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Cirrhosis and Its Complications

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Cirrhosis is a pathologically defined entity that is associated with a spectrum of characteristic clinical manifestations. The cardinal pathologic features reflect irreversible chronic injury of the hepatic parenchyma and include extensive fibrosis in association with the formation of regenerative nodules. These features result from hepatocyte necrosis, collapse of the supporting reticulin network with subsequent connective tissue deposition, distortion of the vascular bed, and nodular regeneration of remaining liver parenchyma. The central event leading to hepatic fibrosis is activation of the hepatic stellate cell. Upon activation by factors released by hepatocytes and Kupffer cells, the stellate cell assumes a myofibroblast-like conformation and, under the influence of cytokines such as transforming growth factor β (TGF- β), produces fibril-forming type I collagen. The precise point at which fibrosis becomes irreversible is unclear. The pathologic process should be viewed as a final common pathway of many types of chronic liver injury. Clinical features of cirrhosis derive from the morphologic alterations and often reflect the severity of hepatic damage rather than the etiology of the underlying liver disease. Loss of functioning hepatocellular mass may lead to jaundice, edema, coagulopathy, and a variety of metabolic abnormalities; fibrosis and distorted vasculature lead to portal hypertension and its sequelae, including gastroesophageal varices and splenomegaly. Ascites and hepatic encephalopathy result from both hepatocellular insufficiency and portal hypertension.

Classification of the various types of cirrhosis based on either etiology or morphology alone is unsatisfactory. A single pathologic pattern may result from a variety of insults, while the same insult may produce several morphologic patterns. Nevertheless, most types of cirrhosis may be usefully classified by a mixture of etiologically and morphologically defined entities as follows: (1) alcoholic; (2) cryptogenic and posthepatic; (3) biliary; (4) cardiac; and (5) metabolic, inherited, and drug-related. This chapter considers the various types of cirrhosis and their complications.

ALCOHOLIC CIRRHOSIS

Definition

Alcoholic cirrhosis is only one of many consequences resulting from chronic alcohol ingestion, and it often accompanies other forms of alcohol-induced liver injury, including alcoholic fatty liver and alcoholic hepatitis (Chap. 288). Alcoholic cirrhosis, historically referred to as *Laennec's cirrhosis*, is the most common type of cirrhosis encountered in North America and many parts of western Europe and South America. It is characterized by diffuse fine scarring, fairly uniform loss of liver cells, and small regenerative nodules, and therefore it is sometimes referred to as *micronodular cirrhosis*. However, micronodular cirrhosis may also result from other types of liver injury (e.g., following jejunoileal bypass),

and thus alcoholic cirrhosis and micronodular cirrhosis are not necessarily synonymous. Conversely, alcoholic cirrhosis may progress to macronodular cirrhosis with time.

Etiology

See Chap. 288, "Alcoholic Liver Disease."

Pathology and Pathogenesis

With continued alcohol intake and destruction of hepatocytes, fibroblasts (including activated hepatic stellate cells that have transformed into myofibroblasts with contractile properties) appear at the site of injury and deposit collagen. Weblike septa of connective tissue appear in periportal and pericentral zones and eventually connect portal triads and central veins. This fine connective tissue network surrounds small masses of remaining liver cells, which regenerate and form nodules. Although regeneration occurs within the small remnants of parenchyma, cell loss generally exceeds replacement. With continuing hepatocyte destruction and collagen deposition, the liver shrinks in size, acquires a nodular appearance, and becomes hard as "end-stage" cirrhosis develops. Although alcoholic cirrhosis is usually a progressive disease, appropriate therapy and strict avoidance of alcohol may arrest the disease at most stages and permit functional improvement. In addition, there is strong evidence that concomitant chronic hepatitis C virus (HCV) infection significantly accelerates development of alcoholic cirrhosis.

Clinical Features

SIGNS AND SYMPTOMS

Alcoholic cirrhosis may be clinically silent, and many cases (10 to 40%) are discovered incidentally at laparotomy or autopsy. In many cases symptoms are insidious in onset, occurring usually after ≥ 10 years of excessive alcohol use and progressing slowly over subsequent weeks and months. Anorexia and malnutrition lead to weight loss and a reduction in skeletal muscle mass. The patient may experience easy bruising, increasing weakness, and fatigue. Eventually the clinical manifestations of hepatocellular dysfunction and portal hypertension ensue, including progressive jaundice, bleeding from gastroesophageal varices, ascites, and encephalopathy. The abrupt onset of one of these complications may be the first event prompting the patient to seek medical attention. In other cases, cirrhosis first becomes evident when the patient requires treatment of symptoms related to alcoholic hepatitis.

A firm, nodular liver may be an early sign of disease; the liver may be either enlarged, normal, or decreased in size. Other frequent findings include jaundice, palmar erythema, spider angiomas, parotid and lacrimal gland enlargement, clubbing of fingers, splenomegaly, muscle wasting, and ascites with or without peripheral edema. Men may have decreased body hair and/or gynecomastia and testicular atrophy, which, like the cutaneous findings, result from disturbances in hormonal metabolism, including increased peripheral formation of estrogen due to diminished hepatic clearance of the precursor androstenedione. Testicular atrophy may reflect hormonal abnormalities or the toxic effect of alcohol on the testes. In women, signs of virilization or menstrual irregularities may

occasionally be encountered. Dupuytren's contractures resulting from fibrosis of the palmar fascia with resulting flexion contracture of the digits are associated with alcoholism but are not specifically related to cirrhosis.

Although the cirrhotic patient may stabilize if drinking is discontinued, over a period of years, the patient may become emaciated, weak, and chronically jaundiced. Ascites and other signs of portal hypertension may become increasingly prominent. Ultimately, most patients with advanced cirrhosis die in hepatic coma, commonly precipitated by hemorrhage from esophageal varices or intercurrent infection. Progressive renal dysfunction often complicates the terminal phase of the illness.

LABORATORY FINDINGS

In advanced alcoholic liver disease, abnormalities of laboratory tests are more common. Anemia may result from acute and chronic gastrointestinal blood loss, coexistent nutritional deficiency (notably of folic acid and vitamin B₁₂), hypersplenism, and a direct suppressive effect of alcohol on the bone marrow. Hemolytic anemia, presumably due to effects of hypercholesterolemia or erythrocyte membranes resulting in unusual spurlike projections (acanthocytosis), has been described in some alcoholics with cirrhosis. Mild or pronounced hyperbilirubinemia may be found, usually in association with varying elevations of serum alkaline phosphatase levels. Levels

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of serum AST (aspartate aminotransferase) are frequently elevated, but levels $>5 \mu\text{kat}$ (300 units) are unusual and should prompt one to look for other coincident or complicating factors. In contrast to viral hepatitis, the serum AST is usually disproportionately elevated relative to ALT (alanine aminotransferase), i.e., AST/ALT ratio >2 . This discrepancy in alcoholic liver disease may result from the proportionally greater inhibition of ALT synthesis by ethanol, which may be partially reversed by pyridoxal phosphate.

The serum prothrombin time is frequently prolonged, reflecting reduced synthesis of clotting proteins, most notably the vitamin K–dependent factors (see “Coagulopathy,” below). The serum albumin level is usually depressed, while serum globulins are increased. Hypoalbuminemia reflects in part overall impairment in hepatic protein synthesis, while hyperglobulinemia is thought to result from nonspecific stimulation of the reticuloendothelial system. Elevated blood ammonia levels in patients with hepatic encephalopathy reflect diminished hepatic clearance because of impaired liver function and shunting of portal venous blood around the cirrhotic liver into the systemic circulation (see “Hepatic Encephalopathy,” below).

A variety of metabolic disturbances may be detected. Glucose intolerance due to endogenous insulin resistance may be present; however, clinical diabetes is uncommon. Central hyperventilation may lead to respiratory alkalosis in patients with cirrhosis. Dietary deficiency and increased urinary losses lead to hypomagnesemia and hypophosphatemia. In patients with ascites and dilutional hyponatremia, hypokalemia may occur from increased urinary potassium losses due in part to hyperaldosteronism. Prerenal azotemia is also observed in such patients.

Diagnosis

Alcoholic cirrhosis should be strongly suspected in patients with a history of prolonged or excessive alcohol intake and physical signs of chronic liver disease. However, since only 10 to 15% of individuals with excessive alcohol intake develop cirrhosis, other causes and types of liver disease may have to be excluded. The clinical features and laboratory findings are usually sufficient to provide reasonable indication of the presence and extent of hepatic injury. Although a percutaneous needle biopsy of the liver is not usually necessary to confirm the typical findings of alcoholic hepatitis or cirrhosis, it may be helpful in distinguishing patients with less advanced liver disease from those with cirrhosis and in excluding other forms of liver injury such as viral hepatitis. Biopsy may also be helpful as a diagnostic tool in evaluating patients with clinical findings suggestive of alcoholic liver disease who deny alcohol intake. In patients with features of cholestasis, ultrasonography may be appropriate to exclude the presence of extrahepatic biliary obstruction. When the clinical status of an otherwise stable cirrhotic patient deteriorates without an obvious explanation, complicating conditions, such as infection, portal vein thrombosis, and hepatocellular carcinoma, should be sought.

Prognosis

Abstinence from alcohol as well as early and appropriate medical care can decrease long-term morbidity and mortality and delay or prevent the appearance of further complications. Patients who have had a major complication of cirrhosis and who continue to drink have a 5-year survival of <50%. However, those patients who remain abstinent have a substantially better prognosis. In general, the overall outlook in patients with advanced liver disease remains poor; most of these patients eventually die as a result of massive variceal hemorrhage and/or profound hepatic encephalopathy.



TREATMENT

Alcoholic cirrhosis is a serious illness that requires long-term medical supervision and careful management. Therapy of the underlying liver disease is largely supportive. Specific treatment is directed at particular complications such as variceal bleeding and ascites (see below). While some studies suggest that administration of glucocorticoids in moderately large doses for 4 weeks is helpful in patients with severe alcoholic hepatitis and encephalopathy, these drugs have no role in the treatment of established alcoholic cirrhosis. One study has suggested survival benefit in alcoholic cirrhosis patients receiving S-adenosyl methionine, which may act to decrease proinflammatory cytokines.

The patient should be made to realize that there is no medication that will protect the liver against the effects of further alcohol ingestion. Therefore, alcohol should be absolutely forbidden. An important component of the complete care of such patients is encouragement to become involved in an appropriate alcohol counseling program.

All medicines must be administered with caution in the patient with cirrhosis, especially those eliminated or modified through hepatic metabolism or biliary pathways. In particular, care must be taken to avoid overzealous use of drugs that may directly or

indirectly precipitate complications of cirrhosis. For example, vigorous treatment of ascites with diuretics may result in electrolyte abnormalities or hypovolemia, which can lead to coma. Similarly, even modest doses of sedatives can lead to deepening encephalopathy. Aspirin should be avoided in patients with cirrhosis because of its effects on coagulation and gastric mucosa. Acetaminophen should be used with caution and in doses of less than 2 g/d. Patients who drink alcohol are more sensitive to the hepatotoxic effects of acetaminophen, probably due to increased metabolism of the drug to toxic intermediates and decreased glutathione levels.

