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Dental Management of Patients with End-Stage Liver Disease

F. John Firriolo, DDS, PhD

Division of Diagnostic Sciences, Department of Diagnostic Sciences, Prosthodontics and Restorative Dentistry, University of Louisville, School of Dentistry, 501 South Preston Street, Room E-32, Louisville, KY 40292, USA

End-stage chronic liver disease, also known as cirrhosis, is the consequence of a sustained wound-healing response to irreversible hepatocellular injury that leads to both fibrosis and nodular regeneration throughout the liver, frequently resulting in jaundice, portal hypertension, ascites, and ultimately biochemical and functional signs of hepatic failure.

Epidemiology

The estimated incidence of chronic liver disease in the United States is 72 cases per 100,000 per year overall, although the rate is much higher for men (over 95 per 100,000) than for women (50 per 100,000) [1]. In the United States, an estimated 5.5 million people have chronic liver disease, including cirrhosis. Over 60% of patients are male and over 80% are between 25 and 64 years of age [2]. According to the National Center for Health and Statistics, chronic liver disease and cirrhosis results in approximately 30,000 deaths each year in the United States, and in 2001 was the 12th leading cause of death overall, although it was ranked fourth in the 45- to 54-year-old age group.

Etiology

Cirrhosis is attributable to numerous etiologies that fall into several broad categories, including infectious (typically viral), toxicologic, immunologic (including autoimmune disease and altered immune response), biliary disease, and obstruction, as well as metabolic and vascular disturbances. The common pathogenic feature of these varied etiologies of cirrhosis is that they all result in persistent hepatocellular necrosis.

E-mail address: fjfirr01@louisville.edu

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The frequency of occurrence of cirrhosis based on etiology also shows considerable geographic and socially variability. Table 1 [3–5] describes the main etiologic categories of cirrhosis along with their approximate frequency in the United States. While alcohol has long been regarded as the principal cause of cirrhosis in the United States and elsewhere in the

Table 1
The etiology of cirrhosis in the United States

Etiology	Approximate frequency in the United States (%)
Chronic hepatitis C	25
Alcoholic liver disease	20
Concurrent chronic hepatitis C and alcoholic liver disease	15
Chronic hepatitis B (which may be coincident with hepatitis D)	15
Cryptogenic cirrhosis (cirrhosis of unknown or indeterminate etiology)	15
All other causes including:	10
Autoimmune chronic hepatitis	
Drug- or toxin-induced liver injury (eg, amiodarone, carbon tetrachloride, methotrexate, vitamin A)	
Nonalcoholic steatohepatitis or fatty liver	
Biliary disorders:	
Primary biliary cirrhosis	
Bile acid disorders (eg, Byler's disease)	
Biliary cirrhosis secondary to chronic large bile duct obstruction	
Primary sclerosing cholangitis	
Biliary atresia	
Congenital paucity of intrahepatic ducts	
Progressive familial intrahepatic cholestasis	
Metabolic diseases:	
$Alpha_1$-antitrypsin deficiency	
Carbohydrate disorders (eg, glycogen storage disease, galactosemia)	
Primary hemochromatosis and other iron disorders	
Tyrosinemia	
Wilson's disease	
Vascular derangements:	
Chronic right-sided heart failure	
Budd-Chiari syndrome	
Long-standing portal vein thrombosis	
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)	
Miscellaneous causes:	
Cystic fibrosis	
Sarcoidosis	
Hereditary storage diseases (eg, Gaucher, Niemann Pick, Wolman)	

Data from Refs. [3–5].

Western world, chronic viral hepatitis (mainly type C) has now emerged as the nation's leading cause of both chronic hepatitis and cirrhosis [6,7]. Patients with cirrhosis may frequently present with concurrent etiologic factors, such as chronic hepatitis C with concomitant chronic alcohol consumption.

Despite advances in diagnostic modalities, approximately 15% of cases of cirrhosis are still considered to be of unknown or indeterminate etiology, and are classified as cryptogenetic cirrhosis.

Clinical presentation

Cirrhosis may cause no symptoms for long periods. Up to 40% of patients with cirrhosis are ''compensated'' and demonstrate no clinical symptoms. In these individuals, cirrhosis may be diagnosed as a result of incidental findings during routine laboratory tests, during surgery, or at autopsy. The onset of symptoms of cirrhosis, when present, may be insidious or, less often, abrupt [8].

Jaundice and scleral icterus are almost always found in cirrhosis, typically occurring when total serum bilirubin reaches levels ≥ 3 mg/dL. However, they are usually not initial signs, and are mild at first, increasing in severity during the later stages of the disease.

Ecchymosis (secondary to thrombocytopenia or coagulation factor deficiency) and dilated superficial periumbilical vein (caput medusae) are frequent integumentary findings. Palmar erythema (mottled redness of the thenar and hypothenar eminences, a reflection of local vasodilatation and most commonly associated with cirrhosis with concurrent alcohol abuse) and spider angiomas of the skin (Each angioma is a central, pulsating, dilated arteriole from which small vessels radiate.) are presumed to be the result of impaired estrogen metabolism and consequent hyperestrogenemia [3]. Additionally, in the male, hyperestrogenemia also leads to hypogonadism and gynecomastia.

