TOPIC IN REVIEW

Cirrhosis of liver

B. S. Anand
Department of Medicine
Baylor College of Medicine and Digestive Diseases Section (111D)
VA Medical Center
2002 Holcombe Blvd.
Houston, TX 77030

Correspondence to:
B.S. Anand
anaO@flash

DEFINITION

The term "cirrhosis" is derived from the Greek work *kirrhos,* meaning "tawny" and referring to the tan color of the liver. Cirrhosis is a histologic diagnosis, based on three essential criteria: diffuse disease, presence of fibrosis, and replacement of normal architecture by abnormal nodules. The initial step is deposition of fibrous tissue at sites of liver cell necrosis, which in the initial stages links portal and central areas or one portal/central area with another. As the disease advances, the fibrous bands become wider and denser, enclosing islands of hepatocytes. These islands, or nodules, are called "pseudolobules" because the normal lobular architecture is lost. Depending upon their size, the defect is termed as "macronodular" (>3 mm in diameter) or "micronodular cirrhosis." The histologic abnormality should involve the entire liver, since localized defects such as focal nodular hyperplasia do not constitute cirrhosis. It should be noted that while fibrosis is a reversible process, cirrhosis is not.

METHODS

The article essentially reflects my practice, amplified by reviews of the latest literature, culled from various sources.

EPIDEMIOLOGY AND PREVALENCE

The exact prevalence of cirrhosis is not known because the disease is often silent. Nearly 30% to 40% of cases are discovered at autopsy, indicating that in a substantial proportion of people, the disease goes undetected during life.[1] The number of deaths from cirrhosis in the United States varies from 12 to 15 per 100,000 population. The death rate dropped sharply to between 7 and 8 during Prohibition (1916-1932), but returned to the baseline after Prohibition laws were withdrawn.[2]

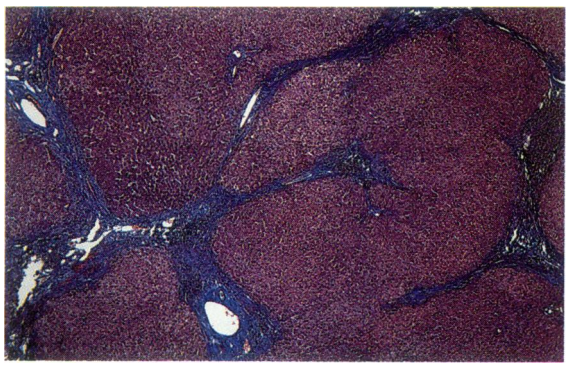

Figure 1 *Cirrhosis of liver. Broad fibrous bands are seen connecting portal tracts and central veins, resulting in the formation of pseudolobules (trichrome stain, x10).*

Summary Points

- The main challenge is to prevent progression to cirrhosis and then, in patients with cirrhosis, to minimize complications.
- Patients with abnormal liver tests should have a basic minimum diagnostic workup. Early diagnosis allows a chance for complete recovery in several diseases.
- Family physicians play a crucial role in prevention. Emphasis should be placed on avoidance of toxins (alcohol, drugs); use of safety measures against transmissible agents (HBV, HCV); and family screening for hereditary illnesses.
- Antiviral drugs have improved the outcome of HBV and HCV infections and should be used in all patients who qualify for this therapy.
- Complications such as variceal bleeding can be effectively controlled and prevented by endoscopic and drug therapies.
- Liver transplantation is the only definitive treatment for end-stage liver disease. Patients should be referred to a specialist before irreversible complications set in.

CLASSIFICATION

Several classifications have been devised, including morphological (macronodular and micronodular); histologic (posthepatitic, postnecrotic); etiological (viral, alcoholic); and clinical (compensated or decompensated cirrhosis). From a practical viewpoint, the most useful classification incorporates the latter two categories. Thus a complete diagnosis should state the cause of liver disease (e.g., alcoholic cirrhosis) and whether or not the patient has decompensated liver disease.

ETIOLOGY AND DIAGNOSIS

The causes of cirrhosis can be divided into three broad groups: hepatocellular, cholestatic, and hepatic venous outflow obstruction (see Table 1). The diagnostic and therapeutic approaches to these conditions are entirely different.

