproteins, and glycans) and matricellular proteins. Kupffer cells (resident macrophages), injured hepatocytes, platelets, and leukocytes aggregate. As a result, reactive O_2 species and inflammatory mediators (eg, platelet-derived growth factor, transforming growth factors, and connective tissue growth factor) are released. Thus, stellate cell activation results in abnormal extracellular matrix, both in quantity and composition.

Myofibroblasts, stimulated by endothelin-1, contribute to increased portal vein resistance and increase the density of the abnormal matrix. Fibrous tracts join branches of afferent portal veins and efferent hepatic veins, bypassing the hepatocytes and limiting their blood supply. Hence, fibrosis contributes both to hepatocyte ischemia (causing hepatocellular dysfunction) and portal hypertension. The

[**Table 27-1.** Disorders and Drugs that Can Cause Hepatic Fibrosis]

extent of the ischemia and portal hypertension determines how the liver is affected. For example, congenital hepatic fibrosis affects portal vein branches, largely sparing the parenchyma. The result is portal hypertension with sparing of hepatocellular function.

Symptoms and Signs

Hepatic fibrosis itself does not cause symptoms. Symptoms may develop secondary to the primary disorder or to portal hypertension. Portal hypertension with splenomegaly is often asymptomatic unless complications, such as variceal GI bleeding, ascites, or portal-systemic encephalopathy, develop. Eventually, cirrhosis supervenes.

Diagnosis

• Biopsy

Hepatic fibrosis is suspected in patients who have an underlying disorder or take a drug that could cause fibrosis or who have unexplained abnormalities in liver function or enzymes. Noninvasive tests (eg, serologic markers) are under study but are not yet ready for routine clinical use. Imaging tests such as ultrasonography, CT, and MRI may detect findings associated with fibrosis (eg, portal hypertension, splenomegaly, cirrhosis) but are not sensitive to parenchymal fibrosis itself. Liver biopsy is currently the only means of detecting hepatic fibrosis. Biopsy is indicated to clarify the diagnosis (eg, nonalcoholic steatohepatitis, primary biliary cirrhosis) and stage its progress (eg, in chronic hepatitis C to determine whether fibrosis is present or whether it has progressed to cirrhosis).

Treatment

• Treatment of cause

Because fibrosis represents a response to hepatic damage, primary treatment should focus on the cause (removing the basis of the liver injury). Such treatment may include eliminating HBC or HCV in chronic viral hepatitis, abstaining from alcohol in alcoholic liver disease, removing heavy metals such as iron in hemochromatosis or copper in Wilson's disease, and decompressing bile ducts in biliary obstruction.

Treatments aimed at reversing the fibrosis are usually too toxic for long-term use (eg, corticosteroids, penicillamine) or have no proven efficacy (eg, colchicine). Other antifibrotic treatments are under study. Simultaneous use of multiple antifibrotic drugs may eventually prove most beneficial.

Cirrhosis

Cirrhosis is a late stage of hepatic fibrosis that has resulted in widespread distortion of normal hepatic architecture. Cirrhosis is characterized by regenerative nodules surrounded by dense fibrotic tissue. Symptoms may not develop for years and are often nonspecific (eg, anorexia, fatigue, weight loss). Late manifestations include portal hypertension, ascites, and, when decompensation occurs, liver failure. Diagnosis often requires liver biopsy. Cirrhosis is usually considered irreversible. Treatment is supportive.

Cirrhosis is a leading cause of death worldwide. The causes of cirrhosis are the same as those of fibrosis (see Table 27-1). In developed countries, most cases result from chronic alcohol abuse or chronic hepatitis C. In parts of Asia and Africa, cirrhosis often results from chronic hepatitis B. Cirrhosis of unknown etiology (cryptogenic cirrhosis) is becoming less common as many specific causes (eg, chronic hepatitis C, steatohepatitis) are identified. Injury to the bile ducts also can result in cirrhosis, as occurs in mechanical bile duct obstruction, primary biliary cirrhosis (see p. 244), and primary sclerosing cholangitis (see p. 278).

Pathophysiology

There are 2 primary factors:

• Hepatic fibrosis

• Regenerating liver cells

In response to injury and loss, growth regulators induce hepatocellular hyperplasia (producing regenerating nodules) and arterial growth (angiogenesis). Among the growth regulators are cytokines and hepatic growth factors (eg, epithelial growth factor, hepatocyte growth factor, transforming growth factor-α, tumor necrosis factor). Insulin, glucagon, and patterns of intrahepatic blood flow determine how and where nodules develop.

Angiogenesis produces new vessels within the fibrous sheath that surrounds nodules. These vessels connect the hepatic artery and portal vein to hepatic venules, restoring the intrahepatic circulatory

pathways. Such interconnecting vessels provide relatively low-volume, high-pressure venous drainage that cannot accommodate as much blood volume as normal. As a result, portal vein pressure increases. Such distortions in blood flow contribute to portal hypertension, which increases because the regenerating nodules compress hepatic venules.

The progression rate from fibrosis to cirrhosis and the morphology of cirrhosis vary from person to person. Presumably, the reason for such variation is the extent of exposure to the injurious stimulus and the individual's response.

Complications: Portal hypertension (see p. 218) is the most common serious complication; it can manifest as GI bleeding from esophageal, gastric, or rectal varices or portal hypertensive gastropathy. Portal hypertension can be massive. Cirrhosis can cause other cardiovascular complications. Vasodilation and intrapulmonary right-to-left shunting and ventilation/perfusion mismatch can result in hypoxia (hepatopulmonary syndrome). A cardiac myopathy can also accompany cirrhosis.

Ascites can develop, with a risk of spontaneous bacterial peritonitis. Splenic congestion with hypersplenism may occur, resulting in splenomegaly, platelet sequestration, and consequent cytopenia.

Progressive loss of hepatic architecture impairs function, leading to hepatic insufficiency; it manifests as coagulopathy, renal failure (hepatorenal syndrome—see p. 223), and hepatic encephalopathy. Hepatocytes secrete less bile, contributing to cholestasis and jaundice. Less bile in the intestine causes malabsorption of dietary fat (triglycerides) and fat-soluble vitamins. Malabsorption of vitamin D may contribute to osteoporosis. Undernutrition is common. It may result from anorexia with reduced food intake or, in patients with alcoholic liver disease, from malabsorption due to pancreatic insufficiency.

Blood disorders are common. Anemia results from hypersplenism, chronic GI bleeding, folate deficiency (particularly in patients with alcoholism), and hemolysis. Clotting may be impaired because of coagulopathy or thrombocytopenia. Coagulopathy results from impaired hepatic synthesis of the factors necessary for clotting, malabsorption of vitamin K due to impaired bile secretion into the duodenum, or both. Thrombocytopenia may be caused by hypersplenism (platelet sequestration), alcohol excess (directly inhibiting the bone marrow), or both. Pancytopenia also occurs with alcoholism.

Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B and C viruses, hemochromatosis, alcohol-related liver disease, $\alpha_1$antitrypsin deficiency, or glycogen storage disease.

Histopathology: Cirrhosis is characterized by regenerating nodules and fibrosis. Incompletely formed liver nodules, nodules without fibrosis (nodular regenerative hyperplasia), and congenital hepatic fibrosis (ie, widespread fibrosis without regenerating nodules) are not true cirrhosis.

Cirrhosis can be micronodular or macronodular. Micronodular cirrhosis is characterized by uniformly small nodules (< 3 mm in diameter) and thick regular bands of connective tissue. Typically, nodules lack lobular organization; terminal (central) hepatic venules and portal triads are distorted. With time, macronodular cirrhosis often develops. The nodules vary in size (3 mm to 5 cm in diameter) and have some rather normal lobular organization of portal triads and terminal hepatic venules. Broad fibrous bands of varying thickness surround the large nodules. Collapse of the normal hepatic architecture is suggested by the concentration of portal triads within the fibrous scars. Mixed cirrhosis (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis. Differentiation between these morphologic types of cirrhosis has limited clinical value.

Symptoms and Signs

Cirrhosis may be asymptomatic for years. One third of patients never develop symptoms. Often, the first symptoms are nonspecific; they include generalized fatigue (due to cytokine release), anorexia, malaise, and weight loss (see Table 27-2). The liver is typically palpable and firm, with a blunt edge, but is sometimes small and difficult to palpate. Nodules usually are not palpable.

Clinical signs that suggest a chronic liver disorder or chronic alcohol use but are not specific for cirrhosis include muscle wasting, palmar erythema, parotid gland enlargement, white nails, clubbing, Dupuytren's contracture, spider angiomas (< 10 may be normal), gynecomastia, axillary hair loss, testicular atrophy, and peripheral neuropathy.

Once complications of cirrhosis develop, decompensation inexorably ensues.

Diagnosis

• Liver function tests, coagulation tests, CBC, and serologic tests for viral cause

• Sometimes biopsy

• Identification of cause based on clinical evaluation and selective testing

General approach: Cirrhosis is suspected in patients with manifestations of any of its complications (see Table 27-2), particularly portal hypertension or ascites. Early cirrhosis should be considered in patients with nonspecific

[**Table 27-2.** Common Symptoms and Signs Due to Complications of Cirrhosis]

symptoms or characteristic laboratory abnormalities detected incidentally during laboratory testing, particularly in patients who have a disorder or take a drug that might cause fibrosis.

Testing seeks to detect cirrhosis and any complications and to determine its cause.

Laboratory tests: Diagnostic testing begins with liver function tests, coagulation tests, CBC, and serologic tests for viral causes (eg, hepatitis B and C). Laboratory tests alone may increase suspicion for cirrhosis but cannot confirm or exclude it. Liver biopsy becomes necessary if a clear diagnosis would lead to better management and outcome.

Test results may be normal or may indicate nonspecific abnormalities due to complications of cirrhosis or alcoholism. ALT and AST levels are often modestly elevated. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are often normal; elevated levels indicate cholestasis or biliary obstruction. Bilirubin is usually normal but increases when cirrhosis progresses, particularly in primary biliary cirrhosis (see p. 244). Decreased serum albumin and a prolonged PT directly reflect impaired hepatic synthesis —usually an end-stage event. Albumin can also be low when nutrition is poor. Serum globulin increases in cirrhosis and in most liver disorders with an inflammatory component. Anemia is common and usually normocytic with a high RBC distribution width. Anemia is often multifactorial; contributing factors may include chronic GI bleeding (usually causing microcytic anemia), folate nutritional deficiency (causing macrocytic anemia, especially in alcohol abuse), hemolysis, and hypersplenism. CBC may detect leukopenia, thrombocytopenia, or pancytopenia.

Diagnostic imaging: Imaging tests are not highly sensitive or specific for the diagnosis of cirrhosis by themselves, but they can often detect its complications. In advanced cirrhosis, ultrasonography shows a small, nodular liver. Ultrasonography also detects portal hypertension and ascites.

CT can detect a nodular texture, but it has no advantage over ultrasonography. Radionuclide liver scans using technetium-99m sulfur colloid may show irregular liver uptake and increased spleen and bone marrow uptake. MRI is more expensive than other imaging tests and has little advantage.

Identification of the cause: Determining the specific cause of cirrhosis requires key clinical information from the history and examination, as well as selective testing. Alcohol is the likely cause in patients with a documented history of alcoholism and clinical findings such as gynecomastia, spider angiomas (telangiectasia), and testicular atrophy plus laboratory confirmation of liver damage (AST elevated more than ALT) and liver enzyme induction (a greatly increased GGT). Fever, tender hepatomegaly, and jaundice suggest the presence of alcoholic hepatitis.

Detecting hepatitis B surface antigen (HBsAg) and IgG antibodies to hepatitis B (IgG anti-HBc) confirms chronic hepatitis B. Identifying serum antibody to hepatitis C (anti-HCV) and HCV-RNA points to hepatitis C.

If common causes such as alcohol or viral hepatitis are not confirmed, other less common causes are sought:

- Presence of antimitochondrial antibodies (in 95%) suggests primary biliary cirrhosis.
- Strictures and dilations of the intrahepatic and extrahepatic bile ducts seen on magnetic resonance cholangiopancreatography (MRCP) suggest primary sclerosing cholangitis.
- Increased serum Fe and transferrin and possibly results of genetic testing suggest hemochromatosis.
- Decreased serum ceruloplasmin and characteristic copper test results suggest Wilson's disease.
- Hypergammaglobulinemia and presence of autoantibodies (eg, antinuclear or anti-smooth muscle antibodies) indicate autoimmune hepatitis.

Liver biopsy: If clinical criteria and noninvasive testing are inconclusive, liver biopsy is usually done. Its sensitivity approaches 100%. Nonalcoholic steatohepatitis (NASH), often associated with obesity, diabetes, or the metabolic syndrome, may be evident on ultrasound scans but requires liver biopsy for confirmation. In obvious cases of cirrhosis with a marked coagulopathy, portal hypertension, ascites, and liver failure, biopsy is not required when results would not change management.

Monitoring: Patients with cirrhosis, particularly if due to chronic viral hepatitis B or C or hemochromatosis, should be screened for hepatocellular carcinoma (eg, measuring α-fetoprotein levels and ultrasonography every 6 to 12 mo—see p. 266).

Prognosis

Prognosis is often unpredictable. It depends on factors such as etiology, severity, presence of complications, comorbid conditions, host factors, and effectiveness of therapy. Patients who continue to drink alcohol, even small amounts, have a very poor prognosis. The Child-Turcotte-Pugh scoring system uses clinical and laboratory information to stratify disease severity, surgical risk, and overall prognosis (see Tables 27-3 and 27-4).

Treatment

- Supportive care

In general, treatment is supportive and includes stopping injurious drugs, providing nutrition (including supplemental vitamins), and treating the underlying disorders and complications. Doses of drugs metabolized in the liver should be reduced. All alcohol and hepatotoxic substances must be avoided. Withdrawal symptoms during hospitalization should be anticipated in patients who have cirrhosis and have continued to abuse alcohol.

Patients with varices need therapy to prevent bleeding (see p. 219). Liver transplantation is indicated for end-stage liver failure in suitable candidates.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune liver disorder characterized by the progressive destruction of intrahepatic bile ducts, leading to cholestasis, cirrhosis, and liver failure. Patients usually are asymptomatic at presentation but may experience fatigue or have symptoms of cholestasis (eg, pruritus, steatorrhea) or cirrhosis (eg, portal hypertension,

ascites). Laboratory tests reveal cholestasis, increased IgM, and, characteristically, antimitochondrial antibodies in the serum. Liver biopsy may be necessary for diagnosis and staging. Treatment includes ursodeoxycholic acid, cholestyramine (for pruritus),

[**Table 27-3.** Child-Turcotte-Pugh Scoring System]

[**Table 27-4.** Interpretation of the Child-Turcotte-Pugh Scoring System]

supplementary fat-soluble vitamins, and, ultimately for advanced disease, liver transplantation.

Etiology

PBC is the most common liver disease associated with chronic cholestasis in adults. Most (95%) cases occur in women aged 35 to 70. PBC also clusters in families. A genetic predisposition, perhaps involving the X chromosome, probably contributes. There may be an inherited abnormality of immune regulation. An autoimmune mechanism has been implicated; antibodies to antigens located on the inner mitochondrial membranes occur in > 95% of cases. These antimitochondrial antibodies (AMAs), the serologic hallmarks of PBC, are not cytotoxic and are not involved in bile duct damage. PBC is associated with other autoimmune disorders, such as RA, systemic sclerosis, Sjogren's syndrome, CREST syndrome, autoimmune thyroiditis, and renal tubular acidosis.

T cells attack the small bile ducts. CD4 and CD8 T lymphocytes directly target biliary epithelial cells. The trigger for the immunologic attack on bile ducts is unknown. Exposure to foreign antigens, such as an infectious (bacterial or viral) or toxic agent, may be the instigating event. These foreign antigens might be structurally similar to endogenous proteins (molecular mimicry); then the subsequent immunologic reaction would be autoimmune and self-perpetuating. Destruction and loss of bile ducts lead to impaired bile formation and secretion (cholestasis). Retained toxic materials such as bile acids then cause further damage, particularly to hepatocytes. Chronic cholestasis thus leads to liver cell inflammation and scarring in the periportal areas. Eventually, hepatic inflammation decreases as hepatic fibrosis progresses to cirrhosis.

Autoimmune cholangitis is sometimes considered to be a separate disorder. It is characterized by autoantibodies, such as antinuclear antibodies (ANAs), anti-smooth muscle antibodies, or both and has a clinical course and response to treatment that are similar to PBC. However, in autoimmune cholangitis, AMAs are absent.

Symptoms and Signs

About half of patients present without symptoms. Symptoms or signs may develop during any stage of the disease and may include fatigue or reflect cholestasis (and the resulting fat malabsorption, which may lead to vitamin deficiencies and osteoporosis), hepatocellular dysfunction, or cirrhosis.