Increased skin pigmentation (a combination of slate-gray, due to iron, and brown, due to melanin, sometimes resulting in bronze color) may be present in cirrhosis secondary to hemochromatosis, while xanthomas may occur in primary biliary cirrhosis.

Nail changes seen in cirrhosis include Muehrcke lines, which are paired parallel white bands that do not change position with growth of the nail and thus reflect a change in the nail bed. Such lines are associated with hypoalbuminemia (typically serum albumin <2 g/dL). Other nail changes include Terry's nails, whereby most of the nail plate turns white with the appearance of ground glass, and the lunula is obliterated.

Peripheral edema, manifested by clubbing of the distal phalanges of the fingers and pedal edema, may also be seen in patients with cirrhosis and is attributed to hypoalbuminemia or right-sided heart failure.

In 70% of cirrhosis cases, the liver is enlarged, palpable, and firm (if not hard), and has a blunt or nodular edge. The left lobe may predominate.

These characteristics are attributable to hepatic inflammation and fluid accumulation. In more advanced disease, a small, nodular liver may be encountered due to significant hepatic necrosis and fibrosis. The liver edge may be grossly irregular because of macroscopic nodular regeneration. Tender hepatomegaly and abdominal pain may be present and is related either to hepatic enlargement (congestive hepatomegaly) and stretching of Glisson's capsule, or to the presence of ascites. Abdominal ascites will develop in approximately 50% of patients with cirrhosis within 10 years. The superficial veins of the abdomen and thorax may be dilated, reflecting the intrahepatic obstruction to portal blood flow. The rectal varices may also be dilated. In patients with portal hypertension, a venous hum may be auscultated over periumbilical veins. Clinical splenomegaly is present in 35% to 50% of cases [8].

Weakness, fatigability, muscle cramps, and weight loss are common in patients with cirrhosis. In advanced cirrhosis, anorexia is usually present and may be extreme, with associated nausea and occasional vomiting. Hematemesis is the presenting symptom in 15% to 25% of patients with cirrhosis.

Fever may be present in 35% of patients on presentation and usually reflects associated alcoholic hepatitis, spontaneous bacterial peritonitis, cholangitis, or some other concurrent infection [8].

Fetor hepaticus is a characteristic body and breath odor that is variously described as "musty" or "sweet and sour," and occurs occasionally in patients with cirrhosis. It is related to the formation of mercaptans by the action of gastrointestinal bacteria on the sulfur-containing amino acid methionine and shunting of splanchnic blood from the portal into the systemic circulation (portosystemic shunting) [3].

The oral cavity may show evidence of cirrhosis with the presence of hemorrhagic changes, petechiae, hematoma, jaundiced mucosal tissues, gingival bleeding, or icteric mucosal changes [9]. Pigmentation of the oral mucosa is only rarely observed in cases of hemochromatosis.

Patients with cirrhosis have been reported to have impaired gustatory function [10] and are frequently malnourished. Nutritional deficiencies can result in glossitis and loss of tongue papillae along with angular or labial cheilitis, which is complicated by concomitant candidal infection [11].

A bilateral, painless hypertrophy of the parotid glands (sialadenosis) is a frequent finding in patients with cirrhosis. The enlarged glands are soft and nontender, and are not fixed to the overlying skin [12,13]. The condition appears to be caused by a demyelinating polyneuropathy that results in abnormal sympathetic signaling, abnormal acinar protein secretion, and acinar cytoplasmic swelling [11].

Diagnosis

Liver biopsy is the gold standard for diagnosing cirrhosis and can sometimes aid in identifying the etiology. For example, fat and Mallory bodies

are typical in alcoholic liver injury, as compared with chronic inflammation and periportal necrosis, which are characteristics of cirrhosis resulting from chronic viral hepatitis. Important histopathologic findings in cirrhosis include [3]:

- Bridging fibrous septae in the form of delicate bands or broad scars linking portal tracts with one another and portal tracts with terminal hepatic veins. This fibrosis is the key feature of progressive damage to the liver.
- Parenchymal nodules containing proliferating hepatocytes encircled by fibrosis, with diameters varying from very small (<3 mm, micronodules) to large (several centimeters, macronodules). The parenchymal injury and consequent fibrosis are diffuse, extending throughout the liver. Focal injury with scarring does not constitute cirrhosis, nor does diffuse nodular transformation without fibrosis.
- Disruption of the normal architecture of the entire liver; vascular architecture is reorganized by the parenchymal damage and scarring, with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow channels. As a result, portal vein and arterial blood partially bypasses the functional hepatocyte mass through these abnormal channels.