Laboratory investigations

Laboratory tests are performed to determine the presence and severity of the liver disease and to establish the etiology.

Liver tests

A predominant increase in serum aminotransferases (ALT and AST) suggests a "hepatitic" or hepatocellular disease, while a predominant increase in alkaline phosphatase indicates "cholestatic" or biliary tract abnormality. The ratio of serum AST to ALT and the level of enzyme elevation also provide useful informa-

Table 1 *Classification of cirrhosis according to etiology*

Hepatocellular	Cholestatic	Venous outflow obstruction
Viral hepatitis (B,C,D)	Biliary obstruction	Veno-occlusive disease
Alcohol	Primary biliary cirrhosis	Budd-Chiari syndrome
Autoimmune	Primary sclerosing cholangitis	Congestive heart failure
Metabolic	Drugs/toxins	Constrictive pericarditis
Steatohepatitis		Drugs/toxins
Drugs/toxins		

Drugs and toxins can cause all 3 forms of liver disease.

Table 2 *Diagnostic tests in chronic liver disease*

Hepatitic liver disease	Cholestatic liver disease	Outflow obstruction
Viral serology (HBV, HCV)	Blood tests	Imaging studies
Autoimmune (ANA, ASMA)	GGT, 5'NT, AMA	Doppler ultrasound
Hemochromatosis (iron saturation)	Imaging studies	MRI
Wilson's (ceruloplasmin, urine Cu)	Ultrasound, CT Scan, MRC	Portal/IVC venography
A1-AT deficiency (serum A1-AT)	ERCP	Cardiac catheterization
Drug and alcohol screen	Drug screen	Drug screen
Liver biopsy	Liver biopsy	Liver biopsy

ANA = antinuclear antibody; ASMA = anti–smooth muscle antibody; GGT = gamma glutamyl transpeptidase; 5'NT = 5' nucleotidase; AMA = antimitochondrial antibody; MRC = magnetic resonance cholangiogram; IVC = inferior vena cava.

tion. In hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, ALT is greater than AST; while in alcoholic liver disease, AST is greater than ALT. Serum ALT values rarely exceed 500 U/L in alcoholic liver disease; while in viral hepatitis, ALT values are often greater than 1000 U/L. The extent of enzyme elevation has no prognostic significance. Indeed, enzyme levels are often normal in cirrhosis. By contrast, abnormalities of serum albumin and prothrombin time indicate severe disease and carry a poor prognosis.

Tests to determine etiology

The type of workup is based on whether there is a hepatitic or cholestatic abnormality (Table 2). Because alkaline phosphatase is released from several organs (e.g., placenta, bone, GI tract), tests more specific for liver disease, such as gamma glutamyl transpeptidase (GGT) and 5' nucleotidase (5'NT), are performed whenever there is doubt about the diagnosis. In all forms of liver disease, liver biopsy helps to establish the diagnosis, severity, and prognosis of the disease and aids in the decision regarding use of antiviral therapy. Diagnostic tests for specific liver diseases are described under individual headings.

CLINICAL FEATURES

General

Patients with chronic liver disease and cirrhosis present in several ways.

Asymptomatic

Some patients are completely asymptomatic and the diagnosis is made incidentally on a routine blood test. These individuals may lead a normal life and die of an unrelated cause.

Vague ill health

Patients with cirrhosis, like those with other chronic disorders, often have vague symptoms such as fatigue, malaise, reduced libido, anorexia, nausea, and weight loss.

Decompensated liver disease

Advanced liver disease is indicated by the development of edema, ascites, easy bruising, and poor concentration and memory. These patients are prone to complications such as spontaneous bacterial peritonitis, portal hypertension (variceal hemorrhage), encephalopathy, hepatorenal syndrome, and liver cancer.