Symptoms usually develop insidiously. Pruritus, fatigue, and dry mouth and eyes are the initial symptoms in > 50% of patients and can precede other symptoms by months or years. Other initial manifestations include right upper quadrant discomfort (10%); an enlarged, firm, nontender liver (25%); splenomegaly (15%); hyperpigmentation (25%); xanthelasmas (10%); and jaundice (10%). Eventually, all the features and complications of cirrhosis occur. Peripheral neuropathy and other autoimmune disorders associated with PBC may also develop.

Diagnosis

• Liver function tests

• Antimitochondrial antibodies

• Ultrasonography and often MRCP

• Liver biopsy

In asymptomatic patients, PBC is detected incidentally when liver function tests detect abnormalities, typically elevated levels of alkaline phosphatase and γ-glutamyl transpeptidase (GGT). PBC is suspected in middle-aged women with classic symptoms (eg, unexplained pruritus, fatigue, right upper quadrant discomfort, jaundice) or laboratory results suggesting cholestatic liver disease: elevated alkaline phosphatase and GGT but minimally abnormal aminotransferases (ALT, AST). Serum bilirubin is usually normal in the early stages; elevation indicates disease progression and a worsening prognosis.

If PBC is suspected, liver function tests and tests to measure serum IgM (increased in PBC) and AMA should be done. ELISA tests are 95% sensitive and 98% specific for PBC; false-positive results can occur in autoimmune hepatitis (type 1). Other autoantibodies (eg, ANAs, anti-smooth muscle antibodies, rheumatoid factor) may be present. Extrahepatic biliary obstruction should be ruled out. Ultrasonography is often done first, but ultimately MRCP and sometimes ERCP are necessary. Unless life expectancy is short or there is a contraindication, liver biopsy is usually done. Liver biopsy confirms the diagnosis; it may detect pathognomonic bile duct lesions, even in early stages. As PBC progresses, it becomes morphologically indistinguishable from other forms of cirrhosis. Liver biopsy also helps stage PBC, which has 4 histologic stages:

• Stage 1: Inflammation, abnormal connective tissue, or both, confined to the portal areas

• Stage 2: Inflammation, fibrosis, or both, confined to the portal and periportal areas

• Stage 3: Bridging fibrosis

• Stage 4: Cirrhosis

Autoimmune cholangitis is diagnosed when AMAs are absent in a patient who otherwise would be diagnosed with PBC.

Prognosis

Usually, PBC progresses to terminal stages over 15 to 20 yr, although the rate of progression varies. PBC may not diminish quality of life for many years. Patients who present without symptoms tend to develop symptoms over 2 to 7 yr but may not do so for 10 to 15 yr. Once symptoms develop, median life expectancy is 10 yr. Predictors of rapid progression include the following:

• Rapid worsening of symptoms

• Advanced histologic changes

• Older patient age

• Presence of edema

• Presence of associated autoimmune disorders

• Abnormalities in bilirubin, albumin, PT, or INR

The prognosis is ominous when pruritus disappears, xanthomas shrink, jaundice develops, and serum cholesterol decreases.

Treatment

• Arresting or reversing liver damage

• Treating complications (chronic cholestasis and liver failure)

• Eventually, doing liver transplantation

All alcohol use and hepatotoxic drugs should be stopped. Ursodeoxycholic acid (15 mg/kg po once/day) decreases liver damage, prolongs survival, and delays the need for liver transplantation. About 20% of patients do not have biochemical improvement after ≥ 4 mo; they may have advanced disease and require liver transplantation in a few years. Other drugs proposed to decrease liver damage have not improved overall clinical outcomes or are controversial.

Pruritus may be controlled with cholestyramine 6 to 8 g po bid. This anionic-binding drug binds bile salts and thus may aggravate fat malabsorption. If cholestyramine is taken long-term, supplements of fat-soluble vitamins should be considered. Cholestyramine can decrease absorption of ursodeoxycholic acid, so these drugs should not be given simultaneously.

Some patients with pruritus respond to ursodeoxycholic acid and ultraviolet light; others may warrant a trial of rifampin or an opioid antagonist, such as naltrexone. Patients with fat malabsorption due to bile salt deficiency should be treated with vitamins A, D, E, and K. For osteoporosis, weight-bearing exercises, bisphosphonates, or raloxifene may be needed in addition to Ca and vitamin D supplements. In later stages, portal hypertension (see p. 218) or complications of cirrhosis (see p. 241) require treatment.

Liver transplantation has excellent results. The general indication is decompensated liver disease (uncontrolled variceal bleeding, refractory ascites, intractable pruritus, and hepatic encephalopathy). Survival rates after liver transplantation are > 90% at 1 yr, > 80% at 5 yr, and > 65% at 10 yr. AMAs tend to persist after transplantation. PBC recurs in 15% of patients in the first few years and in > 30% by 10 yr. So far, recurrent PBC after liver transplantation has a benign course. Cirrhosis rarely occurs.

Chapter 28. Hepatitis

Introduction

Hepatitis is an inflammation of the liver characterized by diffuse or patchy necrosis. Major causes are specific hepatitis viruses, alcohol, and drugs. Less common causes include other viral infections (eg, infectious mononucleosis, yellow fever, cytomegalovirus infection) and leptospirosis. Parasitic infections (eg, schistosomiasis, malaria, amebiasis), pyogenic infections, and abscesses that affect the liver are not considered hepatitis. Liver involvement with TB and other granulomatous infiltrations is sometimes called granulomatous hepatitis, but the clinical, biochemical, and histologic features differ from those of diffuse hepatitis.

Various systemic infections and other illnesses may produce small focal areas of hepatic inflammation or necrosis. This nonspecific reactive hepatitis can cause minor liver function abnormalities but is usually asymptomatic.

Some types of infectious and noninfectious liver inflammation are summarized (see Table 28-1).

Acute Viral Hepatitis

Acute viral hepatitis is diffuse liver inflammation caused by specific hepatotropic viruses that have diverse modes of transmission and epidemiologies. A nonspecific viral prodrome is followed by anorexia, nausea, and often fever or right upper quadrant pain. Jaundice often develops, typically as other symptoms begin to resolve. Most cases resolve spontaneously, but some progress to chronic hepatitis. Occasionally, acute viral hepatitis progresses to acute hepatic failure (fulminant hepatitis). Diagnosis is by liver function tests and serologic tests to identify the virus. Good hygiene can prevent acute viral hepatitis. Depending on the specific virus, preexposure and postexposure prophylaxis may be possible using vaccines or serum globulins. Treatment is usually supportive.

(See also Neonatal Hepatitis B Virus Infection on p. 2825.)

Acute viral hepatitis is a common, worldwide disease that has different causes; each type shares clinical, biochemical, and morphologic features. Liver infections caused by nonhepatitis viruses (eg, Epstein-Barr virus, yellow fever virus, cytomegalovirus) generally are not termed acute viral hepatitis.

Etiology

At least 5 specific viruses appear to be responsible (see Table 28-2). Other unidentified viruses probably also cause acute viral hepatitis.

Hepatitis A virus (HAV): HAV is a single-stranded RNA picornavirus. It is the most common cause of acute viral hepatitis and is particularly common among children and young adults. In some countries, > 75% of adults have been exposed. HAV spreads primarily by fecal-oral contact and thus may occur in areas of poor hygiene. Waterborne and food-borne epidemics occur, especially in underdeveloped countries. Eating contaminated raw shellfish is sometimes responsible. Sporadic cases are also common, usually as a result of person-to-person contact. Fecal shedding of the virus occurs before symptoms develop and usually ceases a few days after symptoms begin; thus, infectivity often has already ceased when hepatitis becomes clinically evident. HAV has no known chronic carrier state and does not cause chronic hepatitis or cirrhosis.

Hepatitis B virus (HBV): HBV is the most thoroughly characterized and complex hepatitis virus. The infective particle consists of a viral core plus an outer surface coat. The core contains circular double-stranded DNA and DNA polymerase, and it replicates within the nuclei of infected hepatocytes. A surface coat is added in the cytoplasm and, for unknown reasons, is produced in great excess.

HBV is the 2nd most common cause of acute viral hepatitis. Prior unrecognized infection is common but is

much less widespread than that with HAV. HBV is often transmitted parenterally, typically by contaminated blood or blood products. Routine screening of donor blood for hepatitis B surface antigen (HBsAg) has nearly eliminated the previously common posttransfusion transmission, but transmission through needles shared by drug users remains common. Risk of HBV is increased for patients in renal dialysis and oncology units and for hospital personnel in contact with blood. The virus may be spread through contact with other body fluids (eg, between sex partners, both heterosexual and homosexual; in closed institutions, such as mental health institutions and prisons), but infectivity is far lower than that of HAV, and the means of transmission is often unknown. The role of insect bites in transmission is unclear. Many cases of acute hepatitis B occur sporadically without a known source.

HBV, for unknown reasons, is sometimes associated with several primarily extrahepatic disorders, including polyarteritis nodosa, other connective tissue diseases, membranous glomerulonephritis, and essential mixed cryoglobulinemia. The pathogenic role of HBV in these disorders is unclear, but autoimmune mechanisms are suggested.

Chronic HBV carriers provide a worldwide reservoir of infection. Prevalence varies widely according to several factors, including geography (eg, < 0.5% in North America and northern Europe, > 10% in some regions of the Far East). Vertical transmission from mother to infant is common (see p. 2644).

[**Table 28-1.** Selected Diseases or Organisms Associated with Liver Inflammation]

Hepatitis C virus (HCV): HCV is a single-stranded RNA flavivirus. Six major HCV subtypes exist with varying amino acid sequences (genotypes); these subtypes vary geographically and in virulence and response to therapy. HCV can also alter its amino acid pattern over time in an infected person, producing quasispecies.

Infection is most commonly transmitted through blood, primarily when parenteral drug users share needles, but also through tattoos or body piercing. Sexual transmission and vertical transmission from mother to infant are relatively rare. Transmission through blood transfusion has become very rare since the advent of screening tests for donated blood. Some sporadic cases occur in patients without apparent risk factors. HCV prevalence varies with geography and other risk factors.

HCV infection sometimes occurs simultaneously with specific systemic disorders, including essential mixed cryoglobulinemia, porphyria cutanea tarda (about 60 to 80% of porphyria patients have HCV infection, but only a few patients infected with HCV develop porphyria), and glomerulonephritis; the mechanisms are uncertain. In addition, up to 20% of patients with alcoholic liver disease harbor HCV. The reasons for this high association are unclear because concomitant alcohol and drug use accounts for only a portion of cases. In these patients, HCV and alcohol act synergistically to exacerbate liver damage.

Hepatitis D virus (HDV): HDV, or delta agent, is a defective RNA virus that can replicate only in the presence of HBV. It occurs uncommonly as a co-infection with acute hepatitis B or as a superinfection in chronic hepatitis B. Infected hepatocytes contain delta particles coated with HBsAg. Prevalence of HDV varies widely geographically, with endemic pockets in several countries. Parenteral drug users are at relatively high risk, but HDV (unlike HBV) has not widely permeated the homosexual community.

Hepatitis E virus (HEV): HEV is an enterically transmitted RNA virus. Outbreaks of acute HEV infection, often waterborne and linked to fecal contamination of the water supply, have occurred in China, India, Mexico, Pakistan, Peru, Russia, and central and northern Africa. These outbreaks have epidemiologic characteristics similar to HAV epidemics. Sporadic cases also occur. No outbreaks have occurred in the US or in Western Europe. Like HAV, HEV does not cause chronic hepatitis or cirrhosis, and there is no chronic carrier state.

Symptoms and Signs

General: Acute infection tends to develop in predictable phases. Infection begins with an incubation period (see Table 28-2), during which the virus multiplies and spreads without symptoms. The prodromal, or pre-icteric, phase follows, causing nonspecific symptoms, such as profound anorexia, malaise, nausea and vomiting, and often fever or right upper quadrant abdominal pain. Urticaria and arthralgias

occasionally occur, especially in HBV infection. After 3 to 10 days, the urine darkens, followed by jaundice (the icteric phase). Systemic symptoms often regress, and the patient feels better despite worsening jaundice. During the icteric phase, the liver is usually enlarged and tender, but the edge of the liver remains soft and smooth. Mild splenomegaly occurs in 15 to 20% of patients. Jaundice usually peaks within 1 to 2 wk and then fades during a 2- to 4-wk recovery phase. Appetite usually returns after the first week. Acute viral hepatitis usually resolves spontaneously 4 to 8 wk after symptom onset.

Sometimes anicteric hepatitis, a minor flulike illness without jaundice, is the only manifestation. It occurs more often than icteric hepatitis in patients with HCV infection and in children with HAV infection.

Recrudescent hepatitis occurs in a few patients and is characterized by recurrent manifestations during the recovery phase. Manifestations of cholestasis may develop during the icteric phase (called cholestatic hepatitis) but usually resolve. When they persist, they cause prolonged jaundice, elevated alkaline phosphatase, and pruritus, despite general regression of inflammation.

Virus-specific: HAV often does not cause jaundice and may not cause any symptoms. It almost invariably resolves after the acute infection, although there can be early recrudescence.

HBV causes a wide spectrum of liver diseases, from a subclinical carrier state to severe or fulminant acute hepatitis, particularly in the elderly, in whom mortality can reach 10 to 15%. Five to 10% of all patients with HBV develop chronic hepatitis or become inactive carriers. Cirrhosis can develop. Hepatocellular carcinoma can ultimately develop in chronic HBV infection, even without being preceded by cirrhosis.

HCV may be asymptomatic during the acute infection. Its severity often fluctuates, sometimes with recrudescent hepatitis and

[**Table 28-2.** Characteristics of Hepatitis Viruses]

roller-coaster aminotransferase levels for many years or even decades. HCV has the highest rate of chronicity (about 75%). The resultant chronic hepatitis is usually asymptomatic or benign but progresses to cirrhosis in 20 to 30% of patients; cirrhosis often takes decades to appear. Hepatocellular carcinoma can result from HCV-induced cirrhosis but results only rarely from chronic infection without cirrhosis (unlike in HBV infection).

Acute HDV infection typically manifests as unusually severe acute HBV infection (co-infection), an acute exacerbation in chronic HBV carriers (superinfection), or a relatively aggressive course of chronic HBV infection.

HEV may be severe, especially in pregnant women.

Diagnosis

- Liver function tests (AST and ALT elevated out of proportion to alkaline phosphatase, usually with hyperbilirubinemia)

- Viral serologic testing

- PT measurement

Initial diagnosis: Acute hepatitis must first be differentiated from other disorders that cause similar symptoms. In the prodromal phase, hepatitis mimics various nonspecific viral illnesses and is difficult to diagnose. Anicteric patients suspected of having hepatitis based on risk factors are tested initially with nonspecific liver function tests, including aminotransferases, bilirubin, and alkaline phosphatase. Usually, acute hepatitis is suspected only during the icteric phase. Thus, acute hepatitis should be differentiated from other disorders causing jaundice (see
Fig. 28-1 and p. 212).

Acute hepatitis can usually be differentiated from other causes of jaundice by its marked elevations of AST and ALT (typically ≥ 400 IU/L). ALT is typically higher than AST, but absolute levels correlate poorly with clinical severity. Values increase early in the prodromal phase, peak before jaundice is maximal, and fall slowly during the recovery phase. Urinary bilirubin usually precedes jaundice. Hyperbilirubinemia in acute viral hepatitis varies in severity, and fractionation has no clinical value. Alkaline phosphatase is usually only moderately elevated; marked elevation suggests extrahepatic cholestasis and prompts imaging tests (eg, ultrasonography). Liver biopsy generally is not needed unless the diagnosis is uncertain. If laboratory results suggest acute hepatitis, particularly if ALT and AST are > 1000 IU/L, PT is measured. Manifestations of portal-systemic encephalopathy, bleeding diathesis, or prolongation of INR suggest fulminant hepatitis (see p. 254).

If acute hepatitis is suspected, efforts are next directed toward identifying its cause. A history of exposure may provide the only clue of drug-induced or toxic hepatitis. The history should also elicit risk factors for viral hepatitis. Prodromal sore throat and diffuse adenopathy suggest infectious mononucleosis rather than viral hepatitis. Alcoholic hepatitis is suggested by a history of drinking, more gradual onset of symptoms, and presence of vascular spiders or signs of chronic alcohol use or chronic liver disease (see also p. 235); aminotransferase levels rarely exceed 300 IU/L, even in severe cases. Also, unlike in viral hepatitis, AST is typically higher than ALT, although this difference by itself does not reliably differentiate the two. In uncertain cases, liver biopsy usually distinguishes alcoholic from viral hepatitis.

Serology: In patients with findings suggesting acute viral hepatitis, the following studies are done to screen for hepatitis viruses A, B, and C:

• IgM antibody to HAV (IgM anti-HAV)

• HBsAg

• IgM antibody to hepatitis B core (IgM anti-HBc)

• Antibody to HCV (anti-HCV)

If any are positive, further serologic testing may be necessary to differentiate acute from past or chronic infection (see Tables 28-3, 28-4, and 28-5). If serology suggests hepatitis B, testing for hepatitis B e antigen (HBeAg) and antibody to hepatitis B e antigen (anti-HBe) is usually done to help determine the prognosis and to guide antiviral therapy. If serologically confirmed HBV is severe, anti-HDV is measured. If the patient has recently traveled to an endemic area, IgM anti-HEV should be measured if the test is available.