POSTHEPATITIC AND CRYPTOGENIC CIRRHOSIS

Definition

Posthepatic or postnecrotic cirrhosis represents the final common pathway of many types of chronic liver disease. *Coarsely nodular cirrhosis* and *multilobular cirrhosis* are terms synonymous with posthepatic cirrhosis. The term *cryptogenic cirrhosis* has been used interchangeably with posthepatic cirrhosis, but this designation should be reserved for those cases in which the etiology of cirrhosis is unknown (approximately 10% of all patients with cirrhosis).

Etiology

Posthepatic cirrhosis is a morphologic term referring to a defined stage of advanced chronic liver injury of either specific or unknown (cryptogenic) causes. Epidemiologic and serologic evidence suggest that in one-fourth to three-fourths of cases of posthepatic cirrhosis, viral hepatitis (hepatitis B or hepatitis C) may be an antecedent factor. In areas where hepatitis B virus (HBV) infection is endemic (e.g., Southeast Asia, sub-Saharan Africa), up to 15% of the population may acquire the infection in early childhood, and cirrhosis may ultimately develop in one-fourth of these chronic carriers. Although HBV infection is much less prevalent in the United States, it is relatively common among certain high-risk groups (e.g., persons with multiple sexual partners, especially men who have sex with men, injection drug users) and contributes to an increased incidence of cirrhosis. In the United States, HCV infection accounts for many cases of cirrhosis following blood transfusions. Before routine screening of blood donors was introduced, hepatitis C occurred in 5 to 10% of blood recipients. Following infection, cirrhosis may ultimately develop in >20% of individuals after 20 years. Increasing recognition of the progressive nature of nonalcoholic fatty liver disease (NAFLD) has revealed that many cases previously designated cryptogenic cirrhosis may be attributable to this disorder (Chap. 290). Posthepatic cirrhosis may also develop in patients with autoimmune hepatitis (Chap. 287).

The most common causes of cirrhosis in the United States that ultimately lead to liver transplantation include chronic HCV infection, alcohol, primary biliary cirrhosis, primary sclerosing cholangitis, and NAFLD. Less common causes of posthepatic cirrhosis, including drugs and toxins, are listed in Table 289-1.

TABLE 289-1 Causes of Cirrhosis and/or Chronic Liver Disease

Infectious Diseases

Brucellosis (Chap. 141)
 Capillariasis (Chap. 201)
 Echinococcosis (Chap. 240)
 Schistosomiasis (Chap. 203)
 Toxoplasmosis (Chap. 198)
 Viral hepatitis [hepatitis B, C, D; cytomegalovirus; Epstein-Barr virus (Chaps. 285, 165, 166)]

Inherited and Metabolic Disorders (Chap. 290)

α_1 -Antitrypsin deficiency (Chap. 290)
 Alagille's syndrome (Chap. 282)
 Biliary atresia (Chap. 292)
 Familial intrahepatic cholestasis (FIC) types 1–3 (Chap. 292)
 Fanconi's syndrome (Chap. 340)
 Galactosemia (Chap. 341)
 Gaucher's disease (Chap. 340)
 Glycogen storage disease (Chap. 341)
 Hemochromatosis (Chap. 336)
 Hereditary fructose intolerance (Chap. 341)
 Hereditary tyrosinemia (Chap. 343)
 Wilson's disease (Chap. 339)

Drugs and Toxins (Chap. 286)

Alcohol (Chap. 288)
 Amioradone
 Arsenicals
 Oral contraceptives (Budd-Chiari)
 Pyrrolidizine alkaloids and antineoplastic agents (venoocclusive disease)

Other Causes

Biliary obstruction (chronic) (Chap. 292)
 Cystic fibrosis (Chap. 241)
 Graft-versus-host disease (Chap. 100)
 Jejunioileal bypass (Chap. 36)
 Nonalcoholic fatty liver disease (Chap. 290)
 Primary biliary cirrhosis (Chap. 289)
 Primary sclerosing cholangitis (Chap. 292)
 Sarcoidosis (Chap. 309)

Pathology

The posthepatic liver is typically shrunken in size, distorted in shape, and composed of nodules of liver cells separated by dense and broad bands of fibrosis. The microscopic picture is consistent with the gross impression. Posthepatic cirrhosis is characterized morphologically by (1) extensive confluent loss of liver cells, (2) stromal collapse and fibrosis resulting in broad bands of connective tissue containing the remains of many portal triads, and (3) irregular

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nodules of regenerating hepatocytes, varying in size from microscopic to several centimeters in diameter.

Clinical Features

In patients with cirrhosis of known etiology in whom there is progression to a posthepatic stage, the clinical manifestations are an extension of those resulting from the initial disease process. Usually clinical symptoms are related to portal hypertension and its sequelae, such as ascites, splenomegaly, hypersplenism, encephalopathy, and bleeding gastroesophageal varices. The hematologic and liver function abnormalities resemble those seen with other types of cirrhosis. In a few patients with posthepatic cirrhosis, the diagnosis may be made incidentally at operation, at postmortem, or by a needle biopsy of the liver performed to investigate abnormal liver function tests or hepatomegaly.

Diagnosis and Prognosis

Posthepatic cirrhosis should be suspected in patients with signs and symptoms of cirrhosis or portal hypertension. Needle or operative liver biopsies confirm the diagnosis, although nonuniformity of the pathologic process may result in sampling errors. The diagnosis of cryptogenic cirrhosis is reserved for those patients in whom no known etiology can be demonstrated. About 75% of patients have progressive disease despite supportive therapy and die within 1 to 5 years from complications, including variceal hemorrhage, hepatic encephalopathy, or superimposed hepatocellular carcinoma.

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TREATMENT

Management is usually limited to treatment of the complications of portal hypertension, including control of ascites, avoidance of drugs or excessive protein intake that may induce hepatic coma, and prompt treatment of infections (see below). In patients with asymptomatic cirrhosis, expectant management alone is appropriate. In those patients in whom posthepatic cirrhosis has developed as a result of a treatable condition, therapy directed at the primary disorder may limit further progression (e.g., Wilson's disease, hemochromatosis).

BILIARY CIRRHOSIS

Biliary cirrhosis results from injury to or prolonged obstruction of either the intrahepatic or extrahepatic biliary system. It is associated with impaired biliary excretion, destruction of hepatic parenchyma, and progressive fibrosis. Primary biliary cirrhosis (PBC) is characterized by chronic inflammation and fibrous obliteration of intrahepatic bile ductules. Secondary biliary cirrhosis (SBC) is the result of long-standing obstruction of the larger extrahepatic ducts. Although primary and secondary biliary cirrhosis are separate pathophysiologic entities with respect to the initial insult, many clinical features are similar.

PRIMARY BILIARY CIRRHOSIS

Etiology and Pathogenesis

The cause of PBC remains unknown. Several observations suggest that a disordered immune response may be involved. PBC is frequently associated with a variety of disorders

presumed to be autoimmune in nature, such as the syndrome of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia (CREST); the sicca syndrome (dry eyes and dry mouth); autoimmune thyroiditis; type 1 diabetes mellitus; and IgA deficiency.

Most important, a circulating IgG antimitochondrial antibody (AMA) is detected in >90% of patients with PBC and only rarely in other forms of liver disease. It has been demonstrated that these autoantibodies recognize inner mitochondrial membrane proteins identified as enzymes of the pyruvate dehydrogenase complex (PDC), the branched chain-2-oxoacid dehydrogenase complex (BCOADC), and the 2-oxoglutarate dehydrogenase complex (OGDC). The major autoantigen in PBC (found in 90% of patients) has been identified as the 74-kDa E2 component of the PDC, dihydrolipoamide acetyltransferase. The antibodies are directed to a region essential for binding of a lipoic acid cofactor and inhibit the overall enzymatic activity of the PDC. Other AMA autoantibodies in PBC patients are directed to similar constituents of BCOADC and OGDC and also inhibit their enzymatic function. It remains unclear whether these properties have a direct pathogenetic role in the development of PBC. In addition to AMA, elevated serum levels of IgM and cryoproteins consisting of immune complexes capable of activating the alternative complement pathway are found in 80 to 90% of patients. Aberrant expression of major histocompatibility complex class II molecules has been found on biliary epithelium in association with PBC, suggesting that these cells may serve as antigen-presenting cells in this setting. Lymphocytes are prominent in the portal regions and surround damaged bile ducts. These histologic findings resemble those noted in graft-versus-host disease following bone marrow transplantation and suggest that damage to bile ducts may be immunologically mediated, perhaps reflecting a defect in a suppressor cell population. While it has been suggested that PBC may be initiated by molecular mimicry following infection or xenobiotic exposure, definitive evidence is lacking.

Pathology

PBC is divided into four stages based on morphologic findings. The earliest recognizable lesion (stage I), termed *chronic nonsuppurative destructive cholangitis*, is a necrotizing inflammatory process of the portal triads. It is characterized by destruction of medium and small bile ducts, a dense infiltrate of acute and chronic inflammatory cells, mild fibrosis, and occasionally, bile stasis. At times, periductal granulomas and lymph follicles are found adjacent to affected bile ducts. Subsequently, the inflammatory infiltrate becomes less prominent, the number of bile ducts is reduced, and smaller bile ductules proliferate (stage II). Progression over a period of months to years leads to a decrease in interlobular ducts, loss of liver cells, and expansion of periportal fibrosis into a network of connective tissue scars (stage III). Ultimately, cirrhosis, which may be micronodular or macronodular, develops (stage IV).

Clinical Features

SIGNS AND SYMPTOMS

Most patients with PBC are asymptomatic, and the disease is initially detected on the basis

of elevated serum alkaline phosphatase levels during routine screening. The majority of such patients remain asymptomatic for prolonged periods, although many ultimately develop progressive liver injury.

Among patients with symptomatic disease, 90% are women age 35 to 60. Often the earliest symptom is pruritus, which may be either generalized or limited initially to the palms and soles. In addition, fatigue is commonly a prominent early symptom. After several months or years, jaundice and gradual darkening of the exposed areas of the skin (melanosis) may ensue. Other early clinical manifestations of PBC reflect impaired bile excretion. These include steatorrhea and the malabsorption of lipid-soluble vitamins. Protracted elevation of serum lipids, especially cholesterol, leads to subcutaneous lipid deposition around the eyes (xanthelasmas) and over joints and tendons (xanthomas). Over a period of months to years, the itching, jaundice, and hyperpigmentation slowly worsen. Eventually, signs of hepatocellular failure and portal hypertension develop and ascites appears. Progression may be quite variable. Whereas a proportion of asymptomatic patients may show no signs of progression for a decade or longer, in others, death due to hepatic insufficiency may occur within 5 to 10 years after the first signs of the illness. Such decompensation is often precipitated by uncontrolled variceal hemorrhage or infection.