Physical signs

The typical physical findings are shown in Table 3. Patients with cirrhosis have a hyperdynamic circulation with tachycardia, a bounding pulse, and warm extremities. An interesting finding is the presence of orthodeoxia, or increased breathlessness (with decrease in PaO_2) in sitting or standing position but not while lying down. This defect is due to shunting of blood through collateral vessels, which are present in greater numbers in the lower lobes of the lungs. Signs of early encephalopathy should be investigated, including poor recall, inability to draw

Table 3 *Typical clinical signs in patients with cirrhosis*

Vitals	Extremities	Skin	Endocrine	Abdomen	CNS
Tachycardia	Clubbing	Petechiae	Gynecomastia	Ascites	Asterixis
↑Pulse pressure	Edema	Purpura	Testicular atrophy	Collaterales	↑Planters*
Orthodeoxia**	Ecchymosis	Hair loss	Amenorrhea	Big spleen	
Low-grade temp		Spiders		Nodular liver	
Palmar erythema				—	

* ↑Planters = upgoing planters; **orthodeoxia = decrease in PaO_2 (with shortness of breath) when patient changes from supine to standing position.

diagrams such as a star or a rectangle, and worsening handwriting. Unprovoked deterioration should prompt the search for complications such as infections, internal bleeding, renal failure, electrolyte imbalance (overenthusiastic diuresis), and hepatocellular cancer.

Associated abnormalities

Several liver diseases are associated with specific abnormalities. Patients with viral hepatitis may develop vasculitis and cryoglobulinemia (causing glomerulonephritis, peripheral neuropathy, etc.). Autoimmune hepatitis is associated with other autoimmune abnormalities. Several organ systems are involved in metabolic liver disorders.

COMPLICATIONS AND MANAGEMENT

Diet

There are no dietary restrictions in uncomplicated cirrhosis. Salt restriction is recommended once edema occurs, because patients with cirrhosis have a diminished ability to excrete sodium. Proteins are restricted only in the presence of hepatic encephalopathy.

Ascites and edema

Salt intake is restricted to 2g (88 mmol)/day. The diuretic of choice is spironolactone (Aldactone), which is combined with furosemide (Lasix) when rapid response is required. The starting dose is 100 mg spironolactone and 40 mg furosemide.[3] Weight loss should be 1 lb/day in the absence of edema, but there are no restrictions in presence of anasarca. If weight loss is suboptimal, 24-hr urine Na should be checked. A value >78 mmol/day indicates poor compliance with salt restriction. If urine Na is <20 mmol/day, the dose of diuretics should be increased by increments of 100 mg spironolactone and 40 mg furosemide to a maximum of 400 mg spironolactone and 160 mg furosemide. A third diuretic should not be added because of risk of electrolyte disturbances. Patients not responding to these measures, including more stringent salt restriction of 1g (44 mmol/day) or even 0.5 g/day (22 mmol/day), have "resistant ascites" and are candidates for liver transplantation. In the interim, large-volume paracentesis should be performed. Alternatively, peritoneo-venous shunts (LeVeen shunt, Denver shunt) may be used. Recently, transjugular intrahepatic portosystemic shunts have been employed with good results, but this indication is experimental.[4]

Spontaneous bacterial peritonitis

Patients who have cirrhosis with ascites are prone to bacterial peritonitis without a precipitating cause such as bowel perforation or intra-abdominal inflammation (diverticulitis, cholecystitis, etc.). Spontaneous bacterial peritonitis is suspected in the presence of fever, unexplained deterioration, and abdominal pain or tenderness.[5] The diagnosis is confirmed if ascitic fluid neutrophil count is >250/mm^3. The drug of choice is cefotaxime (Claforan), 1g qid for 2 weeks. Aminoquinolones (Norfloxacin, Ciprofloxacin) are also very effective.

Portal hypertension

Portal hypertension is a major complication of cirrhosis.[6] One third of patients with cirrhosis who have varices experience variceal bleeding within 2 years of diagnosis. Those who bleed have a 70% risk of rebleeding and a 30% to 50% risk of death. Acute variceal bleeding is treated with combined endoscopic (variceal sclerotherapy or banding) and drug therapy (somatostatin 50 ug/hr by continuous infusion for 5 days). Patients who continue to bleed are considered for transjugular intrahepatic portosystemic shunt or shunt surgery.[7] Since the rebleeding rate is high, some form of prophylaxis should be used, either endoscopic or drug therapy (nonselective betablockers: propranolol or nadolol) to reduce the portal pressure. Beta-blocker therapy is also useful in patients with large varices who have never experienced variceal bleeding.[8] Another complication of portal hypertension is splenomegaly and hypersplenism, which contribute to the leukopenia and thrombocytopenia in cirrhosis.