HAV is present in serum only during acute infection and cannot be detected by clinically available tests. IgM antibody typically develops early in the infection and peaks about 1 to 2 wk after the development of jaundice. It diminishes within several weeks, followed by the development of protective IgG antibody (IgG anti-HAV), which persists usually for life. Thus, IgM antibody is a marker of acute infection, whereas IgG anti-HAV indicates only previous exposure to HAV and immunity to recurrent infection.

HBV has at least 3 distinct antigen-antibody systems that can be tested: HBsAg, hepatitis B core antigen (HBcAg), and HBeAg. HBV-DNA can also be tested. HBV surface coat can be detected in serum as HBsAg. HBsAg characteristically appears during the incubation period, usually 1 to 6 wk before clinical or biochemical

[**Fig. 28-1.** Simplified diagnostic approach to possible acute viral hepatitis.]

illness develops, and implies infectivity of the blood. It disappears during convalescence. However, HBsAg is occasionally transient. The corresponding protective antibody (anti-HBs) appears weeks or months later, after clinical recovery, and usually persists for life; thus, its detection indicates past HBV infection and relative immunity. In 5 to 10% of patients, HBsAg persists and antibodies do not develop; these patients become asymptomatic carriers of the virus or develop chronic hepatitis.

HBcAg reflects the viral core. It is detectable in infected liver cells but not in serum except by special techniques. Antibody to HBcAg (anti-HBc) generally appears at the onset of clinical illness; thereafter, titers gradually diminish, usually over years or life. Its presence with anti-HBs indicates recovery from previous HBV infection. Anti-HBc is also present in chronic HBsAg carriers, who do not mount an anti-HBs response. In acute infection, anti-HBc is mainly of the IgM class, whereas in chronic infection, IgG anti-HBc predominates. IgM anti-HBc is a sensitive marker of acute HBV infection and occasionally is the only marker of recent infection, reflecting a window between disappearance of HBsAg and appearance of anti-HBs.

HBeAg is a protein derived from the viral core (not to be confused with hepatitis E virus).

[Table 28-3. Hepatitis A Serology]

Present only in HBsAg-positive serum, HBeAg tends to suggest more active viral replication and greater infectivity. In contrast, presence of the corresponding antibody (anti-HBe) suggests lower infectivity. Thus, e antigen markers are more helpful in prognosis than in diagnosis. Chronic liver disease develops more often among patients with HBeAg and less often among patients with anti-HBe.

In patients with active HBV infection, HBV-DNA can be detected in the serum with special testing, although this testing is not routinely available.

In **HCV**, serum antibody to HCV (anti-HCV) almost always implies active infection; it is not protective. Anti-HCV usually appears within 2 wk of acute infection but is sometimes delayed; however, HCV-RNA is positive. In a small proportion of patients, anti-HCV merely reflects prior exposure with clearance of the virus rather than active infection. In such cases, ALT and AST levels are usually normal. In unclear cases, HCV-RNA is measured.

[Table 28-4. Hepatitis B Serology*]

[Table 28-5. Hepatitis C Serology]

In **HDV**, anti-HDV implies active infection. It may not be detectable until weeks after the acute illness.

In **HEV**, the test for IgM anti-HEV is not routinely available. In a patient with endemic exposure and compatible clinical findings, anti-HEV suggests acute HEV infection.

Biopsy: Biopsy is usually unnecessary but, if done, usually reveals similar histopathology regardless of the specific virus: patchy cell dropout, acidophilic hepatocellular necrosis, mononuclear inflammatory infiltrate, histologic evidence of regeneration, and preservation of the reticulin framework. HBV can occasionally be diagnosed based on the presence of ground-glass hepatocytes (caused by HBsAg-packed cytoplasm) and using special immunologic stains for the viral components. However, these findings are unusual in acute HBV and are much more common in chronic HBV infection. HCV causation can sometimes be inferred from subtle morphologic clues. Liver biopsy may help predict prognosis in acute hepatitis but is rarely done solely for this purpose. Complete histologic recovery occurs unless extensive necrosis bridges entire acini (bridging necrosis). Most patients with bridging necrosis recover fully. However, some cases progress to chronic hepatitis.

Treatment

• Supportive care

• Occasionally postexposure prophylaxis

No treatments attenuate acute viral hepatitis except, occasionally, postexposure immunoprophylaxis. Alcohol should be avoided because it can increase liver damage. Restrictions on diet or activity, including commonly prescribed bed rest, have no scientific basis. Most patients may safely return to work after jaundice resolves, even if AST or ALT levels are slightly elevated. For cholestatic hepatitis,

cholestyramine 8 g po once/day or bid can relieve itching. Viral hepatitis should be reported to the local or state health department.

Prevention

Because treatments have limited efficacy, prevention of viral hepatitis is very important. Good personal hygiene helps prevent transmission, particularly fecal-oral transmission, as occurs with HAV and HEV. Blood and other body fluids (eg, saliva, semen) of patients with acute HBV and HCV and stool of patients with HAV are considered infectious. Barrier protection is recommended, but isolation of patients does little to prevent spread of HAV and is of no value in HBV or HCV infection. Posttransfusion infection is minimized by avoiding unnecessary transfusions and screening all donors for HBsAg and anti-HCV. Screening has decreased the incidence of posttransfusion hepatitis, probably to about 1/100,000 units of blood component transfused.

Immunoprophylaxis can involve active immunization using vaccines and passive immunization.

HAV: Preexposure HAV prophylaxis should be provided for travelers to highly endemic areas. It should also be considered for military personnel, day-care center employees, diagnostic laboratory workers, and, because they have an increased risk of fulminant hepatitis from HAV, patients with chronic liver disorders (including chronic hepatitis C). Several vaccines against HAV are available, each with different doses and schedules; they are safe, provide protection within about 4 wk, and provide prolonged protection (probably for > 20 yr).

Standard immune globulin, formerly immune serum globulin, prevents or decreases the severity of HAV infection and should be given to family members and close contacts of patients for postexposure prophylaxis; 0.02 mL/kg IM is generally recommended, but some experts advise 0.06 mL/kg (3 to 5 mL for adults).

HBV: Vaccination in endemic areas has dramatically reduced local prevalence. Pre-exposure immunization has long been recommended for people at high risk. However, selective vaccination of high-risk groups in the US and other nonendemic areas has not substantially decreased the incidence of HBV; thus, vaccination is now recommended for all US residents < 18 beginning at birth. Universal worldwide vaccination is desirable but is too expensive to be feasible.

Two recombinant vaccines are available; both are safe, even during pregnancy. Three IM deltoid injections are given: at baseline, at 1 mo, and at 6 mo. Children are given lower doses, and immunosuppressed patients and patients receiving hemodialysis are given higher doses.

After vaccination, levels of anti-HBs remain protective for 5 yr in 80 to 90% of immunocompetent recipients and for 10 yr in 60 to 80%. Booster doses of vaccine are recommended for patients receiving hemodialysis and immunosuppressed patients whose anti-HBs is < 10 mIU/mL.

HBV postexposure immunoprophylaxis combines vaccination with hepatitis B immune globulin (HBIG), a product with high titers of anti-HBs. HBIG probably does not prevent infection but prevents or attenuates clinical illness. For infants born to HBsAg-positive mothers, an initial dose of vaccine plus 0.5 mL of HBIG is given IM in the thigh immediately after birth. For anyone having sexual contact with an HBsAg-positive person or percutaneous or mucous membrane exposure to HBsAg-positive blood, 0.06 mL/kg of HBIG is given IM within days, along with vaccine. Any previously vaccinated patient sustaining a percutaneous HBsAg-positive exposure is tested for anti-HBs; if titers are < 10 mIU/mL, a booster dose of vaccine is given.

HCV, HDV, and HEV: A vaccine is now available for hepatitis E; it appears to have about 95% efficacy in preventing symptomatic infection in males and is safe. Efficacy in other groups, duration of protection, and efficacy in preventing asymptomatic infection are unknown. No product exists for immunoprophylaxis of HCV or HDV. However, prevention of HBV prevents HDV. The propensity of HCV for changing its genome hampers vaccine development.

Fulminant Hepatitis

Fulminant hepatitis is a rare syndrome of massive necrosis of liver parenchyma and a decrease in liver size (acute yellow atrophy) that usually occurs after infection with certain hepatitis viruses, exposure to toxic agents, or drug-induced injury.

HBV is sometimes responsible, and up to 50% of cases of fulminant hepatitis B involve HDV coinfection. Fulminant hepatitis with HAV is rare but may be more likely in people with preexisting liver disorders. The role of HCV remains uncertain.

Patients rapidly deteriorate because portal-systemic encephalopathy develops, often followed by coma within hours or a few days, sometimes with cerebral edema. Bleeding commonly results from hepatic failure or disseminated intravascular coagulation, and functional renal failure (hepatorenal syndrome —see p. 223) may develop. Increasing PT, portal-systemic encephalopathy, and particularly renal failure are ominous.

Meticulous nursing care and aggressive treatment of complications improve the outcome. However, emergency liver transplantation provides the best hope for survival. Survival in adults is uncommon without transplantation; children tend to do better. Patients who survive usually recover fully.

Chronic Hepatitis

Chronic hepatitis is hepatitis that lasts > 6 mo. Common causes include hepatitis B and C viruses, autoimmune mechanisms (autoimmune hepatitis), and drugs. Many patients have no history of acute hepatitis, and the first indication is discovery of asymptomatic aminotransferase elevations. Some patients present with cirrhosis or its complications (eg, portal hypertension). Biopsy is necessary to confirm the diagnosis and to grade and stage the disease. Treatment is directed toward complications and the underlying condition (eg, corticosteroids for autoimmune hepatitis, antiviral therapy for viral hepatitis). Liver transplantation is often indicated for end-stage disease.

Etiology

Hepatitis lasting > 6 mo is generally defined as chronic, although this duration is arbitrary. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequent causes of chronic hepatitis; 5 to 10% of cases of HBV infection, with or without hepatitis D virus (HDV) co-infection, and about 75% of cases of HCV infection become chronic. Hepatitis A and E viruses are not causes. Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient's immune reaction to the infection.

Many cases are idiopathic. A high proportion of idiopathic cases have prominent features of immune-mediated hepatocellular injury (autoimmune hepatitis), including the following:

- The presence of serologic immune markers
- An association with histocompatibility haplotypes common in autoimmune disorders (eg, HLA-B1, HLA-B8, HLA-DR3, HLA-DR4)
- A predominance of T lymphocytes and plasma cells in liver histologic lesions
- Complex in vitro defects in cellular immunity and immunoregulatory functions
- An association with other autoimmune disorders (eg, RA, autoimmune hemolytic anemia, proliferative glomerulonephritis)
- A response to therapy with corticosteroids or immunosuppressants

Sometimes chronic hepatitis has features of both autoimmune hepatitis and another chronic liver disorder (eg, primary biliary cirrhosis, chronic viral hepatitis). These conditions are called overlap syndromes.

Many drugs, including isoniazid, methyldopa, nitrofurantoin, and, rarely, acetaminophen, can cause chronic hepatitis. The mechanism varies with the drug and may involve altered immune responses, cytotoxic intermediate metabolites, or genetically determined metabolic defects.

Other causes of chronic hepatitis include alcoholic hepatitis and nonalcoholic steatohepatitis. Less often, chronic hepatitis results from α_1-antitrypsin deficiency or Wilson's disease.

Cases were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis. A more useful recent classification system specifies the etiology, the intensity of histologic inflammation and necrosis (grade), and the degree of histologic fibrosis (stage). Inflammation and necrosis are potentially reversible; fibrosis generally is not.

Symptoms and Signs

Clinical features vary widely. About one third of cases develop after acute hepatitis, but most develop insidiously de novo. Many patients are asymptomatic, especially in chronic HCV infection. However, malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort. Jaundice is usually absent. Often, particularly with HCV, the first findings are signs of chronic liver disease (eg, splenomegaly, spider nevi, palmar erythema). A few patients with chronic hepatitis develop manifestations of cholestasis. In the autoimmune variant, especially in young women, manifestations may involve virtually any body system and can include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia.

Chronic HCV is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, and perhaps non-Hodgkin B-cell lymphoma. About 1% of patients develop symptomatic cryoglobulinemia with fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and skin rashes (urticaria, purpura, or leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

Diagnosis

• Liver function test results compatible with hepatitis

• Viral serologic tests

• Possibly autoantibodies, immunoglobulins, α_1-antitrypsin level, and other tests

• Usually biopsy

• Serum albumin and PT

The diagnosis is suspected in patients with suggestive symptoms and signs, incidentally noted elevations in aminotransferase levels, or previously diagnosed acute hepatitis. Liver function tests are needed if not previously done and include serum ALT, AST, alkaline phosphatase, and bilirubin. Aminotransferase elevations are the most characteristic laboratory abnormalities. Although levels can vary, they are typically 100 to 500 IU/L. ALT is usually higher than AST. Amino-transferase levels can be normal during chronic hepatitis if the disease is quiescent, particularly with HCV. Alkaline phosphatase is usually normal or only slightly elevated but is occasionally markedly high. Bilirubin is usually normal unless the disease is severe or advanced. However, abnormalities in these laboratory tests are not specific and can result from other disorders, such as alcoholic liver disease, recrudescent acute viral hepatitis, and primary biliary cirrhosis.

If laboratory results are compatible with hepatitis, viral serologic tests are done to exclude HBV and HCV (see Tables 28-4 and 28-5). Unless these tests indicate viral etiology, further testing is required. The first tests done include autoantibodies, immunoglobulins, and α_1-antitrypsin level. Children and young adults are screened for Wilson's disease with a ceruloplasmin level. Marked elevations in serum immunoglobulins suggest chronic autoimmune hepatitis but are not conclusive. Autoimmune hepatitis is normally diagnosed based on the presence of antinuclear (ANA), anti-smooth muscle, or anti-liver/kidney

microsomal type 1 (anti-LKM1) antibodies at titers of 1:80 (in adults) or 1:20 (in children).

Unlike in acute hepatitis, biopsy is necessary. Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions, with normal acinar architecture and little or no fibrosis. Such cases rarely develop into clinically important liver disease or cirrhosis. In more severe cases, biopsy typically shows periportal necrosis with mononuclear cell infiltrates (piecemeal necrosis) accompanied by variable periportal fibrosis and bile duct proliferation. The acinar architecture may be distorted by zones of collapse and fibrosis, and frank cirrhosis sometimes coexists with signs of ongoing hepatitis. Biopsy is also used to grade and stage the disease.

In most cases, the specific cause of chronic hepatitis cannot be discerned via biopsy alone, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components. Autoimmune cases usually have a more pronounced infiltration by lymphocytes and plasma cells. In patients with histologic but not serologic criteria for chronic autoimmune hepatitis, variant autoimmune hepatitis is diagnosed; many have overlap syndromes.

Serum albumin and PT should be measured to determine severity; hepatic insufficiency is suggested by low serum albumin or prolonged PT. If symptoms or signs of cryoglobulinemia develop during chronic hepatitis, particularly with HCV, cryoglobulin levels and rheumatoid factor should be measured; high levels of rheumatoid factor and low levels of complement suggest cryoglobulinemia.

Patients with chronic HBV infection should be screened annually for hepatocellular cancer with ultrasonography and serum α-fetoprotein measurement, although the cost-effectiveness of this practice is debated. Patients with chronic HCV infection should be similarly screened only if cirrhosis is present.

Prognosis

Prognosis is highly variable. Chronic hepatitis caused by a drug often regresses completely when the offending drug is withdrawn. Without treatment, cases caused by HBV can resolve (uncommon), progress rapidly, or progress slowly to cirrhosis over decades. Resolution often begins with a transient increase in disease severity and results in seroconversion from hepatitis B e antigen (HBeAg) to antibody to hepatitis B e antigen (anti-HBe). Co-infection with HDV causes the most severe form of chronic HBV infection; without treatment, cirrhosis develops in up to 70% of patients. Untreated chronic hepatitis due to HCV produces cirrhosis in 20 to 30% of patients, although development may take decades. Chronic autoimmune hepatitis usually responds to therapy but sometimes causes progressive fibrosis and eventual cirrhosis.

Chronic HBV infection increases the risk of hepatocellular cancer. The risk is also increased in chronic HCV infection, but only if cirrhosis has already developed (see p. 265).

Treatment

• Supportive care

• Treatment of cause (eg, corticosteroids for autoimmune hepatitis, antivirals for HBV, interferons for HCV)

Treatment goals include management of complications (eg, ascites, encephalopathy) and treatment of the cause. Drugs that cause hepatitis should be stopped. Underlying disorders, such as Wilson's disease, should be treated. In chronic hepatitis due to HBV, prophylaxis for contacts of patients may be helpful (see p. 254); corticosteroids and immunosuppressive drugs should be avoided because they enhance viral replication. No prophylactic measures are required for contacts of patients with HCV infection.