Physical examination may be entirely normal in the early phase of the disease, when patients are asymptomatic or pruritus is the sole complaint. Later, there may be jaundice of varying intensity, hyperpigmentation of the exposed skin areas, xanthelasmas and tendinous and planar xanthomas, moderate to striking hepatomegaly, splenomegaly, and clubbing of the fingers. Bone tenderness, signs of vertebral compression, ecchymoses, glossitis, and dermatitis may all be noted. Clinical evidence of the sicca syndrome can be found in as many as 75% of patients, and serologic evidence of autoimmune thyroid disease in 25%. Other conditions encountered with increased frequency include rheumatoid arthritis, CREST syndrome, keratoconjunctivitis sicca, IgA deficiency, type 1 diabetes mellitus, scleroderma, pernicious anemia, and renal tubular acidosis. Bone disease is often a significant problem encountered over the course of the disease. While osteomalacia occurs due to diminished vitamin D absorption, accelerated osteoporosis in this patient population (the majority of whom are postmenopausal women) is even more common.

LABORATORY FINDINGS

PBC is increasingly diagnosed at a presymptomatic stage, prompted by the finding of a twofold or greater elevation of the serum alkaline phosphatase during routine screening. Serum 5'-nucleotidase activity and γ -glutamyl transpeptidase levels are also elevated. In this setting, serum bilirubin is usually normal and aminotransferase levels minimally increased. The diagnosis is supported by a positive AMA test (titer > 1:40). The latter is both relatively specific and sensitive; a positive test is found in >90% of symptomatic patients and is present in <5% of patients with other liver diseases. As the disease evolves, the serum bilirubin level rises progressively and may reach 510 $\mu\text{mol/L}$ (30 mg/dL) or more in the final stages. Serum aminotransferase values rarely exceed 2.5 to 3.3 μkat (150 to 200 units). Hyperlipidemia is common, and a striking increase of the serum unesterified cholesterol is often noted. An abnormal serum lipoprotein (lipoprotein X) may be present in PBC but is not specific and appears in other cholestatic conditions. A

deficiency of bile salts in the intestine leads to moderate steatorrhea and impaired absorption of the fat-soluble vitamins and hypoprothrombinemia. Patients with PBC have elevated liver copper levels, but this finding is not specific and is found in all disorders in which there is prolonged cholestasis.

Diagnosis

PBC should be considered in middle-aged women with unexplained pruritus or an elevated serum alkaline phosphatase and in whom there may be other clinical or laboratory features of protracted impairment of biliary excretion. Although a positive serum AMA determination provides important diagnostic evidence, false-positive results do occur; therefore, liver biopsy should be performed to confirm the diagnosis. Rarely, the AMA test may be negative in patients with histologic features of PBC. Frequently, patients have antibodies to the E2 protein in tests using these specific antigens. In some cases with histologic features of PBC and a negative AMA, antinuclear or smooth-muscle antibodies are present (as in autoimmune hepatitis), and the designation *autoimmune cholangitis* is applied. The natural history of this entity, however, appears to resemble that of PBC. If the AMA test is negative, the biliary tract should be evaluated to exclude primary sclerosing cholangitis and remediable extrahepatic biliary tract obstruction, especially in view of the frequent presence of coexisting cholelithiasis.

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TREATMENT

While there is no specific therapy for PBC, ursodiol has been shown to improve biochemical and histologic features and might improve survival, particularly liver transplantation-free survival (although this remains unproven). Ursodiol should be given in doses of 13 to 15 mg/kg per day, but lower doses are sometimes just as effective in reducing serum alkaline phosphatase and aminotransferase levels. Ursodiol should be given with food and can be taken in a single dose daily. Side effects are rare: gastrointestinal intolerance (diarrhea) and skin rashes occur but are uncommon. Isolated instances of severe exacerbation of pruritus have been reported in patients with advanced disease. Ursodiol probably works by replacing the endogenously produced hydrophobic bile acids with urosdeoxycholate, a hydrophilic and relatively nontoxic bile acid.

Unfortunately, ursodiol may not prevent ultimate progression of PBC, which is effectively predicted by the Mayo risk score, and the only established "cure" is liver transplantation. Results of liver transplantation for PBC are excellent, survival exceeding that for patients receiving transplantation for most other forms of end-stage liver disease. Recurrence of PBC after liver transplantation has been reported but is uncommon, and the recurrent disease is only slowly progressive. Most patients remain AMA positive after transplantation, and as many as 25% will have histologic features of PBC on liver biopsy after 5 years. Other therapies such as glucocorticoids, colchicine, methotrexate, azathioprine, cyclosporine, and tacrolimus have been reported as effective in small case series, but none have shown to be effective in adequately controlled trials.

Relief of symptoms is also an important part of management of PBC. As noted, ursodiol may be helpful in controlling symptoms and improving the patient's sense of well-being. Although the mechanism of the protracted pruritus is not entirely clear, cholestyramine, an oral bile salt-sequestering resin, may be helpful in doses of 12 to 16 g/d to decrease both pruritus and hypercholesterolemia. Rifampin, opiate antagonists (naloxone or naltrexone), ondansetron, plasmapheresis, and ultraviolet light have all been tried for control of pruritus, with varying results. Steatorrhea can be reduced by a low-fat diet and substituting medium-chain triglycerides for dietary long-chain triglycerides. Fat-soluble vitamins A, D, E, and K should be given at regular intervals. Zinc supplementation may be necessary if night blindness is refractory to vitamin A therapy. An important part of management of PBC and any cholestatic liver disease is assessment and treatment of osteoporosis and osteomalacia. Patients should be screened periodically by bone densitometry and treated as needed with calcium supplements (1500 mg/d), vitamin D (1000 IU/d), and/or bisphosphonate agents (e.g., alendronate) when osteoporosis is present. Progression of PBC leads to the typical complications of advanced liver disease (see below).

SECONDARY BILIARY CIRRHOSIS

Etiology

SBC results from prolonged partial or total obstruction of the common bile duct or its major branches. In adults, obstruction is most frequently caused by postoperative strictures or gallstones, usually with superimposed infectious cholangitis. Chronic pancreatitis may lead to biliary stricture and secondary cirrhosis. SBC is also an important complication of primary sclerosing cholangitis, a progressive immunologic disorder of the intrahepatic and extrahepatic biliary tree (Chap. 292). Patients with malignant tumors of the common bile duct or pancreas rarely survive long enough to develop SBC. In children, congenital biliary atresia and cystic fibrosis are common causes of SBC. Choledochal cysts, if unrecognized, may also be a rare cause of SBC.

Pathology and Pathogenesis

Unrelieved obstruction of the extrahepatic bile ducts leads to (1) bile stasis and focal areas of centrilobular necrosis followed by periportal necrosis, (2) proliferation and dilatation of the portal bile ducts and ductules, (3) sterile or infected cholangitis with accumulation of polymorphonuclear infiltrates around bile ducts, and (4) progressive expansion of portal tracts by edema and fibrosis. Extravasation of bile from ruptured interlobular bile ducts into areas of periportal necrosis leads to the formation of "bile lakes" surrounded by cholesterol-rich pseudoxanthomatous cells. As in other forms of cirrhosis, injury is accompanied by regeneration in residual parenchyma. These changes gradually lead to a finely nodular cirrhosis. In general, at least 3 to 12 months is required for biliary obstruction to result in cirrhosis. Relief of the obstruction is frequently accompanied by biochemical and morphologic improvement and may even ameliorate cirrhosis.

Clinical Features

The symptoms, signs, and biochemical findings of SBC are similar to those of PBC. Jaundice and pruritus are usually the most prominent features. In addition, fever and/or right upper quadrant pain, reflecting bouts of cholangitis or biliary colic, are typical. The manifestations of portal hypertension are found only in advanced cases. SBC should be considered in any patient with clinical and laboratory evidence of prolonged obstruction to bile flow, especially when there is a history of previous biliary tract surgery or gallstones, bouts of ascending cholangitis, or right upper quadrant pain. Cholangiography (either percutaneous or endoscopic) usually demonstrates the underlying pathologic process. Liver biopsy, although not always necessary from a clinical standpoint, can document the development of cirrhosis.



TREATMENT

Relief of obstruction to bile flow, by either endoscopic or surgical means, is the most important step in the prevention and therapy of SBC. Effective decompression of the biliary tract results in a significant improvement in both symptoms and survival, even in patients with established cirrhosis. When obstruction cannot be relieved, as in sclerosing cholangitis, antibiotics may be helpful acutely in controlling superimposed infection or, when administered on a chronic basis, as prophylactic therapy in suppressing recurring episodes of ascending cholangitis. Without relief of obstruction, there is a steady progression to end-stage cirrhosis and its terminal manifestations.

CARDIAC CIRRHOSIS

Definition

Prolonged, severe right-sided congestive heart failure may lead to chronic liver injury and cardiac cirrhosis. The characteristic pathologic features of fibrosis and regenerative nodules distinguish cardiac cirrhosis from both reversible passive congestion of the liver due to acute heart failure and acute hepatocellular necrosis (“ischemic hepatitis” or “shock liver”) resulting from systemic hypotension and hypoperfusion of the liver.

Etiology and Pathology

In right-sided heart failure, retrograde transmission of elevated venous pressure via the inferior vena cava and hepatic veins leads to congestion of the liver. Hepatic sinusoids become dilated and engorged with blood, and the liver becomes tensely swollen. With prolonged passive congestion and ischemia from poor perfusion secondary to reduced cardiac output, necrosis of centrilobular hepatocytes ensues and leads to fibrosis in these central areas. Ultimately, centrilobular fibrosis develops, with collagen extending outward in a characteristic stellate pattern from the central vein. Gross examination of the liver shows alternating red (congested) and pale (fibrotic) areas, a pattern often referred to as “nutmeg liver.” Improvement in management of cardiac disorders, particularly advances in

surgical treatment, has reduced the frequency of cardiac cirrhosis.

Clinical Features

A range of abnormalities of liver function tests may be found, though none is uniformly present. The serum bilirubin is usually only mildly increased and may be predominantly either conjugated or unconjugated. Mild to moderate elevation in alkaline phosphatase level and prothrombin time prolongation are sometimes present. The AST level is typically mildly elevated but may be transiently very high following a period of marked systemic hypotension (shock liver), when the clinical picture can mimic acute viral or drug-induced hepatitis. In cases of tricuspid insufficiency the liver may be pulsatile, but this finding disappears as cirrhosis develops. With prolonged right-sided heart failure the liver becomes enlarged, firm, and usually nontender. The signs and symptoms of heart failure usually overshadow the liver disease. Bleeding from esophageal varices is rare, but chronic encephalopathy may be prominent, with a waxing and waning course reflecting variations in the severity of right-sided heart failure. Ascites and peripheral edema, often primarily related to the underlying cardiac dysfunction, may be worsened by the superimposed liver disease.