Encephalopathy

Chronic hepatic encephalopathy is characterized by mental slowing, somnolence, memory loss, flapping tremors (asterixis), and, in the late stages, coma. Treatment consists of a low-protein diet (40 g/day) and

lactulose in a dose sufficient to produce three to four bowel movements a day.[9]

Hepatorenal syndrome

Hepatorenal syndrome is defined as oliguric renal failure in patients with advanced liver disease. Typically, the urine has low Na content (<10 mEq/l). The syndrome is caused by reduced renal perfusion and glomerular filtration and is associated with a poor prognosis. There is no structural damage to the kidneys, and the syndrome is completely reversed if hepatic function is restored, such as after liver transplantation. Recently, some success has been obtained with the transjugular intrahepatic portosystemic shunt procedure.[10]

Hepatocellular carcinoma

Cirrhosis is a premalignant condition and is associated with an enhanced risk of hepatocellular cancer. Over the past two decades, the incidence of this type of cancer has increased in the United States, mainly because of the spread of HBV and HCV.[11] Preventive measures include screening with alpha-fetoprotein and ultrasonography every 6 months.

SPECIFIC LIVER DISEASES

Hepatocellular liver diseases

Viral hepatitis

Virus infections constitute the single most frequent cause of cirrhosis. Only HBV or HCV results in chronic liver disease. Hepatitis D virus is an incomplete virus that is pathogenic only in the presence of HBV. Viruses A and E cause a self-limited hepatitis that does not progress to cirrhosis. The newly identified hepatitis G virus does not produce any liver disease. HBV infection is diagnosed by the presence of hepatitis B surface antigen (HBsAg); HCV, by anti-HCV and HCV-RNA. Interferon was the first drug approved for treatment of viral hepatitis, and several preparations are in use: interferon alfa 2a (Roferon), alfa 2b (Intron), and consensus interferon (Infergen). These preparations have similar virus eradication rates and side-effect profiles. Most patients experience flulike symptoms, leukopenia, and thrombocytopenia. Less frequently, hair loss, irritability, depression, and thyroid dysfunction are seen. All adverse effects (except thyroid dysfunction) disappear when treatment stops.

Hepatitis B virus

The recommended dose of interferon is five million units daily for 16 weeks. Complete virus eradication is achieved in 20% of patients.[12] Lamivudine (Epivir), a nucleoside analogue, was recently approved for HBV.[13, 14] The response rate is similar to interferon, but lamivudine is easier to use (one 100-mg tablet/day) and is virtually free of side effects.

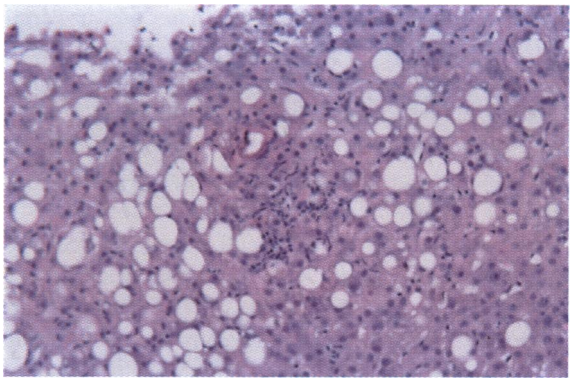

Figure 2 *Diffuse fatty liver in a chronic alcoholic; practically every hepatocyte is filled with fat (H&E stain, x10).*

Hepatitis C virus

Interferon is given in a dose of 3 million units 3 times a week for 12 to 18 months.[15-17] The virus eradication rate is 10% to 20%. In 1998 ribavirin, a guanosine analog, was approved for HCV. The combination of ribavirin and interferon results in virus eradication rates of 40%.