Autoimmune hepatitis: Corticosteroids, with or without azathioprine, prolong survival. Prednisone is usually started at 30 to 40 mg po once/day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. Some experts give concomitant azathioprine 1 to 1.5 mg/kg po once/day; others add azathioprine only if low-dose prednisone fails to maintain suppression. Most patients require long-term, low-dose maintenance treatment. Liver transplantation may be required for end-stage disease.

HBV: Antiviral treatment is indicated for patients with elevated aminotransferase levels, clinical or biopsy evidence of progressive disease, or both. The goal is to eliminate HBV-DNA. Treatment may need to be continued indefinitely and thus may be very expensive; stopping treatment prematurely can lead to relapse, which may be severe. However, treatment may be stopped if HBeAg converts to anti-HBe or if tests for HBsAg become negative. Drug resistance is also a concern. Six antiviral drugs—entecavir, adefovir, lamivudine, interferon-α (INF-α), pegylated INF-α2a (peginterferon-α2a), and telbivudine—are available (see
Table 28-6).

First-line treatment is usually with an oral antiviral drug, such as entecavir (a nucleoside analogue) or adefovir (a nucleotide analogue). Combination therapy has not proved superior to monotherapy.

Entecavir appears to have higher antiviral potency than other commonly used drugs. Resistance to entecavir is uncommon, but the drug has not been in widespread clinical use for very long. Dosage is 0.5 mg po once/day; however, patients who have previously taken

[**Table 28-6.** Comparison of Drugs Commonly Used to Treat Chronic Viral Hepatitis B*]

a nucleoside analogue should take 1 mg po once/day. Dose reduction is required in patients with renal insufficiency. Serious adverse effects appear to be uncommon so far, although the drug can induce tumors in animals.

Adefovir is also relatively potent. Dosage is 10 mg po once/day. Adefovir may cause renal dysfunction, so serum creatinine level must be measured periodically and the dose reduced if necessary.

Alternatively, lamivudine (a nucleoside analogue) 100 mg po once/day is given. It has few adverse effects, which is one of its advantages over other antiviral drugs used to treat chronic HBV infection. INF-α (usually IFN-α2b), formerly first-line treatment, can be used. Dosage is 5 million IU sc once/day or 10 million IU sc 3 times/wk for 4 mo. In about 40% of patients, this regimen eliminates HBV-DNA and causes seroconversion to anti-HBe; a successful response is usually presaged by a temporary increase in aminotransferase levels. The drug must be given by injection and is often poorly tolerated. The first 1 or 2 doses cause an influenza-like syndrome. Later, fatigue, malaise, depression, bone marrow suppression, and, rarely, bacterial infections or autoimmune disorders can occur. In patients with advanced cirrhosis, IFN-α can precipitate hepatic failure and is therefore contraindicated. Other contraindications include renal failure, immunosuppression, solid organ transplantation, cytopenia, and substance abuse. In a few patients, treatment must be stopped because of intolerable adverse effects. The drug should be given cautiously or not at all to patients with ongoing substance abuse or a major psychiatric disorder.

Pegylated IFN-α2 can also be given. Dosage is 180 µg sc once/wk. Adverse effects are similar to those of INF-α but may be less severe.

Telbivudine is a new drug that has greater efficacy than lamivudine but has high rates of resistance.

Liver transplantation should be considered for end-stage liver disease caused by HBV, but the infection aggressively attacks the graft, and prognosis is less favorable than when liver transplantation is done for other indications. Long-term posttransplantation therapy with lamivudine improves the outcome.

HCV: For chronic hepatitis due to HCV, treatment is indicated if aminotransferase levels are elevated and biopsy shows active inflammatory disease with evolving fibrosis. Treatment aims to permanently eliminate HCV-RNA (sustained response), which is associated with permanent normalization of aminotransferase and cessation of histologic progression.

Combination therapy with pegylated IFN-α plus ribavirin has the best results. Pegylated IFN-α2b 1.5 µg/kg sc once/wk and pegylated IFN-α2a 180 µg sc once/wk have comparable results. Ribavirin 500 to 600 mg po bid is usually given, although 400 mg bid may be sufficient for viral genotypes 2 and 3.

HCV genotype and viral load are determined before treatment because results influence treatment.

Genotype 1 is the most common type but is relatively resistant to treatment. Combination therapy is given for 1 yr; a sustained response rate of about 45 to 50% overall occurs. Results are more favorable in patients with early disease and less favorable in those who already have cirrhosis. HCV viral load should be measured at 3 mo and treatment stopped if RNA has not declined by at least 2 log levels compared with pretreatment values.

Less common genotypes 2 and 3 respond more favorably. Combination therapy is required for only 6 mo and gives an overall sustained response rate of about 75%. Longer treatment does not improve the results.

Adverse effects of pegylated IFN are similar to those of IFN-α but may be less severe; contraindications are also similar (see above).

Ribavirin is usually well tolerated but commonly causes anemia due to hemolysis; dosage should be decreased if hemoglobin falls to < 10 g/dL. Ribavirin is teratogenic for both men and women, necessitating contraception until 6 mo after completion of treatment. Patients who cannot tolerate ribavirin should be given pegylated IFN-α, but results are not as good as with combination treatment. Ribavirin monotherapy is of no value.

In most adult transplantation centers, advanced cirrhosis due to HCV is now the most common indication for liver transplantation. Although HCV recurs in the graft, the course is usually indolent, and long-term survival rates are relatively high.

Chapter 29. Vascular Disorders of the Liver

Introduction

The liver has a dual blood supply. The portal vein (which is rich in nutrients and relatively high in O_2) provides two thirds of blood flow to the liver. The hepatic artery (which is O_2-rich) supplies the rest. The hepatic veins drain the liver into the inferior vena cava. When portal vein blood flow increases, hepatic artery flow decreases and vice versa (the hepatic arterial buffer response). This dual, reciprocally compensatory blood supply provides some protection from hepatic ischemia in healthy people.

Despite its dual blood supply, the liver, a metabolically active organ, can be injured by

- **Ischemia:** Ischemia results from reduced blood flow, reduced O_2 delivery, increased metabolic activity, or all three.

- **Insufficient venous drainage:** The cause may be focal or diffuse obstruction. Manifestations of focal venous obstruction depend on the location. Diffuse venous congestion causes congestive hepatopathy. Reduced venous outflow from the liver (originating in the hepatic veins or within the liver itself, usually from cirrhosis) results in portal hypertension.

- **Specific vascular lesions:** The hepatic artery, hepatic vein, or portal vein may be involved. In peliosis hepatis, the vascular lesion occurs in the sinusoids (microvascular anastomoses between the portal and hepatic veins).

Hepatic Ischemia

Diffuse ischemia can cause ischemic hepatitis; focal ischemia can cause hepatic infarction or ischemic cholangiopathy. Hepatic infarction results from hepatic artery disorders.

Ischemic Hepatitis

(Acute Hepatic Infarction; Hypoxic Hepatitis; Shock Liver)

Ischemic hepatitis is diffuse liver damage due to an inadequate blood or O_2 supply.

Causes are most often systemic:

- Impaired hepatic perfusion (eg, due to heart failure or acute hypotension)

- Hypoxemia (eg, due to respiratory failure or carbon monoxide toxicity)

- Increased metabolic demand (eg, due to sepsis)

Focal lesions of the hepatic vasculature are less common causes. Ischemic hepatitis may develop when hepatic artery thrombosis occurs during liver transplantation or when a sickle cell crisis is associated with portal vein thrombosis (thus compromising the dual blood supply to the liver). Centrizonal necrosis develops without liver inflammation (ie, not a true hepatitis).

Symptoms may include nausea, vomiting, and tender hepatomegaly.

Diagnosis

- Clinical evaluation and liver function tests

- Doppler ultrasonography, MRI, or arteriography

Ischemic hepatitis is suspected in patients who have risk factors and laboratory abnormalities:

• Serum aminotransferase increases dramatically (eg, to 1000 to 3000 IU/L).

• LDH increases within hours of ischemia (unlike acute viral hepatitis).

• Serum bilirubin increases modestly, only to ≤ 4 times its normal level.

• PT/INR increases.

Diagnostic imaging helps define the cause: Doppler ultrasonography, MRI, or arteriography can identify an obstructed hepatic artery or portal vein thrombosis.

Treatment

• Hepatic reperfusion

Treatment is directed at the cause, aiming to restore hepatic perfusion, particularly by improving cardiac output and reversing any hemodynamic instability.

If perfusion is restored, aminotransferase decreases over 1 to 2 wk. In most cases, liver function is fully restored. Fulminant liver failure, although uncommon, can occur in patients with preexisting cirrhosis.

Ischemic Cholangiopathy

Ischemic cholangiopathy is focal damage to the biliary tree due to disrupted flow from the hepatic artery via the peribiliary arterial plexus.

Common causes of ischemic cholangiopathy include vascular injury during orthotopic liver transplantation or laparoscopic cholecystectomy, graft-rejection injury, chemoembolization, radiation therapy, and thrombosis resulting from hypercoagulability disorders. Bile duct injury (ischemic necrosis) results, causing cholestasis, cholangitis, or biliary strictures (often multiple).

Symptoms (eg, pruritus, dark urine, pale stools), laboratory tests, and imaging studies indicate cholestasis.

The diagnosis is suspected when cholestasis is evident in patients at risk, particularly after liver transplantation. Ultrasonography is the 1st-line diagnostic imaging test for cholestasis, but most patients require magnetic resonance cholangiopancreatography, ERCP, or both to rule out other causes such as cholelithiasis or cholangiocarcinoma.

Treatment is directed at the cause. After liver transplantation, such treatment includes antirejection therapy and possible retransplantation. Biliary strictures warrant endoscopic balloon dilation and stenting.

Congestive Hepatopathy

(Passive Hepatic Congestion)

Congestive hepatopathy is diffuse venous congestion within the liver that results from right-sided heart failure (usually due to a cardiomyopathy, tricuspid regurgitation, mitral insufficiency, cor pulmonale, or constrictive pericarditis).

Moderate or severe right-sided heart failure increases central venous pressure, which is transmitted to the liver via the inferior vena cava and hepatic veins. Chronic congestion leads to atrophy of hepatocytes, distention of sinusoids, and centrizonal fibrosis, which, if severe, progresses to cirrhosis (cardiac cirrhosis). The basis for liver cell death is probably sinusoidal thrombosis that propagates to the central veins and branches of the portal vein, causing ischemia.

Most patients are asymptomatic. However, moderate congestion causes right upper quadrant discomfort

(due to stretching of the liver capsule) and tender hepatomegaly. Severe congestion leads to massive hepatomegaly and jaundice. Ascites may result from the transmitted central venous hypertension; infrequently, splenomegaly results. With transmitted central venous hypertension, the hepatojugular reflex is present, unlike in hepatic congestion due to Budd-Chiari syndrome.

Diagnosis

• Clinical evaluation

Congestive hepatopathy is suspected in patients who have right-sided heart failure, jaundice, and tender hepatomegaly. Liver biochemistries are modestly abnormal: unconjugated hyperbilirubinemia (total bilirubin < 3 mg/dL), elevated (usually < 2 to 3 fold) aminotransferases, and prolonged PT/INR. Any ascitic fluid has a high albumin content (> 25 g/L) and serum ascites/albumin gradient. (≥ 1.1). Because the laboratory abnormalities are nonspecific, recognition of congestive hepatopathy is ultimately clinical. The liver disorder is more important as an index of the severity of heart failure than as a diagnosis by itself.

Treatment

Treatment is directed at the underlying heart failure.

Hepatic Artery Disorders

The hepatic artery may be occluded. Uncommonly, aneurysms develop.

Hepatic Artery Occlusion

Causes of hepatic artery occlusion include thrombosis (eg, due to hypercoagulability disorders, severe arteriosclerosis, or vasculitis), emboli (eg, due to endocarditis, tumors, therapeutic embolization, or chemoembolization), iatrogenic causes (eg, ligation during surgery), vasculitis (via nonthrombotic mechanisms), structural arterial abnormalities (eg, hepatic artery aneurysm), eclampsia, cocaine use, and sickle cell crisis. Usually, the result is an hepatic infarct. In patients with a liver transplant or preexisting portal vein thrombosis, hepatic artery thrombosis causes ischemic hepatitis (see p. 259). Because of the liver's dual blood supply, the liver is somewhat resistant to ischemic hepatitis and infarction.

Hepatic artery occlusion does not elicit symptoms without hepatic infarction or ischemic hepatitis. Hepatic infarction may be asymptomatic or cause right upper quadrant pain, fever, nausea, vomiting, and jaundice. Leukocytosis and a high aminotransferase level are common.

Diagnosis

• Vascular imaging

Diagnosis of hepatic artery occlusion is confirmed by imaging with Doppler ultrasonography, usually followed by angiography. The choice between CT angiography, magnetic resonance angiography, and celiac arteriography largely depends on availability and expertise. CT may detect a wedge-shaped area of low attenuation.

Treatment

Treatment is directed at the cause.

Aneurysms

Aneurysms of the hepatic artery are uncommon. They tend to be saccular and multiple. Causes include infection, arteriosclerosis, trauma, and vasculitis. Untreated aneurysms may cause death by rupturing into the common bile duct (causing hemobilia), peritoneum (causing peritonitis), or adjacent hollow viscera. Hemobilia may cause jaundice, upper GI bleeding, and abdominal pain in the right upper quadrant.

Diagnosis is suspected if typical symptoms occur or if imaging tests detect an aneurysm. Doppler ultrasonography, followed by contrast CT, is required for confirmation.

Treatment is embolization or surgical ligation.

Hepatic Vein Disorders

Obstruction of hepatic venous outflow can occur in extrahepatic vessels (Budd-Chiari syndrome) or intrahepatic vessels (veno-occlusive disease) but often occurs in both. Obstruction results in congestion of the sinusoids, hepatomegaly, portal hypertension, reduced portal blood flow, ascites, and splenomegaly.

Budd-Chiari Syndrome

Budd-Chiari syndrome is obstruction of hepatic venous outflow that originates anywhere from the small hepatic veins inside the liver to the inferior vena cava and right atrium. Manifestations range from no symptoms to fulminant liver failure. Diagnosis is based on ultrasonography. Treatment includes supportive medical therapy and measures to establish and maintain venous patency, such as thrombolysis, decompression with shunts, and long-term anticoagulation.

Etiology

In the Western world, the most common cause is a clot obstructing the hepatic veins and the adjacent inferior vena cava. Clots commonly result from the following:

- Thrombotic conditions (eg, protein C or S deficiency, antiphospholipid syndrome, antithrombin III deficiency, factor V Leiden mutation, pregnancy, oral contraceptive use)
- Hematologic disorders (eg, myeloproliferative disorders such as polycythemia and paroxysmal nocturnal hemoglobinopathy)
- Inflammatory bowel disease
- Connective tissue disorders
- Trauma
- Infection (eg, hydatid cyst, amebiasis)
- Tumor invasion of the hepatic vein (eg, hepatocellular or renal cell carcinoma)

Sometimes Budd-Chiari syndrome begins during pregnancy and unmasks a previously asymptomatic hypercoagulability disorder.

The cause of obstruction is often unknown. In Asia and South Africa, the basic defect is often a membranous obstruction (webs) of the inferior vena cava above the liver, likely representing recanalization of a prior thrombus in adults or a developmental flaw (eg, venous stenosis) in children. This type of obstruction is called obliterative hepatocavopathy.

Budd-Chiari syndrome usually develops over weeks or months. When it does, cirrhosis and portal hypertension tend to develop.

Symptoms and Signs

Manifestations range from none (asymptomatic) to fulminant liver failure or cirrhosis. Symptoms vary depending on whether the obstruction occurs acutely or over time.

Acute obstruction (in about 20%) causes fatigue, right upper quadrant pain, nausea, vomiting, mild

jaundice, tender hepatomegaly, and ascites. It typically occurs during pregnancy. Fulminant liver failure with encephalopathy is rare. Aminotransferase levels are quite high

Chronic outflow obstruction (developing over weeks to months) may be rather asymptomatic in some patients until it progresses or may cause fatigue, abdominal pain, and hepatomegaly. Lower-extremity edema and ascites may result from venous obstruction, even in the absence of cirrhosis. Cirrhosis may develop, leading to variceal bleeding, massive ascites, splenomegaly, hepatopulmonary syndrome (see p. 1988), or a combination. Complete obstruction of the inferior vena cava causes edema of the abdominal wall and legs plus visibly tortuous superficial abdominal veins from the pelvis to the costal margin.