Diagnosis

The presence of a firm, enlarged liver with signs of chronic liver disease in a patient with valvular heart disease, constrictive pericarditis, or cor pulmonale of long duration (>10 years) should suggest cardiac cirrhosis. Liver biopsy can confirm the diagnosis but is often contraindicated because of coagulopathy or ascites. Coexistent chronic heart and liver disease should also raise the possibility of hemochromatosis (Chap. 336), amyloidosis (Chap. 310), or other infiltrative diseases.

Budd-Chiari syndrome resulting from the occlusion of the hepatic veins or inferior vena cava may be confused with acute congestive hepatomegaly. In this condition the liver is grossly enlarged and tender, and severe intractable ascites is present. However, signs and symptoms of heart failure are notably absent. The most common cause is thrombosis of the hepatic veins, often in the setting of polycythemia rubra vera, myeloproliferative syndromes, paroxysmal nocturnal hemoglobinuria, oral contraceptive use, or other hypercoagulable states; it may also result from invasion of the inferior vena cava by tumor, such as renal cell or hepatocellular carcinoma. Idiopathic membranous obstruction of the inferior vena cava is the most common cause of this syndrome in Japan. Hepatic venography or liver biopsy showing centrilobular congestion and sinusoidal dilatation in the absence of right-sided heart failure establishes the diagnosis of Budd-Chiari syndrome. Venooclusive disease affecting the sublobular branches of the hepatic veins and the hepatic venues may result from hepatic irradiation, treatment with certain antineoplastic agents as preparation for stem cell transplantation, or ingestion of pyrrolizidine alkaloids present in some herbal teas ("bush tea disease") and can mimic congestive hepatomegaly.

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TREATMENT

Prevention or treatment of cardiac cirrhosis depends on the diagnosis and therapy of the underlying cardiovascular disorder. Improvement in cardiac function frequently results in improvement of liver function and stabilization of the liver disease.

METABOLIC, HEREDITARY, DRUG-RELATED, AND OTHER TYPES OF CIRRHOSIS (See Table 289-1)

Cirrhosis or hepatitis may result from a wide variety of other processes encompassing the spectrum of etiologic factors listed in Table 289-2. Although some of these disorders have distinctive clinical or morphologic features, the manifestations of cirrhosis are largely independent of the underlying pathogenic mechanism.

TABLE 289-2 Some Causes of Noncirrhotic Hepatic Fibrosis

<p>Idiopathic portal hypertension (noncirrhotic portal fibrosis, Banti's syndrome); three variants: Intrahepatic phlebosclerosis and fibrosis Portal and splenic vein sclerosis Portal and splenic vein thrombosis Schistosomiasis ("pipe-stem" fibrosis with presinusoidal portal hypertension) Congenital hepatic fibrosis (may be associated with polycystic disease of liver and kidneys)</p>
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NONCIRRHOTIC FIBROSIS OF THE LIVER

Several diseases, either congenital or acquired, may be associated with localized or generalized hepatic fibrosis. They are distinguished from cirrhosis by the absence of hepatocellular damage and the lack of nodular regenerative activity. The clinical manifestations in such cases are largely secondary to portal hypertension. The different types of these disorders are indicated in Table 289-2; with the exception of schistosomiasis in some regions of the world, all these conditions are relatively rare.

MAJOR COMPLICATIONS OF CIRRHOSIS

The clinical course of patients with advanced cirrhosis is often complicated by a number of important sequelae that are independent of the etiology of the underlying liver disease. These include portal hypertension and its consequences (e.g., gastroesophageal varices and splenomegaly), ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatocellular carcinoma.

PORTAL HYPERTENSION

Definition and Pathogenesis

Normal pressure in the portal vein is low (5 to 10 mmHg) because vascular resistance in the hepatic sinusoids is minimal. Portal hypertension (>10 mmHg) most commonly results from increased resistance to portal blood flow. Because the portal venous system lacks valves, resistance at any level between the right side of the heart and splanchnic vessels results in retrograde transmission of an elevated pressure. Increased resistance can occur at three levels relative to the hepatic sinusoids: (1) presinusoidal, (2) sinusoidal, and (3) postsinusoidal. Obstruction in the *presinusoidal* venous compartment may be anatomically outside the liver (e.g., portal vein thrombosis) or within the liver itself but at a functional level proximal to the hepatic sinusoids so that the liver parenchyma is not exposed to the elevated venous pressure (e.g., schistosomiasis).

Postsinusoidal obstruction may also occur outside the liver at the level of the hepatic veins (e.g., Budd-Chiari syndrome), the inferior vena cava, or, less commonly, within the liver (e.g., venoocclusive disease). When cirrhosis is complicated by portal hypertension, the increased resistance is usually *sinusoidal*. While distinctions between pre-, post-, and sinusoidal processes are conceptually appealing, functional resistance to portal flow in a given patient may occur at more than one level. Portal hypertension may also arise from increased blood flow (e.g., massive splenomegaly or arteriovenous fistulas), but the low outflow resistance of the normal liver makes this a rare clinical problem.

Cirrhosis is the most common cause of portal hypertension in the United States. Clinically significant portal hypertension is present in >60% of patients with cirrhosis. *Portal vein obstruction* is the second most common cause; it may be idiopathic or occur in association with cirrhosis, infection, pancreatitis, or abdominal trauma. Idiopathic portal vein thrombosis may develop in a variety of hypercoagulable states including polycythemia vera; essential thrombocythemia; deficiencies of protein C, protein S, or antithrombin III; resistance to activated protein C (factor V Leiden); and a mutation of the prothrombin gene (G20210A). Most of the remaining patients with idiopathic cases have a subclinical myeloproliferative disorder. Hepatic vein thrombosis (Budd-Chiari syndrome) and hepatic venoocclusive disease are relatively infrequent causes of portal hypertension (see above). Portal vein occlusion may result in massive hematemesis from gastroesophageal varices, but ascites is usually found only when cirrhosis is present. Noncirrhotic portal fibrosis (Table 289-2) accounts for only a few cases of portal hypertension.

Clinical Features

The major clinical manifestations of portal hypertension include hemorrhage from gastroesophageal varices, splenomegaly with hypersplenism, ascites, and acute and chronic hepatic encephalopathy. These are related, at least in part, to the development of portal-systemic collateral channels. The absence of valves in the portal venous system facilitates retrograde (hepatofugal) blood flow from the high-pressure portal venous system to the lower-pressure systemic venous circulation. Major sites of collateral flow involve the veins around the cardioesophageal junction (esophagogastric varices), the rectum

(hemorrhoids), retroperitoneal space, and the falciform ligament of the liver (periumbilical or abdominal wall collaterals). Abdominal wall collaterals appear as tortuous epigastric vessels that radiate from the umbilicus toward the xiphoid and rib margins (caput medusae).

A frequent marker of the presence of cirrhosis in a patient being followed for chronic liver disease is a progressive decrease in platelet count. A low-normal platelet count can be the first clue to progression to cirrhosis. Ultimately, a marked decrease in platelets (to 30,000 to 60,000/ μL) and white blood cells can occur.

Diagnosis

In patients with known liver disease, the development of portal hypertension is usually revealed by the appearance of splenomegaly, ascites, encephalopathy, and/or esophageal varices. Conversely, the finding of any of these features should prompt evaluation of the patient for the presence of underlying portal hypertension and liver disease. Varices are most reliably documented by fiberoptic esophagoscopy; their presence lends indirect support to the diagnosis of portal hypertension. Magnetic resonance imaging and intravenous contrast computed tomography are also sensitive tools for detection of the collateral circulation of portal hypertension. Although rarely necessary, portal venous pressure may be measured directly by percutaneous transhepatic "skinny needle" catheterization or indirectly through transjugular cannulation of the hepatic veins. Both free and wedged hepatic vein pressure should be measured. While the latter is elevated in sinusoidal and postsinusoidal portal hypertension, including cirrhosis, this measurement is usually normal in presinusoidal portal hypertension. In patients in whom additional information is necessary (e.g., preoperative evaluation before portal-systemic shunt surgery) or when percutaneous catheterization is not feasible, mesenteric and hepatic angiography may be helpful. Particular attention should be directed to the venous phase to assess the patency of the portal vein and the direction of portal blood flow.

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TREATMENT

Although treatment is usually directed toward a specific complication of portal hypertension, attempts are sometimes made to reduce the pressure in the portal venous system. Surgical decompression procedures have been used for many years to lower portal pressure in patients with bleeding esophageal varices (see below). However, portal-systemic shunt surgery does not result in improved survival rates in patients with cirrhosis. Decompression can now be accomplished without surgery through the percutaneous placement of a portal-systemic shunt, termed a *transjugular intrahepatic portosystemic shunt (TIPS)*. β -Adrenergic blockade with nonselective agents such as propranolol or nadolol reduces portal pressure through vasoconstrictive effects on both the splanchnic arterial bed and the portal venous system in combination with reduced cardiac output. Such therapy has been shown to be effective in preventing both a first variceal bleed and subsequent episodes after an initial bleed. Treatment of patients with clinically significant sequelae of portal hypertension, especially variceal bleeding, is titrated to reduce the hepatic venous pressure gradient

(HVPG = wedged hepatic venous pressure - free hepatic venous pressure) to <12 mmHg or by 20% from baseline. When the HVPG is not available or feasible, reduction of resting pulse by 25% is reasonable if no contraindications to therapy exist.

Vigorous treatment of patients with alcoholic hepatitis and cirrhosis, chronic active hepatitis, or other liver diseases may lead to a fall in portal pressure and to a reduction in variceal size. In general, however, portal hypertension due to cirrhosis is not reversible. In appropriately selected patients, hepatic transplantation will be beneficial.

VARICEAL BLEEDING

Pathogenesis

While vigorous hemorrhage may arise from any portal-systemic venous collaterals, bleeding is most common from varices in the region of the gastroesophageal junction. The factors contributing to bleeding from gastroesophageal varices are not entirely understood but include the degree of portal hypertension (>12 mmHg) and the size of the varices.

Clinical Features and Diagnosis

Variceal bleeding often occurs without obvious precipitating factors and usually presents with painless but massive hematemesis with or without melena. Associated signs range from mild postural tachycardia to profound shock, depending on the extent of blood loss and degree of hypovolemia. Because patients with varices may bleed just as frequently from other gastrointestinal lesions (e.g., peptic ulcer, gastritis), exclusion of other bleeding sources is important even in patients with prior variceal hemorrhage. Endoscopy is the best approach to evaluate upper gastrointestinal hemorrhage in patients with known or suspected portal hypertension.