Vaccination

Very effective and safe vaccines are available against HAV and HBV.[18] The current recommendation is for universal vaccination against HBV, whereas HAV vaccine is used only in high-risk individuals: (1) subjects living in closed environments (such as day-care centers or institutions for the mentally or physically handicapped), homosexual men, and illicit drug users; (2) travelers to endemic areas, who receive a first dose at least 4 weeks before departure; and (3) patients with chronic liver disease.

Alcoholic liver disease

Heavy alcohol use over a prolonged time period (>5 years) may result in liver damage.[19] The critical dose

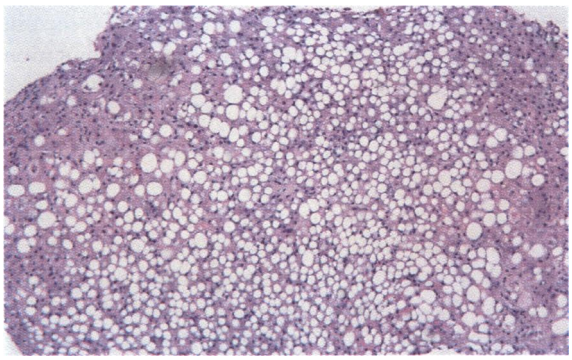

Figure 3 *Steatohepatitis. There is fatty change of the gepatocytes along with acute inflammatory cells in the center of the field (H&E, x20).*

is variable, but quantities greater than 60 g/day (four to five drinks/day, with a drink equal to one can of beer, one shot of liquor, or one glass of wine) are harmful. Only 10% of alcoholics develop liver disease. Women acquire the disease at lower dose and duration. There appears to be a genetic predisposition to alcoholic liver disease. The only effective treatment is complete abstinence. Patients with early disease (alcoholic steatosis) may recover completely. Acute alcoholic hepatitis is a serious illness that may progress despite abstinence. Treatment consists of a nutritious diet containing 1g/kg proteins (reduced to 40 g/day in presence of encephalopathy) and 2000 to 3000 calories, thiamine (100 mg), phosphorus, and magnesium. There is some evidence that prednisone (40 mg/day) is beneficial, but this treatment is controversial.

Autoimmune hepatitis

Autoimmune hepatitis occurs more frequently in women and is often associated with other autoimmune disorders such as thyroiditis, polyarthritis, polymyositis, hemolytic anemia, and glomerulonephritis. Physical signs include striae, Cushingoid features, and acne. Diagnosis is made by the presence of antinuclear and antismooth muscle antibodies and by liver biopsy. Prednisone is started at a dose of 20 to 40 mg/day, tapered off when liver tests become normal. Long-term immune suppression with azathioprine alone or with prednisone is usually required. Disease recurrences are treated with further courses of steroids.

Metabolic liver diseases

This is a group of genetic disorders, all with an autosomal recessive inheritance.

Hemochromatosis

This is the most common inherited disease of white people in the United States, affecting 1:200 to 1:400.[20] There is increased iron deposition in several organs, secondary to enhanced absorption from the bowel. The hemochromatosis gene (termed HFE gene) is seen in 85% of patients and contains a single point mutation (C282Y; cystine to tyrosine). The diagnosis is made by high iron saturation (>50% in women, >60% in men) and confirmed by liver biopsy. In addition to liver damage, there is abnormality of other organs, such as arthritis, heart failure, testicular damage, and bronzed skin. If diagnosed in time, hemochromatosis is completely treatable. Iron is removed by weekly phlebotomies until serum ferritin is <50 ng/ml and iron saturation is <50%, followed by maintenance treatment every 4 weeks. Family members are screened by serum ferritin and iron saturation values.

Wilson's disease

This disease is characterized by excess copper accumulation resulting in abnormalities of the liver, nervous system (tremors, incoordination, spasticity, seizures), arthralgia, renal tubular acidosis, hemolytic anemia, and cataracts.[21] Patients have low serum ceruloplasmin and elevated urinary copper. Treatment consists of chelation therapy with D-penicillamine or Trientrine. Patients are also given oral zinc (50 mg/day) to reduce copper absorption. The disease is curable if diagnosed in time.