Diagnosis

• Clinical evaluation and liver function tests

• Vascular imaging

Budd-Chiari syndrome is suspected in patients with

• Hepatomegaly, ascites, liver failure, or cirrhosis when there is no obvious cause (eg, alcohol abuse, hepatitis) or when the cause is unexplained

• Abnormal liver function test results and risk factors for thrombosis

Liver function tests are usually abnormal; the pattern is variable and nonspecific. Imaging usually begins with abdominal Doppler ultrasonography, which can show the direction of blood flow and the site of obstruction. Magnetic resonance angiography and CT are useful if ultrasonography is not diagnostic. Conventional angiography (venography with pressure measurements and arteriography) is necessary if therapeutic or surgical intervention is planned. Liver biopsy is done occasionally to diagnose the acute stages and determine whether cirrhosis has developed.

Prognosis

Without treatment, most patients with complete venous obstruction die of liver failure within 3 yr. For patients with incomplete obstruction, the course varies.

Treatment

• Supportive care

• Restoration and maintenance of adequate venous outflow

Treatment varies according to its onset (acute vs chronic) and severity (fulminant liver failure vs decompensated cirrhosis vs stable or asymptomatic). The cornerstones of management are

• Giving supportive therapy directed at complications (eg, ascites, liver failure, esophageal varices)

• Decompressing the congested liver (ie, maintaining venous outflow)

• Preventing propagation of the clot

Aggressive interventions (eg, thrombolysis, stents) are used when the disease is acute (eg, within 4 wk and in the absence of cirrhosis). Thrombolysis can dissolve acute clots, allowing recanalization and so relieving hepatic congestion. Radiologic procedures have a major role using angioplasty, stenting, and portosytemic shunts. For caval webs or hepatic venous stenosis, decompression via percutaneous transluminal balloon angioplasty with intraluminal stents can maintain hepatic outflow. When dilation of a hepatic outflow narrowing is not technically feasible, transjugular intrahepatic portosystemic shunting (TIPS) and various surgical shunts can provide decompression by diversion into the systemic circulation. Portosystemic shunts are generally not used if hepatic encephalopathy is present; such shunts worsen

liver function. Further, shunts tend to thrombose, especially when associated with hematologic disorders.

Long-term anticoagulation is often necessary to prevent recurrence. Liver transplantation may be lifesaving in patients with fulminant disease or decompensated cirrhosis.

Veno-Occlusive Disease

(Sinusoidal Obstruction Syndrome)

Hepatic veno-occlusive disease is caused by endothelial injury, leading to nonthrombotic occlusion of the terminal hepatic venules and hepatic sinusoids, rather than of the hepatic veins or inferior vena cava (as in Budd-Chiari syndrome).

Venous congestion causes portal hypertension and ischemic necrosis (which leads to cirrhosis).

Common causes include

• Irradiation

• Graft-vs-host disease resulting from bone marrow or hematopoietic cell transplantation

• Pyrrolizidine alkaloids in crotalaria and senecio plants (eg, medicinal bush teas) and other herbs (eg, comfrey)

• Other hepatotoxins (eg, dimethylnitrosamine, aflatoxin, azathioprine, some anticancer drugs)

Initial manifestations include sudden jaundice, ascites, and tender, smooth hepatomegaly. Onset is within the first 3 wk of transplantation in bone marrow or hematopoietic cell recipients, who either recover spontaneously within a few weeks (or sometimes, with mild cases, after an increase in immunosuppressant therapy) or die of fulminant liver failure. Other patients have recurrent ascites, portal hypertension, splenomegaly, and, eventually, cirrhosis.

Diagnosis

• Clinical evaluation and liver function tests

• Ultrasonography

• Sometimes invasive tests (eg, liver biopsy, measurement of portal-hepatic venous pressure gradient)

The diagnosis is suspected in patients with unexplained clinical or laboratory evidence of liver disease, particularly in those with known risk factors, such as bone marrow or hematopoietic cell transplantation. Laboratory results are nonspecific: elevated aminotransferase and conjugated bilirubin levels. PT/INR becomes abnormal when disease is severe. Ultrasonography shows retrograde flow in the portal vein. If the diagnosis is unclear, invasive tests become necessary—eg, liver biopsy or measurement of the portal-hepatic venous pressure gradient (a pressure gradient > 10 mm Hg suggests veno-occlusive disease). Measuring the pressure across the liver entails inserting a catheter percutaneously into a hepatic vein and then wedging it into the liver. This wedged pressure reflects portal vein pressure. (An exception is portal vein thrombosis; in this case, the pressure is normal despite portal hypertension.)

Treatment

• Supportive care

• Treatment of cause

• For progressive disease, transjugular intrahepatic portosystemic shunting or transplantation

Ursodeoxycholic acid helps prevent graft-vs-host disease in bone marrow or hematopoietic cell transplant recipients. Management includes withdrawing the causative agent (such as herbal teas) and providing supportive therapy. Most patients have mild to moderate disease and do quite well. Those that progress may require transjugular intrahepatic portosystemic shunting (TIPS) for relief of portal hypertension. However, in 25%, veno-occlusive disease is severe, accompanied by fulminant liver failure. Liver transplantation is a last resort.

Portal Vein Disorders

Nearly all portal vein disorders obstruct portal vein blood flow and cause portal hypertension (see p. 218). Obstruction can be

- Extrahepatic—portal vein thrombosis due to a hypercoagulable state, vessel wall lesion (eg, pylephlebitis, omphalitis), an adjacent lesion (eg, pancreatitis, tumor), or congenital atresia of the portal vein

- Intrahepatic (eg, microvascular portal vein obstruction as in schistosomiasis, primary biliary cirrhosis, sarcoidosis, noncirrhotic portal hypertension)

Portal Vein Thrombosis

Portal vein thrombosis causes portal hypertension and consequent GI bleeding from varices, usually in the lower esophagus or stomach. Diagnosis is based on ultrasonography. Treatment involves control of variceal bleeding (usually with endoscopic banding, IV octreotide, or both), prevention of recurrence using β-blockers and sometimes surgical shunts and thrombolysis for acute thrombosis.

Etiology

Common causes vary by age group (see Table 29-1).

Symptoms and Signs

Acute portal vein thrombosis is commonly asymptomatic unless associated with another event, such as pancreatitis (the cause), or another complication, such as mesenteric venous thrombosis. Most often, clinical features—splenomegaly (especially in children) and variceal hemorrhage—develop chronically secondary to portal hypertension. Ascites is uncommon (10%) in postsinusoidal portal hypertension. Ascites may be precipitated when cirrhosis is also present or when serum albumin (and thus oncotic pressure) deceases after high-volume fluid resuscitation for a major GI bleed.

Diagnosis

- Clinical evaluation and liver function tests

- Doppler ultrasonography

Portal vein thrombosis is suspected in patients with the following:

- Manifestations of portal hypertension without cirrhosis

- Mild abnormalities in liver function or enzymes plus risk factors such as neonatal umbilical infection, childhood appendicitis, or a hypercoagulability disorder

Doppler ultrasonography is usually diagnostic, showing diminished or absent portal vein flow and sometimes the thrombus. Difficult cases may require MRI or CT with contrast. Angiography may be required to guide shunt surgery.

[Table 29-1. Common Causes of Portal Vein Thrombosis*]

Treatment

• For some acute cases, thrombolysis

• Long-term anticoagulation

• Management of portal hypertension and its complications

In acute cases, thrombolysis is sometimes successful, best reserved for recent occlusion, particularly in hypercoagulable states. Anticoagulation does not lyse clots but has some value for long-term prevention in hypercoagulable states despite the risk of variceal bleeding. In neonates and children, treatment is directed at the cause (eg, omphalitis, appendicitis). Otherwise, management is directed at the portal hypertension and its complications (see p. 218); treatment can include octreotide IV (a synthetic analog of somatostatin) and endoscopic banding to control variceal bleeding and nonselective β-blockers to prevent rebleeding. These therapies have decreased the use of surgical shunts (eg, mesocaval, splenorenal), which can become occluded and have an operative mortality rate of 5 to 50%. Transjugular intrahepatic portosytemic shunting (TIPS) is not recommended. TIPS requires monitoring (including frequent angiography) to assess patency, may become blocked, and may not adequately decompress the liver.

Peliosis Hepatis

Peliosis hepatis is typically an asymptomatic disorder in which multiple blood-filled cystic spaces develop randomly in the liver.

Measuring a few millimeters to about 3 cm in diameter, the cysts of peliosis hepatis often lack a cell lining and are surrounded by hepatocytes. Some have an endothelial cell lining, accompanied by dilated hepatic sinusoids. The cause is probably damage to the sinusoidal lining cells. Peliosis hepatis is associated with use of hormones (eg, anabolic steroids, oral contraceptives, glucocorticoids), tamoxifen, vinyl chloride, vitamin A, and, particularly in kidney transplant recipients, azathioprine.

Peliosis hepatis is usually asymptomatic, but occasionally cysts rupture, resulting in hemorrhage and sometimes causing death. Some patients develop overt liver disease, characterized by jaundice, hepatomegaly, and liver failure.

Mild cases may be detected incidentally during imaging tests done because liver function test results are slightly abnormal or for other reasons. Ultrasonography or CT can detect cysts.

Chapter 30. Liver Masses and Granulomas

Introduction

Liver masses include cysts, benign tumors, primary liver cancers, and metastatic liver cancer. Certain drugs and disorders can result in granuloma formation in the liver.

Hepatic Cysts

Isolated cysts are commonly detected incidentally on abdominal ultrasonography or CT. These cysts are usually asymptomatic and have no clinical significance. The rare congenital polycystic liver is commonly associated with polycystic disease of the kidneys (see p. 2385) and other organs. It causes progressive nodular hepatomegaly (sometimes massive) in adults. Nevertheless, hepatocellular function is remarkably well preserved, and portal hypertension rarely develops.

Other hepatic cysts include the following:

- Hydatid (echinococcal) cysts (see p. 1362)
- Caroli's disease, which is rare, autosomal recessive, and characterized by segmental cystic dilation of intrahepatic bile ducts (often becoming symptomatic in adulthood, with stone formation, cholangitis, and sometimes cholangiocarcinoma)
- True cystic tumors (rare)

Benign Liver Tumors

Benign liver tumors are relatively common. Most are asymptomatic, but some cause hepatomegaly, right upper quadrant discomfort, or intraperitoneal hemorrhage. Most are detected incidentally on ultrasound or other scans. Liver function tests are usually normal or only slightly abnormal. Diagnosis is usually possible with imaging tests but may require biopsy. Treatment is needed only in a few specific circumstances.

Hepatocellular adenoma: Hepatocellular adenoma is the most important benign tumor to recognize. It occurs primarily in women of childbearing age, particularly those taking oral contraceptives, possibly via estrogen's effects. Most adenomas are asymptomatic, but large ones may cause right upper quadrant discomfort. Rarely, adenomas manifest as peritonitis and shock due to rupture and intraperitoneal hemorrhage. Rarely, they become malignant.

Diagnosis is often suspected based on ultrasound or CT results, but biopsy is sometimes needed for confirmation.

Adenomas due to contraceptive use often regress if the contraceptive is stopped. If the adenoma does not regress or if it is subcapsular or > 5 cm, surgical resection is often recommended.

Focal nodular hyperplasia: This localized hamartoma may resemble macronodular cirrhosis histologically. Diagnosis is usually based on MRI or CT with contrast, but biopsy may be necessary. Treatment is rarely needed.

Hemangiomas: Hemangiomas are usually small and asymptomatic; they occur in 1 to 5% of adults. These tumors often have a characteristic highly vascular appearance. Rupture is rare, even when tumors are large. Hemangiomas are found incidentally during ultrasonography, CT, or MRI. Treatment is usually not indicated.

In infants, hemangiomas often regress spontaneously by age 2 yr. However, large hemangiomas occasionally cause arteriovenous shunting sufficient to cause heart failure and sometimes consumption coagulopathy. In these cases, treatment may include high-dose corticosteroids, sometimes diuretics and digoxin to improve heart function, interferon-α (given sc), surgical removal, selective hepatic artery

embolization, and, rarely, liver transplantation.

Other benign tumors: Lipomas (usually asymptomatic) and localized fibrous tumors (eg, fibromas) rarely occur in the liver.

Benign bile duct adenomas are rare, inconsequential, and usually detected incidentally. They are sometimes mistaken for metastatic cancer.

Primary Liver Cancer

Primary liver cancer is usually hepatocellular carcinoma. The first manifestations of liver cancer are usually nonspecific, delaying the diagnosis. Prognosis is usually poor.

Hepatocellular Carcinoma

Hepatocellular carcinoma (hepatoma) usually occurs in patients with cirrhosis and is common in areas where infection with hepatitis B and C viruses is prevalent. Symptoms and signs are usually nonspecific. Diagnosis is based on α-fetoprotein (AFP) levels, imaging tests, and sometimes liver biopsy. Screening with periodic AFP measurement and ultrasonography is sometimes recommended for high-risk patients. Prognosis is poor when cancer is advanced, but for small tumors that are confined to the liver, ablative therapies are palliative and surgical resection or liver transplantation is sometimes curative.

Hepatocellular carcinoma is the most common type of primary liver cancer and results in about 14,000 deaths annually in the US. However, it is more common outside the US, particularly in East Asia and sub-Saharan Africa; incidence generally parallels geographic prevalence of chronic hepatitis B virus (HBV) infection.

Etiology

Hepatocellular carcinoma is usually a complication of cirrhosis.

The presence of HBV increases risk of hepatocellular carcinoma by > 100-fold among HBV carriers. Incorporation of HBV-DNA into the host's genome may initiate malignant transformation, even in the absence of chronic hepatitis or cirrhosis.

Other disorders that cause hepatocellular carcinoma include cirrhosis due to chronic hepatitis C virus (HCV) infection, hemochromatosis, and alcoholic cirrhosis. Patients with cirrhosis due to other conditions are also at increased risk.

Environmental carcinogens may play a role; eg, ingestion of food contaminated with fungal aflatoxins is believed to contribute to the high incidence of hepatocellular carcinoma in subtropical regions.

Symptoms and Signs

Most commonly, previously stable patients with cirrhosis present with abdominal pain, weight loss, right upper quadrant mass, and unexplained deterioration. Fever may occur. In a few patients, the first manifestation of hepatocellular carcinoma is bloody ascites, shock, or peritonitis, caused by hemorrhage of the tumor. Occasionally, a hepatic friction rub or bruit develops.

Occasionally, systemic metabolic complications, including hypoglycemia, erythrocytosis, hypercalcemia, and hyperlipidemia, occur. These complications may manifest clinically.

Diagnosis

• α-Fetoprotein (AFP) measurement

• Imaging (CT, ultrasonography, or MRI)

Diagnosis is based on AFP measurement and an imaging test. In adults, AFP signifies dedifferentiation of hepatocytes, which most often indicates hepatocellular carcinoma; 40 to 65% of patients with the cancer have high AFP levels (> 400 µg/L). High levels are otherwise rare, except in teratocarcinoma of the testis, a much less common tumor. Lower values are less specific and can occur with hepatocellular regeneration (eg, in hepatitis). Other blood tests, such as AFP-L3 (an AFP isoform) and des-γ-carboxyprothrombin, are being studied as markers to be used for early detection of hepatocellular carcinoma.

Depending on local preferences and capabilities, the first imaging test may be contrast-enhanced CT, ultrasonography, or MRI. Hepatic arteriography is occasionally helpful in equivocal cases and can be used to outline the vascular anatomy when ablation or surgery is planned.

If imaging shows characteristic findings and AFP is elevated, the diagnosis is clear. Liver biopsy, often guided by ultrasonography or CT, is sometimes indicated for definitive diagnosis.

Staging: If a hepatocellular carcinoma is diagnosed, evaluation usually includes chest CT without contrast, imaging of the portal vein (if not already done) by MRI or CT with contrast to exclude thrombosis, and sometimes bone scanning.

Hepatocellular carcinoma is staged based on the following (American Cancer Society classification system—see Table 30-1):

• T: How many primary tumors, how big they are, and whether the cancer has spread to adjacent organs

• N: Whether the cancer has spread to nearby lymph nodes

• M: Whether the cancer has metastasized to other organs of the body

Numbers (0 to 4) are added after T, N, and M to indicate increasing severity. The letter X means no assessment is possible.

Screening: An increasing number of hepatocellular carcinomas are being detected through screening programs. Screening patients with cirrhosis is reasonable, although this measure is controversial and has not been shown to reduce mortality. One common screening method is AFP measurement and ultrasonography every 6 or 12 mo. Many experts advise screening patients with longstanding hepatitis B even when cirrhosis is absent.

Treatment

• Transplantation if tumors are small and few

[**Table 30-1.** Staging Hepatocellular Carcinoma*]

For single tumors < 5 cm or ≤ 3 tumors ≤ 3 cm that are limited to the liver, liver transplantation results in as good a prognosis as liver transplantation done for noncancerous disorders. Alternatively, surgical resection may be done; however, the cancer usually recurs.

Ablative treatments (eg, hepatic arterial chemoembolization, intratumoral ethanol injection, cryoablation, radiofrequency ablation) provide palliation and slow tumor growth; they are used when patients are awaiting liver transplantation.