TREATMENT

Management of Acute Bleeding

(See Fig. 289-1) Variceal bleeding is a life-threatening emergency. Prompt estimation and vigorous replacement of blood loss to maintain intravascular volume are essential and take precedence over diagnostic studies and more specific intervention to stop the bleeding. However, excessive fluid administration can increase portal pressure with resultant further bleeding and should therefore be avoided. Replacement of clotting factors with fresh-frozen plasma is important in patients with coagulopathy. Patients are best managed in an intensive care unit and require close monitoring of central venous or pulmonary capillary wedge pressures, urine output, and mental status. When the patient is hemodynamically stable, attention should be directed toward specific diagnostic studies (especially endoscopy) and other therapeutic modalities to prevent further or recurrent bleeding.

FIGURE 289-1 Approach to the patient with bleeding esophageal varices. Use of a beta blocker is the only intervention demonstrated to offer prophylactic benefit in a patient who has never bled.

TIPS, transjugular intrahepatic portosystemic shunt; HVPG, hepatic venous pressure gradient.

About half of all episodes of variceal hemorrhage cease without intervention, although the risk of rebleeding is very high. The medical management of acute variceal hemorrhage includes the use of vasoconstrictors (somatostatin/octreotide or vasopressin), balloon tamponade, and endoscopic variceal ligation (EVL) or sclerosis of varices (sclerotherapy). Intravenous infusion of *vasopressin* at a rate of 0.1 to 0.4 U/min results in generalized vasoconstriction leading to diminished blood flow in the portal venous system. Intravenous infusion of vasopressin is as effective as selective intraarterial administration. Control of bleeding can be achieved in up to 80% of cases, but bleeding recurs in more than half after the vasopressin is tapered and discontinued. Furthermore, a number of serious side effects, including cardiac and gastrointestinal tract ischemia, acute renal failure, and hyponatremia, may be associated with vasopressin therapy. Concurrent use of venodilators such as nitroglycerin as an intravenous infusion or isosorbide dinitrate sublingually may enhance the effectiveness of vasopressin and reduce complications. *Somatostatin* and its analogue, *octreotide*, are direct splanchnic vasoconstrictors. In some studies somatostatin, given as an initial 250- μ g bolus followed by constant infusion (250 μ g/h), has been found to be as effective as vasopressin. Octreotide at doses of 50 to 100 μ g/h is also effective. These agents are preferable to vasopressin, offering equivalent efficacy with fewer complications. If bleeding is too vigorous or endoscopy is not available, *balloon tamponade* of the bleeding varices may be accomplished with a triple-lumen (Sengstaken-Blakemore) or four-lumen (Minnesota) tube with esophageal and gastric balloons. Because of the high risk of aspiration, endotracheal intubation should be performed prior to placing one of these tubes. After the tube is introduced into the stomach, the gastric balloon is inflated and pulled back into the cardia of the stomach. If bleeding does not stop, the esophageal balloon is inflated for additional tamponade. Complications occur in 15% or more of patients and include aspiration pneumonitis as well as esophageal rupture.

Where available, *endoscopic intervention* should be employed as the first-line treatment to control bleeding acutely (Chaps. 37 and 272). EVL, in which esophageal varices are ligated and strangulated by endoscopically placed small elastic O-rings, has generally supplanted endoscopic injection of sclerosants in the control of acute variceal bleeding. EVL controls acute bleeding in up to 90% of cases and should be repeated until obliteration of all varices is accomplished.

Surgical treatment of portal hypertension and variceal bleeding involves the creation of a portal-systemic shunt to permit decompression of the portal system. Two types of portal systemic shunts have been used: nonselective shunts, to decompress the entire portal system, and selective shunts, intended to decompress only the varices while maintaining blood flow to the liver itself. Nonselective shunts include end-to-side or side-to-side portacaval and proximal splenorenal anastomoses; selective shunts include the distal splenorenal shunt. Nonselective shunts are more likely to be complicated by encephalopathy than selective shunts. Emergency portal-systemic nonselective shunts

may control acute hemorrhage, but such surgery is usually used only as a last resort because early operative mortality can be high.

In TIPS, a technique developed to create a portal-systemic shunt by a percutaneous approach, an expandable metal stent is advanced under angiographic guidance to the hepatic veins and then through the substance of the liver to create a direct portacaval channel. This technique offers an alternative to surgery for refractory bleeding due to portal hypertension. However, stents frequently undergo stenosis or become occluded over a period of months, necessitating revision, a second TIPS, or an alternative approach. Encephalopathy may occur after TIPS, just as in the surgical shunts, and is especially problematic in the elderly and those patients with preexisting encephalopathy. TIPS should be reserved for those individuals who fail endoscopic or medical management and are poor surgical risks. TIPS sometimes serves a useful role as a "bridge" for those patients with end-stage cirrhosis awaiting liver transplantation. Procedures such as esophageal transection have also been advocated for the management of acute variceal bleeding, but their efficacy remains unproven, and these procedures are usually considered a last resort.

The management of bleeding gastric fundal varices, found either alone or in conjunction with esophageal varices, is more problematic, since banding and sclerotherapy are generally not effective. Vasoactive pharmacologic therapy should be instituted, but TIPS or shunt surgery should be considered because of high failure and rebleeding rates. For isolated gastric varices, splenic vein thrombosis should be specifically sought, since splenectomy is curative.

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Prevention of First Hemorrhage

Prophylactic treatment with nonselective β -adrenergic antagonists (propranolol or nadolol) in patients with large ("high-risk") varices that have never bled appears to decrease the incidence of bleeding by 40 to 50% and prolong survival. Thus, endoscopic screening for varices in patients with cirrhosis is desirable; some have suggested this should be repeated every other year.

Although prophylactic banding of esophageal varices in the absence of proven bleeding cannot yet be recommended, one report suggests that banding may be more effective than beta-blockade in primary prevention of variceal bleeding in high-risk patients.

Prevention of Recurrent Hemorrhage

Obliteration of varices by endoscopic band ligation reduces risk of recurrent hemorrhage by >50%. Pharmacologic agents also have demonstrated benefit. While the utility of beta blockers can be limited by concomitant hypotension, a number of studies demonstrate their value in secondary prevention of recurrent variceal hemorrhage. Pharmacologic and endoscopic therapy are comparable in overall reduction of rebleeding risk, but the subgroup of patients who achieve hemodynamic response to pharmacologic therapy appears to experience survival benefit.

Patients with portal hypertension in the absence of specific contraindications should be given propranolol or nadolol in doses that produce a 25% reduction in the resting heart rate or a reduction in the HVPg to 12 mmHg or 20% below baseline, where available. Propranolol may also prevent recurrent bleeding from severe portal hypertensive

gastropathy in patients with cirrhosis. The optimal combination of endoscopic and pharmacologic therapy for prevention of recurrent hemorrhage remains to be established.

The role of portal-systemic shunt surgery after initial control of bleeding by nonoperative means is also uncertain. Surgically created shunts effectively reduce the risk of recurrent hemorrhage, but the overall mortality of patients undergoing such surgery is comparable to that of unoperated patients. Although patients who have undergone portal-systemic surgery succumb to recurrent bleeding less commonly than unoperated patients, this improvement is counterbalanced by increased morbidity from encephalopathy and death from progressive liver failure. Increasingly, therapeutic portal-systemic shunts have been reserved for patients who experience further bleeding despite serial endoscopic therapy.

Portal Hypertensive Gastropathy

Although variceal hemorrhage is the most commonly encountered bleeding complication of portal hypertension, many patients will develop a congestive gastropathy due to the venous hypertension. In this condition, identified by endoscopic examination, the mucosa appears engorged and friable. Indolent mucosal bleeding occurs rather than the brisk hemorrhage typical of a variceal source. β -Adrenergic blockade with propranolol (reducing splanchnic arterial pressure as well as portal pressure) is sometimes effective in ameliorating this condition. Proton pump inhibitors or other agents useful in the treatment of peptic disease are usually not helpful.

SPLENOMEGALY

Definition and Pathogenesis

Congestive splenomegaly is common in patients with severe portal hypertension. Rarely, massive splenomegaly from nonhepatic disease leads to portal hypertension due to increased blood flow in the splenic vein.

Clinical Features

Although usually asymptomatic, splenomegaly may be massive and contribute to the thrombocytopenia or pancytopenia of cirrhosis. In the absence of cirrhosis, splenomegaly in association with variceal hemorrhage should suggest the possibility of splenic vein thrombosis.



TREATMENT

Splenomegaly usually requires no specific treatment, although massive enlargement of the spleen may occasionally necessitate splenectomy at the time of shunt surgery. However, it should be noted that splenectomy without an accompanying shunt may actually increase portal pressure, and portal vein thrombosis may result from splenectomy. Splenectomy may also be indicated if splenomegaly is the cause rather

than the result of portal hypertension (as in splenic vein thrombosis). Thrombocytopenia alone is rarely severe enough to necessitate removal of the spleen. Splenectomy should be avoided in a patient eligible for liver transplantation.

ASCITES

Definition

Ascites is the accumulation of excess fluid within the peritoneal cavity. It is most frequently encountered in patients with cirrhosis and other forms of severe liver disease, but a number of other disorders may lead to either transudative or exudative ascites (Chap. 39).

Pathogenesis

The accumulation of ascitic fluid represents a state of total-body sodium and water excess, but the event that initiates this imbalance is unclear. Three theories have been proposed (Fig. 289-2). The “underfilling” theory suggests that the primary abnormality is inappropriate sequestration of fluid within the splanchnic vascular bed due to portal hypertension and a consequent decrease in effective circulating blood volume. According to this theory, an apparent decrease in intravascular volume (underfilling) is sensed by the kidney, which responds by retaining salt and water. The “overflow” theory suggests that the primary abnormality is inappropriate renal retention of salt and water in the absence of volume depletion. A third, more attractive theory, the peripheral arterial vasodilation hypothesis, may unify the earlier theories and accounts for the constellation of arterial hypotension and increased cardiac output in association with high levels of vasoconstrictor substances that are routinely found in patients with cirrhosis and ascites. Again, sodium retention is considered secondary to arterial vascular underfilling and the result of a disproportionate increase of the vascular compartment due to arteriolar vasodilation rather than from decreased intravascular volume. According to this theory, portal hypertension results in splanchnic arteriolar vasodilation, mediated by nitric oxide, and leading to underfilling of the arterial vascular space and baroreceptor-mediated stimulation of renin-angiotensin, sympathetic output, and antidiuretic hormone release.

FIGURE 289-2 Multiple factors involved in development of ascites. Current concepts suggest that initiating factor may be primary sodium retention (“overflow”), diminished effective intravascular volume (“underfilling”), or arteriolar vasodilation (“vasodilation”). NO, nitric oxide.