A1-AT

Alpha-1 antitrypsin (A1-AT) deficiency inhibits the activity of trypsin and other proteolytic enzymes. In addition to liver damage, A1-AT patients develop emphysema, pancreatic fibrosis, and glomerulonephritis. Liver transplantation is the only treatment for this liver disease.[22]

Nonalcoholic steatohepatitis

Nonalcoholic steatohepatits is increasingly recognized as an important cause of chronic liver disease and cirrhosis. The characteristic histologic abnormality is steatosis (fat in hepatocytes) accompanied with inflammatory cells in nonalcoholic subjects. Diagnosis is made by liver biopsy. Treatment is limited to correction of any associated metabolic abnormalities (obesity, diabetes).[23]

Cholestatic liver diseases

Long-standing biliary obstruction of any etiology results in progressive liver disease and cirrhosis. A common feature is severe pruritus, often accompanied with skin excoriations.

Secondary biliary cirrhosis

This condition is seen with persistent obstruction of the bile ducts due to causes such as gallstones, strictures, and parasitic infestation.

Primary biliary cirrhosis

This is a disease of unknown etiology characterized by damage to the tiny intrahepatic bile ducts.[24] There is a 9:1 female predominance. Patients have hyperpigmentation, steatorrhea, xanthelasmas, and features of associated illnesses like scleroderma, CREST (calcinosis, Raynaud's disease, esophageal dysmotility, sclerodectly, telangiectasia) syndrome, and Sjogren's disease. Diagnosis is made by presence of antimitochondrial antibodies and liver biopsy. Ursodeoxycholic acid is the single most important treatment, improving all aspects of the disease: symptoms, liver tests, liver histology, and survival. Patients are encouraged to lead an active life and maintain good nutrition. Fat-soluble vitamins and calcium supplements are

required, especially for prevention of bone disease (osteoporosis). Treatment for pruritus is cholestyramine; other useful drugs are rifampin and naloxone (opiate antagonist).

Primary sclerosing cholangitis

Patients have fibrotic strictures of the extra- and intrahepatic bile ducts.[25] The most useful diagnostic test is endoscopic retrograde cholangiopancreatography. Associated illnesses are ulcerative colitis (seen in 75% of patients) and cholangiocarcinoma (seen in 15%). No specific medication is of benefit. Ursoedeoxycholic acid improves liver tests but does not alter the outcome. The treatment of pruritus and nutritional management are similar to primary biliary cirrhosis. Endoscopic dilatation is performed if a dominant stricture is present.

Venous outflow obstruction

Obstruction of the tiny intrahepatic veins is termed as veno-occlusive disease, seen after bone marrow transplantation (graft-to-host reaction), use of cytotoxic drugs, radiation to the liver, and consumption of Jamaican bush tea, which contains noxious pyrrolizidine alkaloids. Obstruction of the hepatic veins or of the adjacent inferior vena cava, called Budd-Chiari syndrome, is due to congenital webs or thrombosis of the vessels. Functional venous obstruction may occur in severe congestive heart failure and constrictive pericarditis, which, if not corrected, results in progressive liver failure and cirrhosis. Treatment is directed at removing the vascular obstruction or creating a surgical shunt to decompress the congested liver. Recently, good results have been obtained with the transjugular intrahepatic portosystemic shunt procedure.[26]

Drug-induced liver disease

Drugs and toxins cause a variety of liver abnormalities, including hepatocellular damage (isoniazid, methyldopa, amiodarone, and methotrexate); cholestatic liver disease (phenothiazine, estrogen, and anabolic steroids); and veno-occlusive disease (anticancer drugs).

LIVER TRANSPLANTATION

Since 1963, when the first transplant was performed, the status of liver transplantation has evolved from an experimental therapy to a life-saving procedure. The current survival rate after transplantation at 1 year and 5 years is 85% and 70%,[27] compared with 60% and 20%, respectively, after conservative treatment.[28] Liver transplantation is the definitive treatment for patients with decompensated liver disease (encephalopathy, coagulopathy, hypoalbuminemia) or a major complication (variceal bleeding).