If the tumor is large (> 5 cm), is multifocal, has invaded the portal vein, or is metastatic (ie, stage III or higher), prognosis is much less favorable (eg, 5-yr survival rates of about 5% or less). Radiation therapy is usually ineffective. Some newer chemotherapeutic regimens are promising.

Prevention

Use of vaccine against HBV eventually decreases the incidence, especially in endemic areas. Preventing the development of cirrhosis of any cause (eg, via treatment of chronic hepatitis C, early detection of hemochromatosis, management of alcoholism) can also have a significant effect.

Other Primary Liver Cancers

Other primary liver cancers are uncommon or rare. Diagnosis usually requires biopsy. Prognosis is typically poor. Some cancers, if localized, can be resected. With resection or liver transplantation, survival may be prolonged.

Fibrolamellar carcinoma: This distinct variant of hepatocellular carcinoma has a characteristic morphology of malignant hepatocytes enmeshed in lamellar fibrous tissue. It usually occurs in young adults and has no association with preexisting cirrhosis, HBV, HCV, or other known risk factors. AFP levels are rarely elevated. Prognosis is better than that for hepatocellular carcinoma, and many patients survive several years after tumor resection.

Cholangiocarcinoma: This tumor originates in the biliary epithelium. It is common in China, where underlying infestation with liver flukes is believed to contribute. Elsewhere, it is less common than hepatocellular carcinoma; histologically, the two may overlap. Primary sclerosing cholangitis greatly increases risk of cholangiocarcinoma.

Hepatoblastoma: Although rare, hepatoblastoma is one of the most common primary liver cancers in infants, particularly those with a family history of familial adenomatous polyposis (see p. 192). It can also develop in children. Some patients with hepatoblastoma present with precocious puberty caused by ectopic gonadotropin production, but the cancer is usually detected because of deteriorating general health and a right upper quadrant mass. An elevated AFP level and abnormal imaging test results may help in the diagnosis.

Angiosarcoma: This rare cancer is associated with specific chemical carcinogens, including industrial vinyl chloride.

Metastatic Liver Cancer

Liver metastases are common in many types of cancer, especially those of the GI tract, breast, lung, and pancreas. The first symptoms of metastases are usually nonspecific (eg, weight loss, right upper quadrant discomfort); they are sometimes the first symptoms of the primary cancer. Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. Diagnosis is usually supported by an imaging test, most often ultrasonography, spiral CT with contrast, or MRI with contrast. Treatment usually involves palliative chemotherapy.

Metastatic liver cancer is more common than primary liver cancer and is sometimes the initial clinical manifestation of cancer originating in the GI tract, breast, lung, or pancreas.

Symptoms and Signs

Early liver metastases may be asymptomatic. Nonspecific symptoms of cancer (eg, weight loss, anorexia, fever) often develop first. The liver may be enlarged, hard, or tender; massive hepatomegaly with easily palpable nodules signifies advanced disease. Hepatic bruits and pleuritic-type pain with an overlying friction rub are uncommon but characteristic. Splenomegaly is occasionally present, especially when the primary cancer is pancreatic. Concomitant peritoneal tumor seeding may produce ascites, but jaundice is usually absent or mild initially unless a tumor causes biliary obstruction.

In the terminal stages, progressive jaundice and hepatic encephalopathy presage death.

Diagnosis

• CT with contrast or MRI with contrast

• Sometimes biopsy

Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. If metastases are suspected, liver function tests are often done, but results are usually not specific for the diagnosis. Alkaline phosphatase, γ-glutamyl transpeptidase, and sometimes LDH typically increase earlier or to a greater degree than do other test results; aminotransferase levels vary. Imaging tests have good sensitivity and specificity. Ultrasonography is usually helpful, but CT with contrast or MRI with contrast is often more accurate.

Liver biopsy guided by imaging provides the definitive diagnosis and is done if other tests are equivocal or if histologic information (eg, cell type of the liver metastasis) may help determine the treatment plan.

Treatment

Treatment depends on the extent of metastasis. With solitary or very few metastases due to colorectal cancer, surgical resection may prolong survival. Depending on characteristics of the primary tumor, systemic chemotherapy may shrink tumors and prolong life but is not curative; hepatic intra-arterial chemotherapy sometimes has the same effect but with fewer or milder systemic adverse effects.

Radiation therapy to the liver occasionally alleviates severe pain due to advanced metastases but does not prolong life. Extensive disease is fatal and is best managed by palliation for the patient and support for the family (see p. 3480).

Hematologic Cancers and the Liver

The liver is commonly involved in advanced leukemia and related blood disorders. Liver biopsy is not needed. In hepatic lymphoma, especially Hodgkin lymphoma, the extent of liver involvement determines staging and treatment but may be difficult to assess. Hepatomegaly and abnormal liver function tests may reflect a systemic reaction to Hodgkin lymphoma rather than spread to the liver, and biopsy often shows nonspecific focal mononuclear infiltrates or granulomas of uncertain significance. Treatment is directed at the hematologic cancer.

Hepatic Granulomas

Hepatic granulomas have numerous causes and are usually asymptomatic. However, the underlying disorder may cause extrahepatic manifestations, hepatic inflammation, fibrosis, portal hypertension, or a combination. Diagnosis is based on liver biopsy, but biopsy is necessary only if a treatable underlying disorder (eg, infection) is suspected or if other liver disorders need to be ruled out. Treatment depends on the underlying disorder.

Hepatic granulomas, although sometimes insignificant, more often reflect clinically relevant disease. The term granulomatous hepatitis is often used to describe the condition, but the disorder is not true hepatitis, and the presence of granulomas does not imply hepatocellular inflammation.

Etiology

Hepatic granulomas have many causes (see Table 30-2.); drugs and systemic disorders (often infections) are more common causes than primary liver disorders. Infections must be identified because they require specific treatments. TB and schistosomiasis are the most common infectious causes worldwide; fungal and viral causes are less common. Sarcoidosis is the most common noninfectious cause; the liver is involved in about two thirds of patients, and occasionally, clinical manifestations of sarcoidosis are predominantly hepatic.

Granulomas are much less common in primary liver disorders; primary biliary cirrhosis is the only important cause. Small granulomas occasionally occur in other liver disorders but are not clinically significant.

Idiopathic granulomatous hepatitis is a rare syndrome of hepatic granulomas with recurrent fever, myalgias, fatigue, and other systemic symptoms, which often occur intermittently for years. Some experts believe it is a variant of sarcoidosis.

Pathophysiology

A granuloma is a localized collection of chronic inflammatory cells with epithelioid cells and giant multinucleated cells. Caseation necrosis or foreign body tissue (eg, schistosome eggs) may be present. Most granulomas occur in the parenchyma, but in primary biliary cirrhosis, granulomas may occur in the hepatic triads.

Granuloma formation is incompletely understood. Granulomas may develop in response to poorly soluble exogenous or endogenous irritants. Immunologic mechanisms are involved.

Hepatic granulomas rarely affect hepatocellular function. However, when granulomas are part of a broader inflammatory reaction involving the liver (eg, drug reactions, infectious mononucleosis), hepatocellular dysfunction is present. Sometimes inflammation causes progressive hepatic fibrosis and portal hypertension, typically with schistosomiasis and occasionally with extensive sarcoidal infiltration.

Symptoms and Signs

Granulomas themselves are typically asymptomatic; even extensive infiltration usually causes only minor hepatomegaly and little or no jaundice. Symptoms, if they occur, reflect the underlying condition (eg, constitutional symptoms in infections, hepatosplenomegaly in schistosomiasis).

[Table 30-2. Causes of Hepatic Granulomas]

Diagnosis

• Liver function tests

• Imaging

• Biopsy

Hepatic granulomas are suspected in patients with

• Conditions that commonly cause granulomas

• Unexplained hepatic masses found during imaging tests

• Occasionally, when an imaging test is done to evaluate asymptomatic elevations in liver enzymes, particularly alkaline phosphatase

When granulomas are suspected, liver function tests are usually done, but results are nonspecific and are rarely helpful in diagnosis. Alkaline phosphatase (and γ-glutamyltransferase) is often mildly elevated but occasionally may be markedly elevated. Other test results may be normal or abnormal, reflecting additional hepatic damage (eg, widespread hepatic inflammation due to a drug reaction). Usually, imaging tests, such as ultrasonography, CT, or MRI, are not diagnostic; they may show calcification (if granulomas are long-standing) or filling defects, particularly with confluent lesions.

Diagnosis is based on liver biopsy. However, biopsy is usually indicated only to diagnose treatable causes (eg, infections) or to rule out nongranulomatous disorders (eg, chronic viral hepatitis). Biopsy sometimes detects evidence of the specific cause (eg, schistosome eggs, caseation of TB, fungal organisms). However, other tests (eg, cultures, skin tests, laboratory tests, imaging tests, other tissue specimens) are often needed.

In patients with constitutional or other symptoms suggesting infection (eg, FUO), specific measures are taken to increase the diagnostic sensitivity of biopsy for infections; eg, a portion of the fresh biopsy specimen is sent for culture, or special stains for acid-fast bacilli, fungi, and other organisms are used. Often, cause cannot be established.

Prognosis

Hepatic granulomas caused by drugs or infection regress completely after treatment. Sarcoid granulomas may disappear spontaneously or persist for years, usually without causing clinically important liver disease. Progressive fibrosis and portal hypertension (sarcoidal cirrhosis) rarely develop.

In schistosomiasis, progressive portal scarring (pipestem fibrosis) is typical; liver function is usually preserved, but marked splenomegaly and variceal hemorrhage can occur.

Treatment

• Treatment of cause

Treatment is directed at the underlying disorder. When the cause is unknown, treatment is usually withheld, and follow-up with periodic liver function tests is instituted. However, if symptoms of TB (eg, prolonged fever) and deteriorating health occur, empiric antituberculous therapy may be justified.

Corticosteroids may benefit patients with progressive hepatic sarcoidosis, although whether these drugs prevent hepatic fibrosis is unclear. However, corticosteroids are not indicated for most patients with sarcoidosis and are warranted only if TB and other infections can be excluded confidently.

Chapter 31. Gallbladder and Bile Duct Disorders

Introduction

The liver produces about 500 to 600 mL of bile each day. Bile is isosmotic with plasma and consists primarily of water and electrolytes but also organic compounds: bile salts, phospholipids (mostly lecithin), cholesterol, bilirubin, and other endogenously produced or ingested compounds, such as proteins that regulate GI function and drugs or their metabolites. Bilirubin is a degradation product of heme compounds from worn-out RBCs and is the pigment that gives bile its yellow-green color.

Bile salts (bile acids) are the major organic component in bile. The liver uses active transport to secrete bile salts into the canaliculus, the cleft between adjacent hepatocytes. Canalicular transport is the rate-limiting step in bile formation. Once secreted, bile salts draw other bile components (particularly Na^+ and water) into the canaliculus by osmosis. Bile salts are also biologic detergents that enable the body to excrete cholesterol and potentially toxic compounds (eg, bilirubin, drug metabolites). The function of bile salts in the duodenum is to solubilize ingested fat and fat-soluble vitamins, facilitating their digestion and absorption. From the liver, bile flows from the intrahepatic collecting system into the right or left hepatic duct, then into the common hepatic duct.

During fasting, about 75% of the bile secreted passes from the common hepatic duct into the gallbladder via the cystic duct. The rest flows directly into the common bile duct (formed by the junction of the common hepatic and cystic ducts) into the duodenum. During fasting, the gallbladder absorbs up to 90% of bile water, concentrating and storing bile.

Bile empties from the gallbladder into the common bile duct. The common bile duct joins with the pancreatic duct to form the ampulla of Vater, which empties into the duodenum. Before joining the pancreatic duct, the common bile duct tapers to a diameter of ≤ 0.6 cm.

The sphincter of Oddi, which surrounds both the pancreatic duct and the common bile duct, includes a sphincter for each duct. Bile does not normally flow retrograde into the pancreatic duct. These sphincters are highly sensitive to cholecystokinin and other gut hormones (eg, gastrin-releasing peptide) and to alterations in cholinergic tone (eg, by anticholinergic drugs).

Eating releases gut hormones and stimulates cholinergic nerves, causing the gallbladder to contract and the sphincter of Oddi to relax. As a result, the gallbladder empties 50 to 75% of its contents into the duodenum. Conversely, during fasting, an increase in sphincter tone facilitates gallbladder filling.

Bile salts are poorly absorbed by passive diffusion in the proximal small bowel; most intestinal bile salts reach the terminal ileum, which actively absorbs 90% into the portal venous circulation. Returned to the liver, bile salts are efficiently extracted, promptly modified (eg, conjugated if they arrive in the free form), and secreted back into bile. Bile salts circulate through this pathway from liver to gut to liver—the enterohepatic circulation—10 to 12 times/day.

Cholelithiasis

Cholelithiasis is the presence of one or more calculi (gallstones) in the gallbladder. In developed countries, about 10% of adults and 20% of people > 65 yr have gallstones. Gallstones tend to be asymptomatic. The most common symptom is biliary colic; gallstones do not cause dyspepsia or fatty food intolerance. More serious complications include cholecystitis; biliary tract obstruction (from stones in the bile ducts or choledocholithiasis), sometimes with infection (cholangitis); and gallstone pancreatitis. Diagnosis is usually by ultrasonography. If cholelithiasis causes symptoms or complications, cholecystectomy is necessary.

Risk factors for gallstones include female sex, obesity, increased age, American Indian ethnicity, a Western diet, and a family history. Most disorders of the biliary tract result from gallstones.

Pathophysiology

Biliary sludge is often a precursor of gallstones. It consists of Ca bilirubinate (a polymer of bilirubin), cholesterol microcrystals, and mucin. Sludge develops during gallbladder stasis, as occurs during pregnancy or use of TPN. Most sludge is asymptomatic and disappears when the primary condition resolves. Alternatively, sludge can evolve into gallstones or migrate into the biliary tract, obstructing the ducts and leading to biliary colic, cholangitis, or pancreatitis.

There are several types of gallstones.

Cholesterol stones account for > 85% of gallstones in the Western world. For cholesterol gallstones to form, the following is required:

- Bile must be supersaturated with cholesterol. Normally, water-insoluble cholesterol is made water soluble by combining with bile salts and lecithin to form mixed micelles. Supersaturation of bile with cholesterol most commonly results from excessive cholesterol secretion (as occurs in obesity or diabetes) but may result from a decrease in bile salt secretion (eg, in cystic fibrosis because of bile salt malabsorption) or in lecithin secretion (eg, in a rare genetic disorder that causes a form of progressive intrahepatic familial cholestasis).

- The excess cholesterol must precipitate from solution as solid microcrystals. Such precipitation in the gallbladder is accelerated by mucin, a glycoprotein, or other proteins in bile.

- The microcrystals must aggregate and grow. This process is facilitated by the binding effect of mucin forming a scaffold and by retention of microcrystals in the gallbladder with impaired contractility due to excess cholesterol in bile.

Black pigment stones are small, hard gallstones composed of Ca bilirubinate and inorganic Ca salts (eg, Ca carbonate, Ca phosphate). Factors that accelerate stone development include alcoholic liver disease, chronic hemolysis, and older age.

Brown pigment stones are soft and greasy, consisting of bilirubinate and fatty acids (Ca palmitate or stearate). They form during infection, inflammation, and parasitic infestation (eg, liver flukes in Asia).

Gallstones grow at about 1 to 2 mm/yr, taking 5 to 20 yr before becoming large enough to cause problems. Most gallstones form within the gallbladder, but brown pigment stones form in the ducts. Gallstones may migrate to the bile duct after cholecystectomy or, particularly in the case of brown pigment stones, develop behind strictures as a result of stasis and infection.

Symptoms and Signs

About 80% of people with gallstones are asymptomatic. The remainder have symptoms ranging from biliary-type pain (biliary colic) to cholecystitis to life-threatening cholangitis. Biliary colic is the most common symptom.

Stones occasionally traverse the cystic duct without causing symptoms. However, most gallstone migration leads to cystic duct obstruction, which, even if transient, causes biliary colic. Biliary colic characteristically begins in the right upper quadrant but may occur elsewhere in the abdomen. It is often poorly localized, particularly in diabetics and the elderly. The pain may radiate into the back or down the arm. Episodes begin suddenly, become intense within 15 min to 1 h, remain at a steady intensity (not colicky) for up to 12 h (usually < 6 h), and then gradually disappear over 30 to 90 min, leaving a dull ache. The pain is usually severe enough to send patients to the emergency department for relief. Nausea and some vomiting are common, but fever and chills do not occur unless cholecystitis has developed. Mild right upper quadrant or epigastric tenderness may be present; peritoneal findings are absent. Between episodes, patients feel well.

Although biliary-type pain can follow a heavy meal, fatty food is not a specific precipitating factor. Nonspecific GI symptoms, such as gas, bloating, and nausea, have been inaccurately ascribed to gallbladder disease. These symptoms are common, having about equal prevalence in cholelithiasis,

peptic ulcer disease, and functional GI disorders.