Elevated serum levels of cytosolic hepatocellular enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) reflect hepatocellular injury. In cirrhosis resulting from alcoholic liver disease, there may be mild elevation of ALT and AST, usually less than 300 IU. This elevation does not correlate well with disease severity. AST levels are usually higher than ALT with an AST/ALT ratio >2. This appears to be due to a proportional reduction of ALT production in the damaged liver [14]. In cirrhosis, due to extrahepatic obstruction, there may be moderate elevations of ALT and AST to levels approximating 300 to 500 IU. In viral, toxic, or ischemic cirrhosis there are usually extreme elevations (>500 IU) of ALT and AST [15]. Serum lactate dehydrogenase may also be elevated in cirrhosis due to hepatocellular damage.

Serum alpha-fetoprotein is likely to be increased as the degree of hepatic fibrosis increases [16], especially in cirrhosis. Serum alpha-fetoprotein >17.8 μg/L has a sensitivity of 35%, a specificity of 98.6%, and a positive predictive value of 97.7% for cirrhosis [17]. The liver excretes alkaline phosphatase into the bile and its serum level is considerably increased in cirrhosis due to intra- or extrahepatic obstructive biliary disease.

Serum gamma-glutamyl transpeptidase is usually elevated in cirrhosis as a result of alcoholic liver disease and may also be elevated with biliary obstruction as seen in primary biliary cirrhosis.

Plasma conjugated bilirubin is elevated in liver disease due to reflux from liver cells and occurs in cirrhosis as a result of parenchymal and obstructive causes. Serum albumin is reduced in cirrhosis from impaired manufacture in the liver and associated malnutrition and malabsorption.

Hyponatremia, hypokalemia, and low serum-urea-nitrogen levels are generally common (and characteristic with concurrent alcoholism). However, cirrhosis may be complicated by the development of hepatorenal syndrome with progressive azotemia.

Anemia is fairly common in cirrhosis and usually normocytic. It can also be microcytic; hypochromic, usually as a result of chronic occult or overt blood loss from the gastrointestinal tract; macrocytic, which is usually seen with concurrent alcoholism and results from folate deficiency and suppression of erythropoiesis; or hemolytic secondary to hypersplenism. The white–blood-cell count may be low, elevated, or normal, reflecting hypersplenism or infection. Thrombocytopenia, with a platelet count typically less than 80,000/mm^3, may be secondary to alcoholic marrow suppression, sepsis, folate deficiency, or splenic sequestration [8].

Reduced hepatic synthesis of coagulation factors (fibrinogen; prothrombin; and factors V, VII, IX, and X) reflects the generalized impairment of protein synthesis by the liver and will result in an abnormally elevated prothrombin time.

Ultrasound can be useful in detecting ascites and in delineating the characteristic features of a cirrhotic liver (eg, hepatic nodularity, decrease in size, prominence of the left lobe) but is not diagnostic. Together with Doppler studies, ultrasound may establish patency of the splenic, portal, and hepatic veins.

Electrocardiography frequently shows prolongation of the QT interval, attributable to activation of the sympathetic nervous system in cirrhosis.

Technetium-99m sulfur colloid scanning has also been reported as useful for diagnosing cirrhosis, demonstrating a shift of colloid uptake to the spleen and bone marrow [18].

Antimitochondrial antibody can be detected in the blood of 95% to 98% of patients with primary biliary cirrhosis, and with lesser frequency in patients with cirrhosis resulting from autoimmune hepatitis [15].

Treatment

The initial goals in the treatment of cirrhosis focus on removing or alleviating the underlying cause of cirrhosis (when possible), preventing further liver damage, and preventing potential complications. Examples of these treatment measures include [15]:

- Avoidance of hepatotoxic drugs
- Abstinence from alcohol, especially in patients with alcoholic cirrhosis
- Therapy for chronic hepatitis B (eg, interferon alpha, lamivudine, famciclovir), and chronic hepatitis C (eg, peginterferon alfa-2a/2b in combination with ribavirin)
- Correction of any mechanical obstruction to the bile flow (eg, calculi, strictures)

- For primary biliary cirrhosis, treatment with ursodiol (ursodeoxycholic acid) may normalize bilirubin, extend survival, and lengthen the time before liver transplantation in early disease
- For Wilson's disease, treatment with penicillamine is used to chelate and promote excretion of copper deposits
- For hemochromatosis, removal of excess body iron with phlebotomy or deferoxamine
- For autoimmune chronic hepatitis, treatment with corticosteroids (eg, prednisone, 20–30 mg/day initially) with or without azathioprine
- Therapy for underlying cardiovascular disorders in patients with cardiac cirrhosis

Complications and their management

There are numerous, potentially life-threatening, complications associated with cirrhosis. Portal hypertension occurs when portal venous pressure exceeds the pressure in the nonportal abdominal veins (eg, inferior vena cava) by at least 5 mm Hg. In cirrhosis, increased portal pressure results primarily from increased resistance to blood flow through the shrunken, fibrotic liver. Increased intrahepatic resistance results both from fixed obstruction to flow by extracellular matrix and from dynamic organ and sinusoidal contraction by activated stellate cells (also referred to as myofibroblasts). Because pressure is a function of both resistance and flow, independent increases in portal inflow due to the hyperdynamic circulation of cirrhosis and to splanchnic arteriolar vasodilation also elevate portal pressure [4].