References

1 Conn HO, Atterbury CE. Cirrhosis. In: Schiff L, Schiff ER, editors. Diseases of the liver, 6th ed. Philadelphia: Lippincott; 1987. p. 725-864.
2 Zakim D, Boyer TD, Montgomery C. Alcoholic liver disease. In: Zakim D, Boyer TD, eds. Hepatology: a textbook of liver disease, 2nd ed. Philadelphia: W. B. Saunders; 1990. p. 821-869.
3 Runyon BA. Management of adult patients with ascites caused by cirrhosis. Hepatology 1998;27:264-272.
4 Gerbes AL, Gulberg V, Waggershauser T, et al. Renal effects of transjugular portosystemic shunt in cirrhosis: comparison of patients with ascites, with refractory ascites, or without ascites. Hepatology 1998;28:683-688.
5 Garcia-Tsao G. Spontaneous bacterial peritonitis. GE Clin N A 1992;21:257-275.
6 Grace ND. Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. Am J Gastroenterol 1997;92:1081-1091.
7 Chau TN, Patch D, Chan YW, et al. Salvage transjugular intrahepatic portosystemic shuns: gastric fundal compared with esophageal variceal bleeding. Gastroenterology 1998;114:981-987.
8 Bernard B, Lebrec D, Mathurin P, et al. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. Hepatology 1997;25:63-70.
9 Cordoba J, Blei AT. Treatment of hepatic encephalopathy. Am J Gastroenterol 1997;92:1429–1439.
10 Guevara M, Gines P, Bandi JC, et al. Transjugular portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 1998;28:416-422.
11 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745-750.
12 Wong DKH, Cheung AM, O'Rourke K, et al. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B: a meta-analysis. Ann Intern Med 1993;119:312-323.
13 Nevens F, Main J, Honkoop P, et al. Lamivudine therapy for chronic hepatitis B: a six month randomized dose-ranging study. Gastroenterology 1997;113:1258-1263.
14 Lai C-L, Chien R-N, Leung N, et al. A one year trial of lamivudine for chronic hepatitis B. N Engl J Med 1998;339:61-68.
15 National Institutes of Health Consensus Development Conference Panel Statement: management of hepatitis C. Hepatology 1997;26(Suppl. 1):2S-10S.
16 McHutchison JD, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485-1492.
17 Davis GL, Estaban-Mur R, Rustgi V, et al. Interferon alfa-2b alone or in combination with ribavirin for treatment of relapse of chronic hepatitis C. N Engl J Med 1998;339:1493-1499.
18 Dolan SA. Vaccines for hepatitis A and B: the latest recommendations on safe and extended protection. Postgraduate Med 1997;102:74-80.
19 McCullough AJ, O'Connor JFB. Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. Am J Gastroenterol 1998;91:2022-2036.
20 Bacon BR. Iron overload states. Clinics Liv Dis 1998;2:63-75.
21 Ferenci P. Wilson's disease. Clinics Liv Dis 1998;2:31-49.
22 Rosen HR. Liver disease associated with alpha1-antitrypsin deficiency. Clinics Liv Dis 1998;2:175-185.
23 Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri A. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994;107:1103-1109.
24 Jones DEJ, James OFW, Bassendine MF. Primary biliary cirrhosis: clinical and associated autoimmune features and natural history. Clinics Liv Dis 1998;2:265-282.
25 Bergquist A, Broome U. Clinical features in primary sclerosing cholangitis. Clinics Liv Dis 1998;2:283-301.
26 Ganger DR, Klapman JB, McDonald V, et al. Transjugular intrahepatic portosystemic shunt (TIPS) for Budd-Chiari syndrome or portal vein thrombosis. Am J Gastroenterol 1999;94:603-608.
27 Yoshida EM, Lake JR. Selection of patients for liver transplantation in 1997 and beyond. Clinics Liv Dis 1997:1:247-261.
28 D'Amico G, Morabito A, Pagilaro L, et al. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci 1986;31:468-475.