Little correlation exists between the severity and frequency of biliary colic and pathologic changes in the gallbladder. Biliary colic can occur in the absence of cholecystitis. If colic lasts > 12 h, particularly if it is accompanied by vomiting or fever, acute cholecystitis or pancreatitis is likely.

Diagnosis

• Ultrasonography

Gallstones are suspected in patients with biliary colic. Abdominal ultrasonography is the method of choice for detecting gallbladder stones; sensitivity and specificity are 95%. Ultrasonography also accurately detects sludge. CT, MRI (see p. 230), and oral cholecystography (rarely available now, although quite accurate) are alternatives. Endoscopic ultrasonography accurately detects small gallstones (< 3 mm) and may be needed if other tests are equivocal. Laboratory tests usually are not helpful; typically, results are normal unless complications develop. Asymptomatic gallstones and biliary sludge are often detected incidentally when imaging, usually ultrasonography, is done for other reasons. About 10 to 15% of gallstones are calcified and visible on plain x-rays.

Prognosis

Patients with asymptomatic gallstones become symptomatic at a rate of about 2%/yr. The symptom that develops most commonly is biliary colic rather than a major biliary complication. Once biliary symptoms begin, they are likely to recur; pain returns in 20 to 40% of patients/yr, and about 1 to 2% of patients/yr develop complications such as cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis.

Treatment

• Laparoscopic cholecystectomy for symptomatic stones

• Expectant for asymptomatic stones; sometimes stone dissolution

Most asymptomatic patients decide that the discomfort, expense, and risk of elective surgery are not worth removing an organ that may never cause clinical illness. However, if symptoms occur, gallbladder removal (cholecystectomy) is indicated because pain is likely to recur and serious complications can develop.

Surgery: Surgery can be done with an open or laparoscopic technique.

Open cholecystectomy, which involves a large abdominal incision and direct exploration, is safe and effective. Its overall mortality rate is about 0.1% when done electively during a period free of complications.

Laparoscopic cholecystectomy is the treatment of choice. Using video endoscopy and instrumentation through small abdominal incisions, the procedure is less invasive than open cholecystectomy. The result is a much shorter convalescence, decreased postoperative discomfort, improved cosmetic results, yet no increase in morbidity or mortality. Laparoscopic cholecystectomy is converted to an open procedure in 2 to 5% of patients, usually because biliary anatomy cannot be identified or a complication cannot be managed. Older age typically increases the risks of any type of surgery.

Cholecystectomy effectively prevents future biliary colic but is less effective for preventing atypical symptoms such as dyspepsia. Cholecystectomy does not result in nutritional problems or a need for dietary limitations. Some patients develop diarrhea, often because bile salt malabsorption in the ileum is unmasked. Prophylactic cholecystectomy is warranted in asymptomatic patients with cholelithiasis only if they have large gallstones (> 3 cm) or a calcified gallbladder (porcelain gallbladder); these conditions increase the risk of gallbladder carcinoma.

Stone dissolution: For patients who decline surgery or who are at high surgical risk (eg, because of

concomitant medical disorders or advanced age), gallbladder stones can sometimes be dissolved by ingesting bile acids orally for many months. The best candidates for this treatment are those with small, radiolucent stones (more likely to be composed of cholesterol) in a functioning nonobstructed gallbladder (indicated by normal filling detected during cholescintigraphy or oral cholecystography or by absence of stones in the neck).

Ursodeoxycholic acid 8 to 10 mg/kg/day po dissolves 80% of tiny stones < 0.5 cm in diameter within 6 mo. For larger stones (the majority), the success rate is much lower, even with higher doses of ursodeoxycholic acid. Further, after successful dissolution, stones recur in 50% within 5 yr. Most patients are thus not candidates and prefer laparoscopic cholecystectomy. However, ursodeoxycholic acid can help prevent stone formation in morbidly obese patients who are losing weight rapidly after bariatric surgery or while on a very low calorie diet.

Stone fragmentation (extracorporeal shock wave lithotripsy) to assist stone dissolution and clearance is now unavailable.

Cholecystitis

Cholecystitis, which is inflammation of the gallbladder, can be acute or chronic.

Acute Cholecystitis

Acute cholecystitis is inflammation of the gallbladder that develops over hours, usually because a gallstone obstructs the cystic duct. Symptoms include right upper quadrant pain and tenderness, sometimes accompanied by fever, chills, nausea, and vomiting. Abdominal ultrasonography detects the gallstone and sometimes the associated inflammation. Treatment usually involves antibiotics and cholecystectomy.

Acute cholecystitis is the most common complication of cholelithiasis. Conversely, ≥ 95% of patients with acute cholecystitis have cholelithiasis. When a stone becomes impacted in the cystic duct and persistently obstructs it, acute inflammation results. Bile stasis triggers release of inflammatory enzymes (eg, phospholipase A, which converts lecithin to lysolecithin, which then may mediate inflammation). The damaged mucosa secretes more fluid into the gallbladder lumen than it absorbs. The resulting distention further releases inflammatory mediators (eg, prostaglandins), worsening mucosal damage and causing ischemia, all of which perpetuate inflammation. Bacterial infection can supervene. The vicious circle of fluid secretion and inflammation, when unchecked, leads to necrosis and perforation. If acute inflammation resolves, the gallbladder becomes fibrotic and contracted and does not concentrate bile or empty normally—features of chronic cholecystitis.

Acute acalculous cholecystitis: Acalculous cholecystitis is cholecystitis without stones. It accounts for 5 to 10% of cholecystectomies done for acute cholecystitis. Risk factors include the following:

• Critical illness (eg, major surgery, burns, sepsis, or trauma)

• Prolonged fasting or TPN (both predispose to bile stasis)

• Shock

• Immune deficiency

• Vasculitis (eg, SLE, polyarteritis nodosa)

The mechanism probably involves inflammatory mediators released because of ischemia, infection, or bile stasis. Sometimes an infecting organism can be identified (eg, *Salmonella* sp or cytomegalovirus in immunodeficient patients). In young children, acute acalculous cholecystitis tends to follow a febrile illness without an identifiable infecting organism.

Symptoms and Signs

Most patients have had prior attacks of biliary colic or acute cholecystitis. The pain of cholecystitis is similar in quality and location to biliary colic but lasts longer (ie, > 6 h) and is more severe. Vomiting is common, as is right subcostal tenderness. Within a few hours, Murphy's sign (deep inspiration exacerbates the pain during palpation of the right upper quadrant and halts inspiration) develops along with involuntary guarding of upper abdominal muscles on the right side. Fever, usually low grade, is common.

In the elderly, the first or only symptoms may be systemic and nonspecific (eg, anorexia, vomiting, malaise, weakness, fever). Sometimes fever does not develop.

Acute cholecystitis begins to subside in 2 to 3 days and resolves within 1 wk in 85% of patients.

Complications: Without treatment, 10% of patients develop localized perforation, and 1% develop free perforation and peritonitis. Increasing abdominal pain, high fever, and rigors with rebound tenderness or ileus suggest empyema (pus in the gallbladder), gangrene, or perforation. When acute cholecystitis is accompanied by jaundice or cholestasis, partial common duct obstruction is likely, usually due to stones or inflammation. Other complications include the following:

• Mirizzi's syndrome: Rarely, a gallstone becomes impacted in the cystic duct or Hartman's pouch and compresses and obstructs the common bile duct, causing cholestasis.

• Gallstone pancreatitis: Gallstones pass from the gallbladder into the biliary tract and block the pancreatic duct.

• Cholecystoenteric fistula: Infrequently, a large stone erodes the gallbladder wall, creating a fistula into the small bowel (or elsewhere in the abdominal cavity); the stone may pass freely or obstruct the small bowel (gallstone ileus).

Acute acalculous cholecystitis: The symptoms are similar to those of acute cholecystitis with gallstones but may be difficult to identify because patients tend to be severely ill (eg, ICU setting) and may be unable to communicate clearly. Abdominal distention or unexplained fever may be the only clue. Untreated, the disease can rapidly progress to gallbladder gangrene and perforation, leading to sepsis, shock, and peritonitis; mortality approaches 65%.

Diagnosis

• Ultrasonography

• Cholescintigraphy if ultrasonography results are equivocal or if acalculous cholecystitis is suspected

Acute cholecystitis is suspected based on symptoms and signs.

Transabdominal ultrasonography is the best test to detect gallstones. The test may also elicit local abdominal tenderness over the gallbladder (ultrasonographic Murphy's sign). Pericholecystic fluid or thickening of the gallbladder wall indicates acute inflammation.

Cholescintigraphy is useful when results are equivocal; failure of the radionuclide to fill the gallbladder suggests an obstructed cystic duct (ie, an impacted stone). False-positive results may be due to the following:

• A critical illness

• Receiving TPN and no oral foods (because gallbladder stasis prevents filling)

• Severe liver disease (because the liver does not secrete the radionuclide)

• Previous sphincterotomy (which facilitates exit into the duodenum rather than the gallbladder)

Morphine provocation, which increases tone in the sphincter of Oddi and enhances filling, helps eliminate false-positive results.

Abdominal CT identifies complications such as gallbladder perforation or pancreatitis.

Laboratory tests are done but are not diagnostic. Leukocytosis with a left shift is common. In uncomplicated acute cholecystitis, liver function tests are normal or only slightly elevated. Mild cholestatic abnormalities (bilirubin up to 4 mg/dL and mildly elevated alkaline phosphatase) are common, probably indicating inflammatory mediators affecting the liver rather than mechanical obstruction. More marked increases, especially if lipase (amylase is less specific) is elevated > 2-fold, suggest bile duct obstruction. Passage of a stone through the biliary tract increases aminotransferases (ALT, AST).

Acute acalculous cholecystitis: Acute acalculous cholecystitis is suggested if a patient has no gallstones but has ultrasonographic Murphy's sign or a thickened gallbladder wall and pericholecystic fluid. A distended gallbladder, biliary sludge, and a thickened gallbladder wall without pericholecystic fluid (due to low albumin or ascites) may result simply from a critical illness. CT identifies extrabiliary abnormalities. Cholescintigraphy is more helpful; failure of a radionuclide to fill may indicate edematous cystic duct obstruction. Giving morphine helps eliminate a false-positive result due to gallbladder stasis.

Treatment

• Supportive care (hydration, analgesics, antibiotics)

• Cholecystectomy

Management includes hospital admission, IV fluids, and analgesia with an NSAID (ketorolac) or an opioid. Nothing is given orally, and nasogastric suction is instituted if vomiting or an ileus is present. Parenteral antibiotics are usually initiated to treat possible infection, but evidence of benefit is lacking. Empiric coverage, directed at gram-negative enteric organisms, involves IV regimens such as ceftriaxone 2 g q 24 h plus metronidazole 500 mg q 8 h, piperacillin/tazobactam 4 g q 6 h, or ticarcillin/clavulanate 4 g q 6 h.

Cholecystectomy cures acute cholecystitis and relieves biliary pain. Early cholecystectomy is generally preferred, best done during the first 24 to 48 h in the following situations:

• The diagnosis is clear and patients are at low surgical risk.

• Patients are elderly or have diabetes and are thus at higher risk of infectious complications.

• Patients have empyema, gangrene, perforation, or acalculous cholecystitis.

Surgery may be delayed when patients have an underlying severe chronic disorder (eg, cardiopulmonary) that increases the surgical risks. In such patients, cholecystectomy is deferred until medical therapy stabilizes the comorbid disorders or until cholecystitis resolves. If cholecystitis resolves, cholecystectomy may be done ≥ 6 wk later. Delayed surgery carries the risk of recurrent biliary complications. Percutaneous cholecystostomy is an alternative to cholecystectomy for patients at very high surgical risk, such as the elderly, those with acalculous cholecystitis, and those in an ICU because of burns, trauma, or respiratory failure.

Chronic Cholecystitis

Chronic cholecystitis is long-standing gallbladder inflammation almost always due to gallstones.

Chronic cholecystitis almost always results from gallstones and prior episodes of acute cholecystitis (even if mild). Damage ranges from a modest infiltrate of chronic inflammatory cells to a fibrotic, shrunken gallbladder. Extensive calcification due to fibrosis is called porcelain gallbladder.

Symptoms and Signs

Gallstones intermittently obstruct the cystic duct and so cause recurrent biliary colic. Such episodes of pain are not necessarily accompanied by overt gallbladder inflammation; the extent of inflammation does not correlate with the intensity or frequency of biliary colic. Upper abdominal tenderness may be present, but usually fever is not. Fever suggests acute cholecystitis. Once episodes begin, they are likely to recur.

Diagnosis

• Ultrasonography

Chronic cholecystitis is suspected in patients with recurrent biliary colic plus gallstones. Ultrasonography or another imaging test usually shows gallstones and sometimes a shrunken, fibrotic gallbladder. The diagnosis is made in patients with a history of recurrent biliary colic and evidence of gallstones on ultrasonography. Cholescintigraphy may show nonvisualization of the gallbladder but is less accurate.

Treatment

Laparoscopic cholecystectomy is indicated to prevent symptom recurrence and further biliary complications. This procedure is particularly valid for the porcelain gallbladder associated with gallbladder carcinoma.

Acalculous Biliary Pain

Acalculous biliary pain is biliary colic without gallstones, resulting from structural or functional disorders; it is sometimes treated with laparoscopic cholecystectomy.

Biliary colic can occur in the absence of gallstones, particularly in young women. Acalculous biliary pain accounts for up to 15% of laparoscopic cholecystectomies. Common causes of such biliary pain include the following:

• Microscopic stones—not detected by routine abdominal ultrasonography

• Abnormal gallbladder emptying

• An overly sensitive biliary tract

• Sphincter of Oddi dysfunction

• Hypersensitivity of the adjacent duodenum

• Possibly gallstones that have spontaneously passed

Some patients eventually develop other functional GI disorders.

Diagnosis

Acalculous biliary pain is suspected in patients with biliary colic when diagnostic imaging cannot detect gallstones. Imaging should include ultrasonography and, where available, endoscopic ultrasonography (for small stones < 1 cm). Abnormal laboratory tests may reveal evidence of a biliary tract abnormality (eg, elevated alkaline phosphatase, bilirubin, ALT, or AST) or a pancreatic abnormality (eg, elevated lipase) during an episode of acute pain. Cholescintigraphy with cholecystokinin infusion measures gallbladder emptying (ejection fraction); potentially interfering drugs such as Ca channel blockers, opioids, and anticholinergics should not be used. ERCP with biliary manometry detects sphincter of Oddi dysfunction. The best diagnostic approach remains problematic.

Treatment

Laparoscopic cholecystectomy improves outcomes for patients with microscopic stones and possibly

abnormal gallbladder motility. The role of laparoscopic cholecystectomy or endoscopic sphincterotomy remains problematic. Drug therapies have no proven benefit.

Postcholecystectomy Syndrome

Postcholecystectomy syndrome is occurrence of abdominal symptoms after cholecystectomy.

Postcholecystectomy syndrome occurs in 5 to 40% of patients. It refers to presumed gallbladder symptoms that continue or that develop after cholecystectomy or to other symptoms that result from cholecystectomy. Removal of the gallbladder, the storage organ for bile, normally has few consequences on biliary tract function or pressures. In about 10%, biliary colic appears to result from functional or structural abnormalities of the sphincter of Oddi, resulting in altered biliary pressures or heightened sensitivity.

The most common symptoms are dyspepsia or otherwise nonspecific symptoms rather than true biliary colic. Papillary stenosis, which is rare, is fibrotic narrowing around the sphincter, perhaps caused by trauma and inflammation due to pancreatitis, instrumentation (eg, ERCP), or prior passage of a stone. Other causes include a retained bile duct stone, pancreatitis, and gastroesophageal reflux.

Diagnosis

• ERCP with biliary manometry or biliary nuclear scanning

• Exclusion of extrabiliary pain

Patients with postcholecystectomy pain should be evaluated as indicated for extra-biliary as well as biliary causes. If the pain suggests biliary colic, alkaline phosphatase, bilirubin, ALT, amylase, and lipase should be measured, and ERCP with biliary manometry or biliary nuclear scanning should be done. Elevated liver enzymes suggest sphincter of Oddi dysfunction; elevated amylase and lipase suggest dysfunction of the sphincter's pancreatic portion.

Dysfunction is best detected by biliary manometry done during ERCP, although ERCP has a risk of inducing pancreatitis. Manometry shows increased pressure in the biliary tract when pain is reproduced. A slowed hepatic hilum-duodenal transit time on a scan also suggests sphincter of Oddi dysfunction. Diagnosis of papillary stenosis is based on a clear-cut history of recurrent episodes of biliary pain and abnormal liver (or pancreatic) enzyme tests.

Treatment

Endoscopic sphincterotomy can relieve recurrent pain due to sphincter of Oddi dysfunction, especially if due to papillary stenosis. It is controversial for patients who have postcholecystectomy pain and no objective abnormalities.