Regardless of the initiating event, a number of factors contribute to accumulation of fluid in the abdominal cavity (Fig. 282-2). Elevated levels of serum epinephrine and norepinephrine have been well documented. *Increased central sympathetic outflow* is found in patients with cirrhosis and ascites but not in those with cirrhosis alone. Increased sympathetic output results in diminished natriuresis by activation

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of the renin-angiotensin system and diminished sensitivity to atrial natriuretic peptide.

Portal hypertension plays an important role in the formation of ascites by raising hydrostatic pressure within the splanchnic capillary bed. *Hypoalbuminemia* and *reduced plasma oncotic pressure* also favor the extravasation of fluid from plasma to the peritoneal cavity, and thus ascites is infrequent in patients with cirrhosis unless both portal hypertension and hypoalbuminemia are present. Hepatic lymph may weep freely from the surface of the cirrhotic liver due to distortion and obstruction of hepatic sinusoids and lymphatics and contributes to ascites formation. In contrast to the contribution of transudative fluid from the portal vascular bed, hepatic lymph may weep into the peritoneal cavity even in the absence of marked hypoproteinemia because the endothelial lining of the hepatic sinusoids is discontinuous. This mechanism may account for the high protein concentration present in the ascitic fluid of some patients with venoocclusive disease or the Budd-Chiari syndrome.

Renal factors also play an important role in perpetuating ascites. Patients with ascites fail to excrete a water load in a normal fashion. They have increased renal sodium reabsorption by both proximal and distal tubules, the latter due largely to increased plasma renin activity and secondary hyperaldosteronism. Insensitivity to circulating atrial natriuretic peptide, often present in elevated concentrations in patients with cirrhosis and ascites, may be an important contributory factor in many patients. This insensitivity has been documented in those patients with the most severely impaired sodium excretion, who typically also exhibit low arterial pressure and marked overactivity of the renin-aldosterone axis. Renal vasoconstriction, perhaps resulting from increased serum prostaglandin or catecholamine levels, may also contribute to sodium retention. Recently a role for endothelin, a potent vasoconstrictor peptide, has been proposed. While elevated levels have been reported by some, this has not been observed by others.

Clinical Features and Diagnosis

Usually ascites is first noticed by the patient because of increasing abdominal girth. More pronounced accumulation of fluid may cause shortness of breath because of elevation of the diaphragm. When peritoneal fluid accumulation exceeds 500 mL, ascites may be demonstrated on physical examination by the presence of shifting dullness, a fluid wave, or bulging flanks. Ultrasound examination, preferably with a Doppler study, can detect smaller quantities of ascites and should be performed when physical examination is equivocal or when the cause of the recent onset of ascites is not clear (e.g., exclude Budd-Chiari syndrome).



TREATMENT

(See Fig. 289-3) A thorough search should be made for precipitating factors in the patient with recent onset of or worsening ascites, e.g., excessive salt intake, medication noncompliance, superimposed infection, worsening liver disease, portal vein thrombosis, or development of hepatocellular carcinoma. When ascites develops in the setting of severe, acute liver disease, resolution of ascites is likely to follow improvement in liver function. More commonly, ascites develops in patients with stable or steadily worsening liver function. Paracentesis should usually be performed with a small-gauge needle at the time of initial evaluation or at the time of any clinical

deterioration of a cirrhotic patient with ascites. A small amount of fluid (<200 mL) should be obtained and examined for evidence of infection, tumor, or other possible causes and complications of ascites. Therapeutic intervention is indicated both to prevent potential complications and to control progressive increase in ascites, which may become pronounced enough to cause physical discomfort. For the patient with a modest accumulation, therapy can be undertaken as an outpatient and should be gentle and incremental (see below). The goal is the loss of no more than 1.0 kg/d if both ascites and peripheral edema are present and no more than 0.5 kg/d in patients with ascites alone. In some patients, particularly those with a large accumulation of fluid, it may be desirable to hospitalize the patient so that daily weights and frequent serum electrolyte levels can be monitored and compliance ensured. Although abdominal girth measurements are frequently used as an index of fluid loss, they tend to be unreliable.

FIGURE 289-3 Approach to the patient with ascites [and spontaneous bacterial peritonitis (SBP)]. PMN, polymorphonuclear leukocytes; TIPS, transjugular intrahepatic portosystemic shunt. *Calculate SAAG [serum ascites albumin gradient = serum albumin - ascites albumin (g/dL)] to confirm high gradient (>1.1 g/dL) in portal hypertension. †If PMN >250/ μ L but culture is negative = culture negative neutrocytic ascites; begin empirical antibiotic and retap at 48 h; if culture is positive but PMN < 250/ μ L normal = monomicrobial nonneutrocytic bacterascites; retap; treat if PMN > 250/ μ L: if polymicrobial infection, exclude secondary peritonitis. U_{Na} , urinary sodium; U_{Ka} , urinary potassium; BUN, blood urea nitrogen.

Salt restriction is the cornerstone of therapy. A diet containing 800 mg sodium (2 g NaCl) is often adequate to induce a negative sodium balance and permit diuresis. Response to salt restriction alone is more likely to occur if the ascites is of recent onset, the underlying liver disease is reversible, a precipitating factor can be corrected, or the patient has a high urinary sodium excretion (>25 mmol/d) and normal renal function. Fluid restriction of approximately 1000 mL/d does little to enhance diuresis but may be necessary to correct hyponatremia. If sodium restriction alone fails to result in diuresis and weight loss, diuretics should be prescribed. Because of the role of hyperaldosteronism in sustaining salt retention, spironolactone or other distal tubule-acting diuretics (triamterene, amiloride) are the drugs of choice. The development of azotemia or hyperkalemia may be limiting or even warrant a reduction in the dose of these medications. In some patients, diuresis does not occur despite maximal doses of distal tubule-acting agents because of avid proximal tubular sodium absorption. More potent, proximally acting diuretics (furosemide, bumetanide, torasemide) may be added to the regimen. Thus, spironolactone is initially given at a dose of 100 mg/d with or without furosemide, 40 mg/d, and both agents may be increased by 100- and 40-mg increments respectively: total dose should not exceed 400 mg/d and 160 mg/d, respectively. An indication of the minimum effective dose of spironolactone may be obtained by monitoring urinary electrolyte concentrations for a rise in sodium and fall in potassium concentrations, reflecting effective

competitive inhibition of aldosterone. Great caution should be exercised to avoid plasma volume depletion, azotemia, and hypokalemia, which may lead to encephalopathy.

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In patients with pronounced ascites, particularly those requiring hospitalization, large-volume paracentesis has proven to be an effective and less costly approach to initial management than prolonged bed rest and conventional diuretic treatment. In this approach, ascitic fluid is removed by peritoneal cannula using strict aseptic techniques and monitoring hemodynamic and renal function. This can be safely accomplished in a single session. Concomitant albumin replacement by intravenous infusion is prudent in the patient without peripheral edema, to avoid depleting the intravascular space and precipitating hypotension. Maintenance diuretic therapy in conjunction with sodium restriction may then be instituted to avoid recurrent ascites.

A minority of patients with advanced cirrhosis have “refractory ascites” or rapidly reaccumulate fluid after control by paracentesis. In some patients, a side-to-side *portacaval shunt* may result in improvement in ascites, although generally these patients are extremely poor surgical risks. In the past, intractable ascites has also been treated with the surgical implantation of a plastic *peritoneovenous shunt*, which has a pressure-sensitive, one-way valve allowing ascitic fluid to flow from the abdominal cavity to the superior vena cava. However, the usefulness of this technique is limited by a high rate of complications such as infection, disseminated intravascular coagulation, and thrombosis of the shunt. More recently, in selected patients, TIPS has been used effectively to control refractory ascites, although portal decompression, while mobilizing ascitic fluid, has precipitated severe hepatic encephalopathy in some patients. None of these shunts has been shown to extend life expectancy.

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Patients with ascites and cirrhosis may develop acute bacterial peritonitis without an obvious primary source of infection. Patients with advanced liver disease are particularly susceptible to SBP, which portends a poor prognosis (Chap. 112).

HEPATORENAL SYNDROME

Definition and Pathogenesis

Hepatorenal syndrome is a serious complication in the patient with cirrhosis and ascites and is characterized by worsening azotemia with avid sodium retention and oliguria in the absence of identifiable specific causes of renal dysfunction. The exact basis for this syndrome is not clear, but altered renal hemodynamics appear to be involved. There is evidence for inappropriate intense renal vasoconstriction, perhaps in response to the splanchnic vasodilation accompanying cirrhosis. The kidneys are structurally intact; urinalysis and pyelography are usually normal. Renal biopsy, although rarely needed, is also normal, and in fact, kidneys from such patients have been used successfully for renal transplantation.

CLINICAL FEATURES AND DIAGNOSIS

Worsening azotemia, hyponatremia, progressive oliguria, and hypotension are the hallmarks of the hepatorenal syndrome. This syndrome, which is distinct from prerenal azotemia, may

be precipitated by severe gastrointestinal bleeding, sepsis, or overly vigorous attempts at diuresis or paracentesis; it may also occur without an obvious cause. It is essential to exclude other causes of renal impairment often seen in these patients. These include prerenal azotemia or acute tubular necrosis due to hypovolemia (e.g., secondary to gastrointestinal bleeding or diuretic therapy) or an increased nitrogen load such as that seen as a result of bleeding. Drug nephrotoxicity is also often a consideration, particularly in the patient who has received agents such as aminoglycosides or contrast dye. The diagnosis rests on the finding of an elevated serum creatinine level [$>133 \mu\text{mol/L}$ ($>1.5 \text{ g/dL}$)] that fails to improve with volume expansion or withdrawal of diuretics, together with an unremarkable urine sediment. The diagnosis is supported by the demonstration of avid urinary sodium retention. Typically, the urine sodium concentration is $<5 \text{ mmol/L}$, a concentration lower than that generally found in uncomplicated prerenal azotemia.



TREATMENT

Treatment is usually unsuccessful. Although some patients with hypotension and decreased plasma volume may respond to infusions of salt-poor albumin, volume expansion must be undertaken with caution to avoid precipitating variceal bleeding. Vasodilator therapy, including intravenous infusions of low dose dopamine, is not effective. Evidence for the benefit of systemic vasoconstrictors alone or in combination with other agents such as terlipressin, norepinephrine with albumin, and octreotide with midodrine has emerged recently, but additional study is needed. While TIPS has been reported to improve renal function in some patients, its use cannot be recommended. In appropriate candidates, the treatment of choice for hepatorenal syndrome is liver transplantation. In patients with spontaneous bacterial peritonitis, early intravenous albumin infusion can prevent development of hepatorenal syndrome in some patients.

HEPATIC ENCEPHALOPATHY

Definition

Hepatic (portal-systemic) encephalopathy is a complex neuropsychiatric syndrome characterized by disturbances in consciousness and behavior, personality changes, fluctuating neurologic signs, asterixis or “flapping tremor,” and distinctive electroencephalographic changes. Encephalopathy may be *acute* and reversible or *chronic* and progressive. In severe cases, irreversible coma and death may occur. Acute episodes may recur with variable frequency.