Clinical manifestations and complications of portal hypertension include ascites, splenomegaly, thrombocytopenia, distention of abdominal wall veins (caput medusae), and, most significantly, portosystemic collateral varices that most commonly develop in the esophagus and proximal stomach, where they can cause clinically significant bleeding in the upper gastrointestinal tract. Gastroesophageal varices occur in about 65% of patients with advanced cirrhosis, and variceal hemorrhage is the most serious complication of portal hypertension, accounting for approximately one fifth to one third of all deaths in cirrhotic patients [19]. The mortality rate after a variceal bleed ranges from 20% to 70% in various series, with an average of approximately 50% within 6 weeks [20,21].

Goals in the management of gastroesophageal varices are to prevent a first bleed, control any acute bleeding should it occur, and then to prevent recurrent bleeding. Prevention of gastroesophageal variceal bleeding is directed at reducing portal pressure. Nonselective beta-blockers, considered the first-line treatment for primary and secondary prevention of variceal hemorrhage, can reduce the risk of rebleeding by approximately 40% and risk of death by 20% [22]. Beta-blockade decreases portal pressure by providing unopposed alpha-adrenergic–mediated arteriolar vasoconstriction,

bradycardia, and decreased cardiac output. Furthermore combination therapy of isosorbide mononitrate with a nonselective beta-blocker has a synergistic effect and is found to be superior to beta-blockers alone in the prevention of variceal hemorrhage [8,23,24].

Local measures used in the control of hemorrhage and obliteration of esophageal varices include endoscopic sclerotherapy, endoscopic ligation (banding), balloon tamponade, and surgical devascularization.

Endoscopic sclerotherapy (EST) is the repeated injection of a sclerosant (eg, 5% sodium morrhuate, or 1–3% sodium tetradecyl sulfate) into varices to produce variceal thrombosis and obliteration. Injections may be directed into the veins (intravariceal injection) or into the esophageal wall adjacent to the variceal channels (paravariceal injection). EST is successful in controlling acute esophageal variceal bleeding in 80% to 90% of patients, and in reducing frequency and severity of recurrent variceal bleeding [25,26]. After the initial injection to control bleeding, a follow-up session 2 to 3 days later is common practice, usually followed by weekly or biweekly procedures until variceal obliteration is achieved. Thereafter, surveillance for reappearance of varices is usually conducted at intervals that extend from 1 month to 3 months and then 6 months [19].

EST has also been investigated for obliteration of esophageal varices that have never bled (ie, prophylactic sclerosis) and demonstrated benefits in clinical trials appear positive, but are still somewhat equivocal [27–31].

Endoscopic variceal ligation (EVL), also referred to as variceal banding, is the placement of an elastic O-ring that compresses a varix. The high frequency of complications after EST led to the development of EVL [20,21]. This technique was developed on the basis of principles established for the banding of hemorrhoids and involves the placement of elastic O-ring ligatures on the varices, thereby causing strangulation of the veins. Endoscopic variceal ligation achieves hemostasis in 90% of cases [32], and is considered preferable to EST because of lower rebleeding rates and fewer complications [33,34].

Percutaneous transhepatic embolization of gastroesophageal varices involves catheterization of the gastric collaterals that supply blood to varices via the transhepatic route. A variety of materials have been used for embolization, with varying degrees of success in controlling acute bleeding [35]. Generally, this procedure is less effective than EST for treatment of variceal hemorrhage and is much less effective compared with medical and surgical options. Percutaneous transhepatic embolization is usually reserved for situations in which acute variceal bleeding is not controlled by pharmaceutical treatment, EST, or EVL, and in which contraindications for surgical management are present [36].

Approximately 5% to 10% of patients with esophageal variceal hemorrhage cannot be controlled by endoscopic or pharmacologic treatment. Balloon tamponade (eg, Minnesota tube, Sengstaken–Blakemore tube, Linton–Nachlas tube) may be used as a temporary option in the emergency

management (cessation) of esophageal variceal hemorrhage before more definitive therapy, such as surgery or a transjugular intrahepatic portosystemic shunt, is undertaken [36]. Balloon tamponade can control active bleeding in more than 90% of cases. However, on deflation of the balloons, rebleeding occurs in a high proportion of patients. In addition, balloon tamponade may result in serious complications, including esophageal perforation, aspiration pneumonia, and, rarely, asphyxiation [19].

Surgical devascularization is transabdominal devascularization of the lower 5 cm of the esophagus and the upper two thirds of the stomach, with surgical staple gun transection of the lower esophagus. This is rarely performed but may have a role in patients with portal and splenic vein thrombosis who are not suitable candidates for shunt procedures (described below) and who continue to have variceal bleeding despite endoscopic and pharmacologic treatment [36].