Choledocholithiasis and Cholangitis

Choledocholithiasis is the presence of stones in bile ducts; the stones can form in the gallbladder or in the ducts themselves. These stones cause biliary colic, biliary obstruction, gallstone pancreatitis, or cholangitis (bile duct infection and inflammation). Cholangitis, in turn, can lead to strictures, stasis, and choledocholithiasis. Diagnosis usually requires visualization by magnetic resonance cholangiopancreatography or ERCP. Early endoscopic or surgical decompression is indicated.

Stones may be described as

• Primary stones (usually brown pigment stones), which form in the bile ducts

• Secondary stones (usually cholesterol), which form in the gallbladder but migrate to the bile ducts

• Residual stones, which are missed at the time of cholecystectomy (evident < 3 yr later)

• Recurrent stones, which develop in the ducts > 3 yr after surgery

In developed countries, > 85% of common duct stones are secondary; affected patients have additional stones located in the gallbladder. Up to 10% of patients with symptomatic gallstones also have associated common bile duct stones. After cholecystectomy, brown pigment stones may result from stasis (eg, due to a postoperative stricture) and the subsequent infection. The proportion of ductal stones that are pigmented increases with time after cholecystectomy.

Bile duct stones may pass into the duodenum asymptomatically. Biliary colic occurs when the ducts become partially obstructed. More complete obstruction causes duct dilation, jaundice, and, eventually, cholangitis (a bacterial infection). Stones that obstruct the

[
Table 31-1. Causes of Bile Duct Obstruction]

ampulla of Vater can cause gallstone pancreatitis. Some patients (usually the elderly) present with biliary obstruction due to stones that have caused no symptoms previously.

In **acute cholangitis,** bile duct obstruction allows bacteria to ascend from the duodenum. Most (85%) cases result from common bile duct stones, but bile duct obstruction can result from tumors or other conditions (see Table 31-1). Common infecting organisms include gram-negative bacteria (eg, *Escherichia coli, Klebsiella* sp, *Enterobacter* sp); less common are gram-positive bacteria (eg, *Enterococcus* sp) and mixed anaerobes (eg, *Bacteroides* sp, *Clostridia* sp). Symptoms include abdominal pain, jaundice, and fever or chills (Charcot's triad). The abdomen is tender, and often the liver is tender and enlarged (often containing abscesses). Confusion and hypotension predict about a 50% mortality rate and high morbidity.

Recurrent pyogenic cholangitis (Oriental cholangiohepatitis, hepatolithiasis) is characterized by intrahepatic brown pigment stone formation. This disorder occurs in Southeast Asia. It consists of sludge and bacterial debris in the bile ducts. Undernutrition and parasitic infestation (eg, *Clonorchis sinensis*, *Opisthorchis viverrini*) increase susceptibility. Parasitic infestation can cause obstructive jaundice with intrahepatic ductal inflammation, proximal stasis, stone formation, and cholangitis. Repeating cycles of obstruction, infection, and inflammation lead to bile duct strictures and biliary cirrhosis. The extrahepatic ducts tend to be dilated, but the intrahepatic ducts appear straight because of periductal fibrosis.

In AIDS-related cholangiopathy or cholangitis, direct cholangiography may show abnormalities similar to those in primary sclerosing cholangitis or papillary stenosis (ie, multiple strictures and dilations involving the intrahepatic and extrahepatic bile ducts). Etiology is probably infection, most likely with cytomegalovirus, *Cryptosporidium* sp, or microsporidia.

Diagnosis

• Liver function tests

• Ultrasonography

Common duct stones should be suspected in patients with jaundice and biliary colic. Fever and leukocytosis further suggest acute cholangitis. Elevated levels of bilirubin, alkaline phosphatase, ALT, and γ-glutamyltransferase are consistent with extrahepatic obstruction, suggesting stones, particularly in patients with features of acute cholecystitis or cholangitis.

Ultrasonography may show stones in the gallbladder and occasionally in the common duct (less accurate). The common duct is dilated (> 6 mm in diameter if the gallbladder is intact; > 10 mm after a cholecystectomy). If the ducts are not dilated early in the presentation (eg, first day), stones have probably passed. If doubt exists, magnetic resonance cholangiopancreatography (MRCP) is highly accurate for retained stones. ERCP is done if MRCP is equivocal; it can be therapeutic as well as

diagnostic. CT, though less accurate than ultrasonography, can detect liver abscesses.

For suspected acute cholangitis, CBC and blood cultures are essential. Leukocytosis is common, and aminotransferases may reach 1000 IU/L, suggesting acute hepatic necrosis, often due to microabscesses. Blood cultures guide antibiotic choice.

Treatment

• ERCP and sphincterotomy

If biliary obstruction is suspected, ERCP and sphincterotomy are necessary to remove the stone. Success rate exceeds 90%; up to 7% of patients have complications (eg, bleeding pancreatitis, infection with fibrosis and subsequent duct stricture). Laparoscopic cholecystectomy, which is not as well suited for operative cholangiography or common duct exploration, can be done electively following ERCP and sphincterotomy. Mortality and morbidity after open cholecystectomy with common duct exploration are higher. In patients at high risk of complications with cholecystectomy (eg, the elderly), sphincterotomy alone is an alternative.

Acute cholangitis is an emergency requiring aggressive supportive care and urgent removal of the stones, endoscopically or surgically. Antibiotics are given, similar to those used for acute cholecystitis (see p. 274) An alternative regimen for very ill patients is imipenem and ciprofloxacin, plus metronidazole to cover anaerobes.

For recurrent pyogenic cholangitis, management aims to provide supportive care (eg, broad-spectrum antibiotics), eradicate any parasites, and mechanically clear the ducts of stones and debris endoscopically (via ERCP) or surgically.

Sclerosing Cholangitis

Sclerosing cholangitis refers to chronic cholestatic syndromes characterized by patchy inflammation, fibrosis, and strictures of the intrahepatic and extrahepatic bile ducts. Progression obliterates the bile ducts and leads to cirrhosis, liver failure, and sometimes cholangiocarcinoma.

Sclerosing cholangitis may be primary (with no known cause) or secondary due to immune deficiencies (congenital in children, acquired in adults as AIDS cholangiopathy) often associated with superimposed infections (eg, cytomegalovirus, *Cryptosporidium*), histiocytosis X, or use of drugs (eg, intraarterial floxuridine). Both primary and secondary sclerosing cholangitis cause similar inflammatory and fibrosing lesions scarring the bile ducts. Other causes of bile duct strictures are choledocholithiasis, postoperative biliary stricture, ischemic bile duct injury (during liver transplantation), congenital biliary abnormalities, cholangiocarcinoma, and parasitic infestations.

Diagnosis of biliary strictures and dilations requires imaging techniques such as ultrasonography and cholangiography. Treatment focuses on relieving biliary obstruction (eg, dilating and stenting strictures) and, when possible, eradicating responsible organisms or treating the cause (eg, HIV).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC), the most common form of sclerosing cholangitis, has no known cause. However, 80% of patients have inflammatory bowel disease, most often ulcerative colitis. Other associated conditions include connective tissue disorders, alloimmune disorders, and immunodeficiency syndromes, sometimes complicated by opportunistic infections. Fatigue and pruritus develop insidiously and progressively. Diagnosis is by cholangiography (magnetic resonance cholangiopancreatography or ERCP). Liver transplantation is indicated for advanced disease.

Most (70%) patients with PSC are men. Mean age at diagnosis is 40 yr.

Etiology

Although the cause is unknown, PSC is associated with inflammatory bowel disease, which is present in 80% of patients. About 5% of patients with ulcerative colitis and about 1% with Crohn's disease develop PSC. This association and the presence of several autoantibodies (eg, anti-smooth muscle and perinuclear antineutrophilic antibodies [pANCA]) suggest immune-mediated mechanisms. T cells appear to be involved in the destruction of the bile ducts, implying disordered cellular immunity. A genetic predisposition is suggested by a tendency for the disorder to develop in multiple family members and a higher frequency in people with HLAB8 and HLADR3, which are often correlated with autoimmune disorders. An unknown trigger (eg, bacterial infection, ischemic duct injury) probably causes PSC to develop in genetically predisposed people.

Symptoms and Signs

Onset is usually insidious, with progressive fatigue and then pruritus. Jaundice tends to develop later. About 10 to 15% of patients present with repeated episodes of right upper quadrant pain and fever, possibly due to ascending bacterial cholangitis. Steatorrhea and deficiencies of fat-soluble vitamins can develop. Persistent jaundice harbingers advanced disease. Symptomatic gallstones and choledocholithiasis tend to develop in about 75% of patients. Some patients, asymptomatic until late in the course, first present with hepatosplenomegaly or cirrhosis. PSC tends to slowly and inexorably progress. The terminal phase involves decompensated cirrhosis, portal hypertension, ascites, and liver failure. The time from diagnosis to liver failure is about 12 yr.

Despite the association between PSC and inflammatory bowel disease, the two diseases tend to run separate courses. Ulcerative colitis may appear years before PSC yet tends to have a milder course when associated with PSC. Similarly, total colectomy does not change the course of PSC. The presence of both diseases increases the risk of colorectal carcinoma, regardless of whether a liver transplantation has been done for PSC. Cholangiocarcinoma develops in 10 to 15% of patients.

Diagnosis

• Magnetic resonance cholangiopancreatography (MRCP)

PSC is suspected in patients with unexplained abnormalities in liver biochemical tests, particularly in those with inflammatory bowel disease. A cholestatic pattern is typical: elevated alkaline phosphatase and γ-glutamyltransferase (GGT) rather than aminotransferases. Gamma globulin and IgM levels tend to be increased. Anti-smooth muscle antibodies and pANCA are usually positive. Antimitochondrial antibody, positive in primary biliary cirrhosis, is characteristically negative.

Imaging of the hepatobiliary system begins with ultrasonography to exclude extrahepatic biliary obstruction. Although ultrasonography or CT can show ductal dilation, diagnosis requires cholangiography to show multiple strictures and dilations in the intrahepatic and extrahepatic bile ducts. Imaging should begin with MRCP. ERCP is usually a 2nd choice because it is invasive. Liver biopsy is generally not required for diagnosis; when done, it shows bile duct proliferation, periductal fibrosis, inflammation, and loss of bile ducts. With disease progression, periductal fibrosis extends from the portal regions and eventually leads to secondary biliary cirrhosis.

Measurement of serum tumor markers and ERCP surveillance with brush cytology should be done regularly to check for cholangiocarcinoma.

Treatment

• Supportive care

• ERCP dilation for major (dominant) strictures

• Transplantation for recurrent bacterial cholangitis or complications of end-stage liver disease

Asymptomatic patients usually require only monitoring (eg, physical examination and liver biochemical tests twice/yr). Ursodeoxycholic acid (up to 15 mg/kg/day reduces itching and improve biochemical markers but not survival. Chronic cholestasis (see p. 212) and cirrhosis require supportive treatment. Episodes of bacterial cholangitis warrant antibiotics and therapeutic ERCP, as needed. If a single stricture appears to be the major cause of obstruction (a dominant stricture, found in about 20% of patients), ERCP dilation (with brush cytology to check for tumors) and stenting can relieve symptoms.

Liver transplantation is the only treatment that improves life expectancy in patients with PSC and offers a cure. Recurrent bacterial cholangitis or complications of end-stage liver disease (eg, intractable ascites, portal-systemic encephalopathy, bleeding esophageal varices) are reasonable indications for liver transplantation.

AIDS Cholangiopathy

AIDS cholangiopathy is biliary obstruction secondary to biliary tract strictures caused by various opportunistic infections.

Before the advent of highly active antiretroviral therapy, cholangiopathy occurred in 25% of patients with AIDS, especially in those with a low CD4 count (< 100/µL). The most common pathogen is *Cryptosporidium parvum*. Others include cytomegalovirus, microsporidia, and *Cyclospora* sp. Papillary stenosis or intrahepatic or extrahepatic sclerosing cholangitis develops in most patients. Over half have both.

Common symptoms include right upper quadrant and epigastric pain and diarrhea. A few patients have fever and jaundice. Severe pain usually indicates papillary stenosis. Milder pain suggests sclerosing cholangitis. The diarrhea reflects small-bowel infection, often cryptosporidiosis.

Diagnosis

• Usually ERCP and ultrasonography

ERCP provides the diagnosis, identification of the causal organism by small-bowel biopsy, and a therapeutic opportunity to relieve strictures. Ultrasonography is noninvasive and very accurate (> 95%). CT and magnetic resonance cholangiopancreatography likely have supportive roles.

Liver biochemistry is consistent with cholestasis, especially a high alkaline phosphatase level.

Treatment

• Endoscopic procedures

Endoscopic sphincterotomy can markedly relieve pain, jaundice, and cholangitis in patients with papillary stenosis. Isolated or dominant strictures can be stented endoscopically. Although the cause is an infectious agent, antimicrobial therapy alone does not relieve the biliary tract damage or its sequelae. Because of its use in primary sclerosing cholangitis, ursodeoxycholic acid may have a role in treating intrahepatic ductal sclerosis and cholestasis.

Tumors of the Gallbladder and Bile Ducts

Gallbladder and bile duct tumors can cause extrahepatic biliary obstruction. Symptoms may be absent but often are constitutional or reflect biliary obstruction. Diagnosis is based on ultrasonography plus CT cholangiography or magnetic resonance cholangiopancreatography. Prognosis is grim. Mechanical bile drainage can often relieve pruritus, recurrent sepsis, and pain due to biliary obstruction.

Cholangiocarcinomas and other bile duct tumors are rare (1 to 2/100,000 people) but are usually malignant. Cholangiocarcinomas occur predominantly in the extrahepatic bile ducts: 60 to 70% in the perihilar region (Klatskin tumors), about 25% in the distal ducts, and the rest in the liver. Risk factors

include primary sclerosing cholangitis, older age, infestation with liver flukes, and a choledochal cyst.

Gallbladder carcinoma is uncommon (2.5/100,000). It is more common among American Indians, patients with large gallstones (> 3 cm), and those with extensive gallbladder calcification due to chronic cholecystitis (porcelain gallbladder). Nearly all (70 to 90%) patients also have gallstones. Median survival is 3 mo. Cure is possible when cancer is found early (eg, incidentally at cholecystectomy).

Gallbladder polyps are usually asymptomatic benign mucosal projections that develop in the lumen of the gallbladder. Most are < 10 mm in diameter and composed of cholesterol ester and triglycerides; the presence of such polyps is called cholesterolosis. They are found in about 5% of people during ultrasonography. Other, much less common benign polyps include adenomas (causing adenomyomatosis) and inflammatory polyps. Small gallbladder polyps are incidental findings that do not require treatment.

Symptoms and Signs

Most patients with cholangiocarcinomas present with pruritus and painless obstructive jaundice, typically at age 50 to 70 yr. Early perihilar tumors may cause only vague abdominal pain, anorexia, and weight loss. Other features include acholic stool, a palpable mass, hepatomegaly, or a distended gallbladder (Courvoisier's sign, with distal cholangiocarcinoma). Pain may resemble that of biliary colic (reflecting biliary obstruction) or may be constant and progressive. Sepsis (acute cholangitis), though unusual, may be induced by ERCP.

Manifestations of gallbladder carcinoma may range from incidental findings at cholecystectomy done for biliary pain to cholelithiasis to advanced disease with constant pain, weight loss, and an abdominal mass or obstructive jaundice.

Most gallbladder polyps cause no symptoms.

Diagnosis

Cholangiocarcinomas are suspected when extrahepatic biliary obstruction is unexplained. Laboratory test results reflect the degree of cholestasis. In patients with primary sclerosing cholangitis, serum carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9 levels are used for surveillance to detect the development of cholangiocarcinoma. Diagnosis is based on ultrasonography (or endoscopic ultrasonography) and CT cholangiography or magnetic resonance cholangiopancreatography. When these methods are inconclusive, ERCP with percutaneous transhepatic cholangiography (PTC) becomes necessary. ERCP not only detects the tumor but also, with brushings, can provide a tissue diagnosis, sometimes making ultrasonography- or CT-guided needle biopsy unnecessary. Contrast-enhanced CT assists in staging.

Gallbladder carcinomas are better defined by CT than by ultrasonography. Open laparotomy is necessary to determine disease extent, which guides treatment.

Treatment

• For cholangiocarcinomas, stenting (or another bypass procedure) or occasionally resection

For cholangiocarcinoma, stenting or surgically bypassing the obstruction relieves pruritus, jaundice, and perhaps fatigue.

Hilar cholangiocarcinomas with CT evidence of spread are stented via PTC or ERCP. Distal duct cholangiocarcinomas are stented endoscopically with ERCP. If cholangiocarcinoma appears localized, surgical exploration determines resectability by hilar resection or pancreaticoduodenectomy. However, successful resection is uncommon.

Liver transplantation is not indicated because of the high recurrence rate. Effectiveness of adjuvant chemotherapy and radiation therapy for cholangiocarcinomas is unproved as yet.

Many gallbladder carcinomas are treated symptomatically.