Pathogenesis

The specific cause of hepatic encephalopathy is unknown. The most important factors in the pathogenesis are severe hepatocellular dysfunction and/or intrahepatic and extrahepatic shunting of portal venous blood into the systemic circulation so that the liver is largely bypassed. As a result of these processes, various toxic substances absorbed from the intestine are not detoxified by the liver and lead to metabolic abnormalities in the central nervous system (CNS). *Ammonia* is the substance most often incriminated in the

pathogenesis of encephalopathy. Many, but not all, patients with hepatic encephalopathy have elevated blood ammonia levels, and recovery from encephalopathy is often accompanied by declining blood ammonia levels. Other compounds and metabolites that may contribute to the development of encephalopathy include mercaptans (derived from intestinal metabolism of methionine), short-chain fatty acids, and phenol. *False neurochemical transmitters* (e.g., octopamine), resulting in part from alterations in plasma levels of aromatic and branched-chain amino acids, may also play a role. An increase in the permeability of the blood-brain barrier to some of these substances may be an additional factor involved in the pathogenesis of hepatic encephalopathy. Several observations suggest that excessive concentrations of γ -aminobutyric acid (GABA), an inhibitory neurotransmitter, in the CNS are important in the reduced levels of consciousness seen in hepatic encephalopathy. Increased CNS GABA may reflect failure of the liver to extract precursor amino acids efficiently or to remove GABA produced in the intestine. In support of this, there is also evidence to suggest that endogenous benzodiazepines, which act through the GABA receptor, may contribute to the development of hepatic encephalopathy. This evidence includes isolation of 1,4-benzodiazepines from brain tissue of patients with fulminant hepatic failure as well as the partial response observed in some patients and experimental animals after administration of flumazenil, a benzodiazepine antagonist. However, the inconsistent effect of flumazenil in patients with encephalopathy, as well as potential methodologic pitfalls in the measurement of endogenous benzodiazepines, preclude definitive attribution of a role to these substances in the pathogenesis of hepatic encephalopathy. The finding of direct enhancement of GABA receptor activation by ammonia suggests that several of the factors described above may be operating via a final common pathway to produce the neuronal depression of hepatic encephalopathy. Finally, the observation of hyperintensity in the basal ganglia by magnetic resonance imaging in cirrhotic patients suggests that excessive *manganese* deposition

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may also contribute to the pathogenesis of hepatic encephalopathy. Further studies are needed to determine whether chelation therapy exerts long-term benefit.

In the patient with otherwise stable cirrhosis, hepatic encephalopathy often follows a clearly identifiable precipitating event (Table 289-3). Perhaps the most common predisposing factor is *gastrointestinal bleeding*, which leads to an increase in the production of ammonia and other nitrogenous substances, which are then absorbed. Similarly, *increased dietary protein* may precipitate encephalopathy as a result of increased production of nitrogenous substances by colonic bacteria. *Electrolyte disturbances*, particularly hypokalemic alkalosis secondary to overzealous use of diuretics, vigorous paracentesis, or vomiting, may precipitate hepatic encephalopathy. Systemic alkalosis causes an increase in the amount of nonionic ammonia (NH_3) relative to ammonium ions (NH_4). Only nonionic (uncharged) ammonia readily crosses the blood-brain barrier and accumulates in the CNS. Hypokalemia also directly stimulates renal ammonia production. Injudicious use of CNS-depressing drugs (e.g., barbiturates, benzodiazepines) and acute infection may trigger or aggravate hepatic encephalopathy, although the mechanisms involved are not clear. Other potential precipitating factors include superimposed acute viral hepatitis, alcoholic hepatitis, extrahepatic bile duct obstruction, constipation, surgery, and other coincidental medical complications.

TABLE 289-3 Common Precipitants of Hepatic Encephalopathy

<p>Increased nitrogen load</p> <p>Gastrointestinal bleeding</p> <p>Excess dietary protein</p> <p>Azotemia</p> <p>Constipation</p> <p>Electrolyte and metabolic imbalance</p> <p>Hypokalemia</p> <p>Alkalosis</p> <p>Hypoxia</p> <p>Hyponatremia</p> <p>Hypovolemia</p> <p>Drugs</p> <p>Narcotics, tranquilizers, sedatives</p> <p>Diuretics (see "Electrolyte imbalance")</p> <p>Miscellaneous</p> <p>Infection</p> <p>Surgery</p> <p>Superimposed acute liver disease</p> <p>Progressive liver disease</p> <p>Portal-systemic shunts</p>

Hepatic encephalopathy has protean manifestations, and any neurologic abnormality, including focal deficits, may be encountered. In patients with acute encephalopathy, neurologic deficits are completely reversible upon correction of underlying precipitating factors and/or improvement in liver function, but in patients with chronic encephalopathy, the deficits may be irreversible and progressive. Cerebral edema is frequently present and contributes to the clinical picture and overall mortality in patients with both acute and chronic encephalopathy.

The diagnosis of hepatic encephalopathy should be considered when four major factors are present: (1) acute or chronic hepatocellular disease and/or extensive portal-systemic collateral shunts (the latter may be either spontaneous, e.g., secondary to portal hypertension, or mechanically created, e.g., TIPS); (2) disturbances of awareness and mentation, which may progress from forgetfulness and confusion to stupor and finally coma; (3) shifting combinations of neurologic signs, including asterixis, rigidity, hyperreflexia, extensor plantar signs, and rarely, seizures; and (4) a characteristic (but nonspecific) symmetric, high-voltage, triphasic slow-wave (2 to 5 per second) pattern on the electroencephalogram. Asterixis ("liver flap," "flapping tremor") is a nonrhythmic asymmetric lapse in voluntary sustained position of the extremities, head, and trunk. It is best demonstrated by having the patient extend the arms and dorsiflex the hands. Because elicitation of asterixis depends on sustained voluntary muscle contraction, it is not present in the comatose patient. Asterixis is nonspecific and also occurs in patients with other

forms of metabolic brain disease. Disturbances of sleep with reversal of sleep/wake cycles are among the earliest signs of encephalopathy. Alterations in personality, mood disturbances, confusion, deterioration in self-care and handwriting, and daytime somnolence are additional clinical features of encephalopathy. *Fetor hepaticus*, a unique musty odor of the breath and urine believed to be due to mercaptans, may be noted in patients with varying stages of hepatic encephalopathy.

Grading or classifying the stages of hepatic encephalopathy is often helpful in following the course of the illness and assessing response to therapy. One useful classification is shown in Table 289-4.

TABLE 289-4 Clinical Stages of Hepatic Encephalopathy

Stage	Mental Status	Asterixis	EEG
I	Euphoria or depression, mild confusion, slurred speech, disordered sleep	+/-	Triphasic waves
II	Lethargy, moderate confusion	+	Triphasic waves
III	Marked confusion, incoherent speech, sleeping but arousable	+	Triphasic waves
IV	Coma; initially responsive to noxious stimuli, later unresponsive	-	Delta activity

The diagnosis of hepatic encephalopathy is usually one of exclusion. There are no diagnostic liver function test abnormalities, although an elevated serum ammonia level in the appropriate clinical setting is highly suggestive of the diagnosis. Examination of the cerebrospinal fluid is unremarkable, and computed tomography of the brain shows no characteristic abnormalities until late in stage IV when cerebral edema may supervene. A number of conditions, particularly disorders related to acute and chronic alcoholism, can mimic the clinical features of hepatic encephalopathy. These include acute alcohol intoxication, sedative overdose, delirium tremens, Wernicke's encephalopathy, and Korsakoff's psychosis (Chap. 361). Subdural hematoma, meningitis, and hypoglycemia or

other metabolic encephalopathies must also be considered, especially in patients with alcoholic cirrhosis. In young patients with liver disease and neurologic abnormalities, Wilson's disease should be excluded.

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TREATMENT

(See Fig. 289-4) Early recognition and prompt treatment of hepatic encephalopathy are essential. Patients with acute, severe hepatic encephalopathy (stage IV) require the usual supportive measures for the comatose patient. Specific treatment of hepatic encephalopathy is aimed at (1) elimination or treatment of precipitating factors and (2) lowering of blood ammonia (and other toxin) levels by decreasing the absorption of protein and nitrogenous products from the intestine. In the setting of acute gastrointestinal bleeding, blood in the bowel should be promptly evacuated with laxatives (and enemas if necessary) in order to reduce the nitrogen load. Protein should be excluded from the diet, and constipation should be avoided. Ammonia absorption can be decreased by the administration of lactulose, a nonabsorbable disaccharide that acts as an osmotic laxative. Metabolism of lactulose by colonic bacteria may also result in an acid pH that favors conversion of ammonia to the poorly absorbed ammonium ion. In addition, lactulose may actually diminish ammonia production through its direct effects on bacterial metabolism. Acutely, lactulose syrup can be administered in a dose of 30 to 60 mL every hour until diarrhea occurs; thereafter the dose is adjusted (usually 15 to 30 mL three times daily) so that the patient has two to four soft stools daily. Intestinal ammonia production by bacteria can also be decreased by oral administration of a "nonabsorbable" antibiotic such as neomycin (0.5 to 1.0 g every 6 h). However, despite poor absorption, neomycin may reach sufficient concentrations in the bloodstream to cause renal toxicity. Equal benefits may be achieved with broad-spectrum antibiotics such as metronidazole. Flumazenil, a short-acting benzodiazepine antagonist, may have a role in management of hepatic encephalopathy precipitated by use of benzodiazepines, if there is a need for urgent therapy. Hemoperfusion to remove toxic substances and therapy directed primarily toward coincident cerebral edema in acute encephalopathy are also of unproven value. The efficacy of extracorporeal liver assist devices employing hepatocytes of porcine or human origin to bridge patients to recovery or transplantation is as yet unproven but is currently being studied.

FIGURE 289-4 Approach to the patient with hepatic encephalopathy. BUN, blood urea nitrogen.

Chronic encephalopathy may be effectively controlled by administration of lactulose. Management of patients with chronic encephalopathy should include dietary protein restriction (usually to 60 g/d) in combination with low doses of lactulose or neomycin. Nephrotoxicity or ototoxicity may be limiting in prolonged usage of neomycin. There are suggestions that vegetable protein may be preferable to animal protein.

OTHER SEQUELAE OF CIRRHOSIS

Coagulopathy

Patients with cirrhosis often demonstrate a variety of abnormalities in both cellular and humoral clotting function. Thrombocytopenia may result from hypersplenism. In the alcoholic patient, there may be direct bone marrow suppression by ethanol. Diminished protein synthesis may lead to reduced production of fibrinogen (factor I), prothrombin (factor II), and factors V, VII, IX, and X. Reduction in levels of all factors except factor V may be worsened by the coincident malabsorption of the fat-soluble cofactor vitamin K due to cholestasis (Chap. 275). Of these, factor VII appears to be pivotal. In cirrhosis, it is the first of the factors to become depleted and, because of its short half-life, replacement with plasma often fails to correct an elevated prothrombin time. Preliminary studies suggest that selective replacement of factor VII can correct the prothrombin time in patients with cirrhosis.