A transjugular intrahepatic portosystemic shunt (TIPS) is an angiographically placed expandable metal stent inserted between a branch of the hepatic vein and portal vein over a catheter inserted via the internal jugular vein, creating a shunt between a hepatic vein and portal vein to decompress the portal circulation. The use of TIPS has been found to be superior to endoscopic local control measures in the prevention of rebleeding from esophageal varices and in the treatment of variceal bleeding refractory to endoscopic. The use of TIPS has also been shown to be beneficial in the treatment of severe refractory ascites. The overall variceal rebleeding rate with TIPS is 19% compared with 47% with endoscopic therapy [37]. Complications with TIPS include hepatic encephalopathy in 20% to 30% of cases, infection, shunt stenosis (up to 75% after 6–12 months), and shunt occlusion in up to 30% of cases [8]. Long-term patency usually requires periodic shunt revisions.

Ascites, which is the accumulation of excess fluid in the abdomen, is often among the first signs of decompensation in patients with chronic liver disease. It usually becomes clinically detectable when at least 500 mL of ascitic fluid has accumulated, but many liters may collect and cause massive abdominal distention. Approximately 50% of patients with cirrhosis develop ascites within 10 years. The development of ascites in the setting of cirrhosis is an important landmark in the progression of chronic liver disease because approximately 50% of patients die within 2 years [4].

Many complex factors contribute to the pathogenesis of ascites in a patient with cirrhosis. According to Gines and colleagues [38] the chief factor contributing to ascites is splanchnic vasodilatation. Increased hepatic resistance to portal flow due to cirrhosis causes the gradual development of portal hypertension, collateral-vein formation, and shunting of blood to the systemic circulation. As portal hypertension develops, local production of vasodilators, mainly nitric oxide, increases, leading to splanchnic arterial vasodilatation. In the advanced stages of cirrhosis, splanchnic arterial vasodilatation is so pronounced that the effective arterial blood volume decreases

markedly and arterial pressure falls. As a consequence, arterial pressure is maintained by homeostatic activation of vasoconstrictor and antinatriuretic factors, resulting in sodium and fluid retention. The combination of portal hypertension and splanchnic arterial vasodilatation alters intestinal capillary pressure and permeability, facilitating the accumulation of retained fluid within the abdominal cavity.

General measures in the management of ascites in patients with cirrhosis include dietary sodium reduction and fluid intake restriction. In all patients with cirrhotic ascites, reduction of sodium intake is beneficial, particularly in those with severe sodium retention that does not respond or responds only minimally to diuretics. A low-sodium diet (60–90 mEq/day, equivalent to approximately 1500–2000 mg of salt per day) may facilitate the elimination of ascites and delay the reaccumulation of fluid [38]. More stringent restriction is not recommended because it is poorly tolerated. Fluid intake should be restricted to approximately 1000 mL/day only in patients with dilutional hyponatremia, a condition characterized by a serum sodium concentration of $<$130 mmol/L in the presence of ascites, edema, or both. Dilutional hyponatremia results from impaired renal excretion of free water due to inappropriately high concentrations of antidiuretic hormone [38].

In patients with moderate-volume ascites, a negative sodium balance and loss of ascitic fluid are quickly achieved with low doses of diuretics. The diuretic of choice is either spironolactone (50–200 mg/day) or amiloride (5–10 mg/day). Low doses of furosemide (20–40 mg/day) may be added during the first few days to increase natriuresis, especially when peripheral edema is present, and the drug should be administered while monitoring blood pressure, urinary output, mental status, and serum electrolytes, especially potassium. The response to diuretics can be evaluated on the basis of changes in body weight and by physical examination. The recommended goal of weight loss to prevent renal failure of prerenal origin is 300 to 500 g/day in patients without peripheral edema and 800 to 1000 g/day in those with peripheral edema [38].

Large-volume ascites is defined as ascites in an amount large enough to cause marked abdominal discomfort that interferes with regular daily activities. The two therapeutic strategies for large-volume ascites are large-volume paracentesis (LVP), which typically consists of draining of about 4 to 6 L of ascitic fluid, and the administration of diuretics at increasing doses until loss of ascitic fluid is achieved. Diuretics used in the treatment of large-volume ascites include spironolactone with an initial dose of 100 mg/day, which can be titrated to a maximum of 400 mg/day, plus furosemide with an initial dose of 40 mg/day, which can be titrated up to 160 mg/day [39].

Refractory ascites, which occurs in 5% to 10% of patients with ascites, is defined as a lack of response to maximum doses of diuretics (eg, 400 mg of spironolactone plus 160 mg of furosemide per day). Current therapeutic strategies include repeated LVP with the use of plasma expanders (albumin)

and TIPS. TIPS is superior to LVP in preventing the reaccumulation of ascites [39]. With TIPS, increased renal sodium excretion and control of ascites refractory to diuretics can be achieved in about 75% of patients. The success rate for TIPS in controlling ascites is lower in patients with underlying renal insufficiency. While some claim that TIPS, as compared with LVP, improves survival in patients with refractory ascites [40], two recent, randomized studies failed to confirm that assertion [41,42] and TIPS is associated with greater morbidity and mortality when placed in patients with advanced liver disease. Therefore, the use of TIPS should not be recommended as the treatment of choice for refractory ascites. This method should probably be reserved for patients without severe liver failure or encephalopathy and who have loculated fluid that cannot be treated with paracentesis, and for those who are unwilling to undergo repeated paracentesis [38].

Hepatic encephalopathy (HE) is a neuropsychiatric disorder caused by hepatic insufficiency. It is characterized by a spectrum of signs and symptoms, including intellectual (cognitive) impairment; motor function impairment; and disturbances in consciousness, ranging from subtle behavioral abnormalities and changes in personality, to marked confusion and stupor, to deep coma. Because the clinical manifestations of HE are so variable, it should be suspected in any cirrhotic patient with a neuropsychiatric abnormality. Table 2 presents a commonly used numerical scale for grading the severity of HE based upon the clinical presentation of the patient. Subclinical HE (Stage 0) occurs in 50% to 80% of patients with cirrhosis, with the most common symptoms being insomnia, reversal of the day–night sleep cycle, and subtle deficits in concentration and hand–eye coordination, which contribute to falls and traffic accidents [4]. Symptoms of HE may be debilitating in a significant number of patients with cirrhosis and are observed in 24% to 53% of patients who undergo hepatic portosystemic shunt surgery. Approximately 30% of patients with terminal cirrhosis experience severe HE, approaching coma [43].

The precise pathogenesis of HE is unknown and a number of theories have been postulated regarding its possible pathogenesis in patients with cirrhosis. Patients may have altered brain energy metabolism and increased permeability of the blood–brain barrier. The latter may facilitate the passage of neurotoxins into the brain. Putative neurotoxins and pathogenic factors include short-chain fatty acids, mercaptans, false neurotransmitters (eg, tyramine, octopamine, and beta-phenylethanolamines), ammonia, enhanced sensitivity of central nervous system neurons to the inhibitory neurotransmitter gamma-aminobutyric acid, and deposition of manganese in the basal ganglia [8,43]. Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, amino acids, purines, and urea. Normally, ammonia is detoxified in the liver by conversion to urea and glutamine. In cirrhosis, increased arterial levels of ammonia are commonly seen, but there is little correlation between blood levels and the severity of neuropsychiatric impairment despite the fact that ammonia appears to play a role in the

Table 2
Numerical scale for grading the severity of hepatic encephalopathy

Grade	Clinical presentation
0	Subclinical; normal mental status, but minimal changes in memory, concentration, intellectual function, coordination
1	Mild confusion, euphoria or depression; decreased attention; slowing of ability to perform mental tasks; irritability; disorder of sleep pattern (ie, inverted sleep cycle)
2	Drowsiness, lethargy, gross deficits in ability to perform mental tasks; obvious personality changes; inappropriate behavior; intermittent disorientation (usually for time)
3	Somnolent but arousable; unable to perform mental tasks; disorientation to time and place; marked confusion; amnesia; occasional fits of rage; speech is present but incomprehensible
4	Coma, with or without response to painful stimuli

From Davern TJ, Scharschmidt BF. Biochemical liver tests. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger and Fordtran's gastrointestinal and liver disease, 7th edition. Philadelphia: Elsevier; 2002. p. 1236.

pathogenesis of HE [4]. The presence of a hepatic portosystemic shunt in patients with cirrhosis has been implicated as a contributing factor in the development of HE. Portosystemic shunts allow the putative neurotoxins associated with HE to bypass the liver, where they normally are metabolized. After bypassing the liver, these toxic substances cross the blood–brain barrier and exert direct or indirect neurotoxic effects on the central nervous system.

HE is usually reversible if the underlying hepatic dysfunction can be corrected, but in patients with cirrhosis, it portends a poor prognosis with a 1-year survival rate of 40% [4]. Treatment of HE initially consists of identifying and eliminating any nonhepatic causes of altered mental function. Medications that depress central nervous system function, including narcotics, tranquilizers, and sedatives that are metabolized or excreted by the liver, should be avoided. These especially include benzodiazepines. Precipitants of HE (eg, metabolic disturbances, gastrointestinal bleeding, infection, constipation) should be corrected. Medical treatment of HE is based on efforts to control the production and action of the putative neurotoxins. Lactulose can be administered orally in patients with milder, chronic symptoms of HE, or via either a nasogastric tube or rectal tube in hospitalized patients with the acute onset of severe HE. This nonabsorbable disaccharide stimulates the passage of ammonia from tissues into the gut lumen and inhibits intestinal ammonia production. Orally administered neomycin sulfate or other antibiotics (eg, metronidazole, oral vancomycin, paromomycin, oral quinolones) serve as second-line agents in the treatment of HE. These antibiotics are effective in treating HE by decreasing the concentration of ammonia-producing intestinal bacterial flora [8]. Some sources recommend that dietary protein should be withheld during acute episodes of HE. When the patient resumes oral intake, protein intake is started at 20 g/day and increased by 10 g every 3 to 5

days to 60 to 80 g/day as tolerated. Vegetable protein is better tolerated than meat protein [8]. For patients with chronic HE symptoms, in some estimations, dietary protein restriction is rarely necessary. Furthermore, many patients with cirrhosis have protein-calorie malnutrition at baseline. The routine restriction of dietary protein intake increases their risk for worsening malnutrition [43].