Hepatocellular Carcinoma

See Chap. 78.

HYPOXEMIA AND HEPATOPULMONARY SYNDROME

Definition and Pathogenesis

Mild hypoxemia occurs in approximately one-third of patients with chronic liver disease. The hepatopulmonary syndrome is typically manifest by hypoxemia, platypnea, and orthodeoxia. Hypoxemia usually results from right-to-left intrapulmonary shunts through dilatations in intrapulmonary vessels that can be detected by contrast-enhanced echocardiography or a macroaggregated albumin lung perfusion scan. The mechanisms of shunt formation are unclear, but one animal model suggests that endothelin-1 levels and pulmonary nitric oxide, raised in cirrhosis, correlate with degree of shunting.



TREATMENT

No specific treatment is consistently effective, though large arteriovenous shunts may be embolized. It is now increasingly recognized that liver transplantation may eventually lead to amelioration of the hepatopulmonary syndrome in cases that have not yet been complicated by advanced pulmonary hypertension.

FURTHER READING

DIXON JB et al: Nonalcoholic fatty liver disease: Predictors of nonalcoholic steatohepatitis and liver disease in the severely obese. *Gastroenterology* 121:91, 2001

DUVOUX C et al: Effects of noradrenaline and albumin in patients with type I

hepatorenal syndrome: A pilot study. *Hepatology* 36:374, 2002

KAPLAN MM et al: Medical progress: Primary biliary cirrhosis. *N Engl J Med* 335:1570, 1996

McCULLOUGH AJ, O'CONNOR JFB: Alcoholic liver disease: Recommendations for the American College of Gastroenterology. *Am J Gastroenterol* 93:2022, 1998

RIORDAN SM, WILLIAMS R: Treatment of hepatic encephalopathy. *N Engl J Med* 337:473, 1997

RUNYON BA et al: Management of adult patients with ascites caused by cirrhosis. *Hepatology* 27:264, 1998

SHARARA AI et al: Gastroesophageal variceal hemorrhage. *N Engl J Med* 345: 669, 2001

VILLANUEVA C et al: Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med* 345:647, 2001

BIBLIOGRAPHY

Alcoholic, Postnecrotic, and Cryptogenic Cirrhosis

BROWN J et al: Seroprevalence of hepatitis C virus nucleocapsid antibodies in patients with cryptogenic chronic liver disease. *Hepatology* 15:175, 1992

CALDWELL H et al: Cryptogenic cirrhosis: Clinical characterization and risk factors for underlying disease. *Hepatology* 29:664, 1999

DUFOUR JF et al: Regression of hepatic fibrosis in hepatitis C with long-term interferon treatment. *Dig Dis Sci* 43:2573, 1998

FRIEDMAN SL: The cellular basis of hepatic fibrosis. *N Engl J Med* 328:1828, 1993

JEFFERS LJ et al: Prevalence of antibodies to hepatitis C virus among patients with cryptogenic chronic hepatitis and cirrhosis. *Hepatology* 15:187, 1992

LIEBER CS: Alcohol and the liver: 1994 update. *Gastroenterology* 106:1085, 1994

MATO JM et al: S-adenosylmethionine in alcoholic liver cirrhosis: A randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol* 6:1081, 1999

MATTEONI CA et al: Nonalcoholic fatty liver disease: A spectrum of clinical and pathologic severity. *Gastroenterology* 116:1413, 1999

Biliary and Cardiac Cirrhosis

BEUERS U et al: Ursodeoxycholic acid in cholestasis: Potential mechanisms of action and therapeutic applications. *Hepatology* 28:1449, 1998

BONIS P et al: Methotrexate improves biochemical tests in patients with primary biliary cirrhosis who respond incompletely to ursodial. *Gastroenterology* 117:400, 1999

BONNAND AM et al: Clinical significance of serum bilirubin levels under ursodeoxycholic acid therapy in patients with primary biliary cirrhosis. *Hepatology* 29:39, 1999

CHRISTENSEN E et al: Updating prognosis in primary biliary cirrhosis using a time-dependent Cox regression model. *Gastroenterology* 105:1865, 1993

CORPECHOT C et al: The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. *Hepatology* 32:1196, 2000

DICKSON ER et al: Prognosis in primary biliary cirrhosis: Model for decision making. *Hepatology* 10:1, 1989

FREGEAU DR et al: Antimitochondrial antibodies of primary biliary cirrhosis recognize dihydrolipoamide acyltransferase and inhibit enzyme function of the branched chain-ketoacid dehydrogenase complex. *J Immunol* 142:3815, 1989

LOCKE GR III et al: Time course of histological progression in primary biliary cirrhosis. *Hepatology* 23:52, 1996

MARKUS BH et al: Efficacy of liver transplantation in patients with primary biliary

cirrhosis. N Engl J Med 320:1709, 1989

MATTALIA A et al: Characterization of antimitochondrial antibodies in healthy adults. Hepatology 27:656, 1998

OKUDA K et al: Proposal of a new nomenclature for Budd-Chiari syndrome: Hepatic vein thrombosis versus thrombosis of the inferior vena cava at its hepatic portion. Hepatology 28:1191, 1998

POUPON RE et al: Ursodiol for the long-term treatment of primary biliary cirrhosis. N Engl J Med 330:1342, 1994

POUPON RE et al: Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 113:884, 1997

SZOSTECKI C et al: Autoantibodies against "nuclear dots" in primary biliary cirrhosis. Semin Liver Dis 17:71, 1997

TSUNEYAMA K et al: Abnormal expression of the E2 component of the pyruvate dehydrogenase complex on the luminal surface of biliary epithelium before major histocompatibility complex class II and BB1/BB7 expression. Hepatology 21:103, 1995

WOLFHAGEN FH et al: Oral naltrexone treatment for cholestatic pruritus: A double-blind, placebo-controlled study. Gastroenterology 113:1264, 1997

Hepatic Encephalopathy

BASILE AS, JONES EA: Ammonia and GABAergic neurotransmission: Interrelated factors in the pathogenesis of hepatic encephalopathy. Hepatology 25:1303, 1997

JALAN R et al: Review article: Pathogenesis and treatment of chronic hepatic encephalopathy. Aliment Pharmacol Ther 10:681, 1996

JONES EA et al: The neurobiology of hepatic encephalopathy. Hepatology 4:1235, 1984

KRIEGER D et al: Manganese and chronic hepatic encephalopathy. Lancet 346:270, 1995

MORGAN MY, HAWLEY KE: Lactitol vs. lactulose in the treatment of acute hepatic encephalopathy in cirrhotic patients: A double-blind randomized study. *Hepatology* 7:1278, 1987

Variceal Hemorrhage

BERNARD B et al: Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: A meta-analysis. *Hepatology* 25:63, 1997

CELLO JP et al: Endoscopic sclerotherapy compared with percutaneous transjugular intrahepatic portosystemic shunt after initial sclerotherapy in patients with acute variceal hemorrhage. *Ann Intern Med* 126:858, 1997

GARCIA-VILLARREAL L et al: Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal rebleeding after recent variceal hemorrhage. *Hepatology* 29:27, 1999

GRACE ND: Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. *Am J Gastroenterol* 92:1081, 1997

LAINE L et al: Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: A meta-analysis. *Ann Intern Med* 123:280, 1995

LAINE L et al: Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med* 119:1, 1993

LO G-H et al: A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. *Hepatology* 22:466, 1995

SANYAL AJ et al: Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage. *Ann Intern Med* 126:849, 1997

SARIN SK et al: Comparison of endoscopic ligation and propranolol for the primary prevention of variceal hemorrhage. *N Engl J Med* 340:988, 1999

SARIN SK et al: Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 340:988, 1999

SUNG JJY et al: Octreotide infusion or emergency sclerotherapy for variceal haemorrhage. Lancet 342:637, 1993

Portal Hypertension and Ascites

ANGELI P et al: Reversal of type I hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 6:1690, 1999

ARROYO V et al: Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 23:164, 1996

ARROYO V, GINÉS P: Arteriolar vasodilation and the pathogenesis of the hyperdynamic circulation and renal sodium and water retention in cirrhosis. Gastroenterology 102:1077, 1992

CHAMOUARD P et al: Frequent factor II G20210A mutation in idiopathic portal vein thrombosis. Gastroenterology 116:144, 1999

CHUNG RT et al: Complications of chronic liver disease. Crit Care Clin 11:431, 1995

D'AMICO G et al: The treatment of portal hypertension: A meta-analytic review. Hepatology 22:332, 1995

FLORAS JS et al: Increased sympathetic outflow in cirrhosis and ascites: Direct evidence from intraneural recordings. Ann Intern Med 114:373, 1991

GINÉS P et al: Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites: Results of a randomized study. Gastroenterology 93:234, 1987

GINÉS P et al: Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 105:229, 1993

GINÉS P et al: Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. N Engl J Med 325:829, 1991

MARTIN P-Y et al: Nitric oxide as a mediator of hemodynamic abnormalities and salt

and water retention in cirrhosis. N Engl J Med 339:533, 1998

OCHS A et al: The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. N Engl J Med 332:1192, 1995

PINTO PC et al: Large-volume paracentesis in nonedematous patients with tense ascites: Its effect on intravascular volume. Hepatology 8:207, 1988

RING EJ et al: Using transjugular intrahepatic portosystemic shunts to control variceal bleeding before liver transplantation. Ann Intern Med 116:304, 1992

SHIFFMAN ML et al: The role of transjugular intrahepatic portosystemic shunt for treatment of portal hypertension and its complications: A conference sponsored by the National Digestive Diseases Advisory Board. Hepatology 22:1591, 1995

SORT P et al: Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 341:403, 1999

STANLEY AJ et al: Long-term follow of transjugular intrahepatic portosystemic stent shunt (TIPS) for the treatment of portal hypertension: Results in 130 patients. Gut 39:479, 1996

STIEGMANN GV et al: Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med 326:1527, 1992

Spontaneous Bacterial Peritonitis

CHANG C et al: Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology 28:1187, 1998

Other Complications of Cirrhosis

ABRAMS GA et al: Use of macroaggregated albumin lung scan to diagnose hepatopulmonary syndrome: A new approach. Gastroenterology 114:305, 1998

BERNSTEIN DE et al: Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: A preliminary study. Gastroenterology 113:1930, 1997

LUO B et al: Endothelin-1 in the rat bile duct ligation model of hepatopulmonary syndrome: Correlation with pulmonary dysfunction. J Hepatol 29:571, 1998

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