Patients with cirrhosis demonstrate an increased susceptibility to infection due to a number of contributory and predisposing factors. Patients with cirrhosis have abnormal function of the endoplasmic reticulum cells, which contributes to a high incidence of bacteremias. These patients experience a decrease in phagocytosis efficiency because of both a decrease in serum opsonic activity, probably as a consequence of decreased serum complement and fibronectin, and a decrease in Kupffer cell activity, which facilitates infections. The phagocytic and bactericidal capacity of neutrophils is also impaired in patients with cirrhosis. Portal venous shunts contribute to systemic spread of infection by bypassing the hepatic filtration [44].

Anasarca and malnutrition associated with cirrhosis predispose to poor wound-healing and soft tissue infection. Because patients with cirrhosis may be hypothermic and their peripheral white–blood-cell counts are frequently depressed because of hypersplenism, infection may present without fever and leukocytosis [4].

Spontaneous bacterial peritonitis (SBP) is usually considered to be the infectious complication most closely associated with cirrhosis and ascites. SBP has an estimated prevalence of 10% to 30% in cirrhotic patients with ascites admitted to hospital, and of these patients with SBP, 70% have severe cirrhosis (Child–Turcotte–Pugh class C, (Table 3)) [46]. SBP is an ominous complication of cirrhosis because even with intensive treatment, the in-hospital mortality is still between 10% and 30% [46] and the probabilities of survival after 1 and 2 years are in the range of 30% and 20%, respectively, among survivors of an episode of SBP with cirrhosis [47]. In at least one study [48] the mortality rate for SBP in patients with cirrhosis was 100% when associated with progressive renal impairment.

Common causative organisms in SBP include in *Escherichia coli*, *Pneumococcus, Klebsiella*, and anaerobes. However, the exact pathogenesis of SBP remains uncertain. Facultative gram-negative bacilli appear to be increased in the jejunal flora of many patients with cirrhosis, some of whom have decreased motility. This change in intestinal flora may increase the risk of gram-negative bacteremia by way of translocation through the gut wall and a disruption of the normal intestinal permeability barrier. Hypoalbuminemia and ascites contribute to gut wall edema, predisposing to bacterial translocation. The impaired capacity of hepatic and splenic macrophages to clear portal bacteremia, or the presence of a large volume of peritoneal fluid conducive to bacterial growth also appear to play a role in pathogenesis of SBP [4]. A broad range of signs and symptoms are seen in SBP, and its clinical presentation depends on the stage at which

Table 3
Child–Turcotte–Pugh classification[a] to assess severity of chronic liver disease

Biochemical or clinical parameter	Points scored for increasing abnormality		
	1 point	2 points	3 points
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (PT) (seconds above control time) or	<4.0	4.0–6.0	>6.0
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3
Ascites	None	Mild (or controlled by diuretics)	At least moderate despite diuretic treatment
Encephalopathy	None	Mild to Moderate (grade 1–2)[b]	Moderate to severe (grade 3–4)[b]

When the total point score is 5 or 6, Child–Turcotte–Pugh classification s class A for mild disease. When the total point score is 7–9, Child–Turcotte–Pugh classification is class B for moderate disease. When the total point score is 10–15. Child–Turcotte–Pugh classification is class C for severe disease.

[a] also known as the Child–Pugh classification.

[b] see Table 2 for numerical scale for grading the severity of hepatic encephalopathy.

Modified from Davern TJ, Scharshmidt BF. Biochemical liver tests. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger and Fordtran's gastrointestinal and liver disease, 7th edition. Philadelphia: Elsevier; 2002. p. 1236.

the infection is diagnosed. In the early stages, most patients are asymptomatic. Completely asymptomatic cases of SBP have been reported in as many as 30% of patients [45]. As SBP progresses, patients show signs and symptoms of peritoneal infection. Fever is the most common presenting symptom, and is present in as many two thirds of patients at the time of diagnosis. Fever and chills eventually develop in 80% of patients with SBP. Approximately half of patients present with abdominal pain, tenderness, or discomfort. Worsening or unexplained encephalopathy resulting in altered mental status is present in about half of patients with SBP. About one third present with diarrhea or paralytic ileus. Hypotension is found in 5% to 14% of patients [36,37].

A polymorphonuclear cell count of greater than 250/mL in ascitic fluid is currently considered diagnostic of SBP and warrants the prompt start of empiric antibiotic treatment [49]. Empiric antibiotic regimens used in the treatment of SBP include cefotaxime 2 g intravenously every 12 hours for 5 days, or ceftriaxone 2 g intravenously every 24 hours for 5 days [46]. Use of intravenous albumin as an adjunct to antibiotic therapy may lower the incidence of renal failure and improve survival, particularly in patients with poor baseline liver and renal function. Adequate response to therapy should be documented by demonstrating a 50% reduction in ascitic fluid polymorphonuclear cell count.

In patients who have recovered from an episode of SBP, recurrence of SBP is common, and estimated to be 43% at 6 months and 69% at 1 year [50]. Prophylactic antibiotic therapy can reduce the recurrence rate of SBP to approximately 20%. Three specific groups of patients with cirrhosis known to benefit from the use of prophylactic antibiotic therapy to prevent SBP include those with gastrointestinal bleeding, those with ascites who are recovering from a prior episode of SBP, and those with an ascitic albumin concentration of less than 1 g/dL [51]. Recommended antibiotic regimens for the prevention of SBP in cirrhotic patients with ascites and prior SBP or an ascitic albumin concentration less than 1 g/dL include norfloxacin 400 mg orally every 24 hours, or ciprofloxacin 750 mg orally every week, or trimethoprim/sulfamethoxazole 160:800 mg once daily. In patients with ascites and prior SBP, antibiotic prophylaxis should continue until the resolution of ascites or until liver transplantation. Prolonged use of oral antibiotics leads to selection of resistant organisms in the gut flora. Therefore, only hospitalized patients with ascitic fluid albumin concentration of <1 g/dL should undergo prophylactic antibiotic therapy, and therapy should be discontinued at the time of discharge [46,51].

Hepatorenal syndrome (HRS) is defined as renal failure associated with severe liver disease without an intrinsic abnormality of the kidneys. HRS occurs in up to 10% of patients with advanced cirrhosis. Sodium retention, impaired free-water excretion, and decreased renal perfusion and glomerular filtration rate are the main renal functional abnormalities. Several factors are involved the development of HRS, including a decreased renal perfusion pressure due to systemic vasodilation, activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arteriolae, and increased synthesis of renal vasoactive mediators, which further decrease glomerular filtration [3]. Ascites is invariably present.

Major diagnostic criteria for HRS includes:

- Low glomerular filtration rate as indicated by serum creatinine >1.5 mg/dL or 24-hour creatinine clearance <40 mL/min
- Absence of shock, ongoing bacterial infection, and fluid losses, and current treatment with nephrotoxic agents
- Lack of sustained improvement in renal function on discontinuation of diuretics and volume expansion by 1.5 L of a plasma expander
- Proteinuria <500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease [51]

Two types of HRS have been described. Type-1 HRS is characterized by a rapidly progressive reduction in renal function as defined by doubling of serum creatinine to a level of 2.5 mg/dL or a 50% reduction of initial 24-hour creatinine clearance to a level less than 20mL/min in less than 2 weeks. Type-2 HRS is slowly progressive or stable renal dysfunction not meeting the criteria for type-1 HRS [52]. Type-1 HRS is usually associated with a precipitating stress factor, such as infection, gastrointestinal hemorrhage, or

a major surgical procedure, while type-2 HRS is usually associated with progressive destabilization of circulatory physiology, frequently in the setting of severe refractory ascites [3].

The development of HRS, especially type 1, is associated with a poor prognosis, with more than 95% of patients dying within a few weeks of the onset of azotemia without therapy. The median survival time for type-2 HRS is approximately 6 months without therapy. Spontaneous recovery of renal function is rare [4].

Treatment of HRS with vasoconstrictor agents, such as terlipressin (a vasopressin analog), or alpha-adrenergic agonists, such as midodrine or noradrenaline, in combination with albumin infusion, are beneficial in almost two thirds of the patients with HRS [39]. Patients with HRS who respond to vasoconstrictor agents have a better prognosis for survival than those who do not respond. Therefore, vasoconstrictor agents increase the likelihood that patients with HRS will survive long enough to undergo liver transplantation. In addition, these agents offer the advantage of improving renal function before transplantation, a benefit that may reduce post-transplantation morbidity and mortality [38].

Hepatopulmonary syndrome (HPS) is a disease process that consists of hepatic impairment (most commonly cirrhosis), widespread intrapulmonary vasodilatation, and gas exchange abnormalities (presenting with increased alveolar arterial oxygen gradient that results ultimately in hypoxemia), all occurring in the absence of intrinsic cardiopulmonary disease. Approximately 8% of patients with cirrhosis manifest clinically evident HPS during the course of their disease. Clinical characteristics of HPS include cyanosis, clubbing, dyspnea (which occurs when the patient assumes the standing position (platypnea)), and arterial hypoxemia (defined as $PaO_2 < 60$ mm Hg, and which typically is worse when changing from the supine to the standing position (orthodeoxia)), reflecting the intrapulmonary vasodilatation that occurs predominantly in the lung bases [4].

The treatment of HPS is directed at correcting the underlying portal hypertension. In the case of patients with cirrhosis, TIPS has also been shown to improve pulmonary functions and is a useful bridge to eventual liver transplantation, after which the pulmonary failure often resolves. Some patients with HPS may benefit from the use of supplemental oxygen therapy. However, the response is variable, can only improve symptoms related to hypoxemia, and cannot reverse the underlying intrapulmonary vascular defects.

As previously discussed, patients with cirrhosis frequently have anemia, thrombocytopenia, and impaired hemostasis. For iron deficiency anemia, ferrous sulfate administered in 0.3-g enteric-coated tablets, one tablet three times daily after meals, is usually effective. Folic acid, 300 mg/day orally, is indicated in the treatment of macrocytic anemia associated with cirrhosis, especially with concurrent alcoholism. Transfusions with packed red blood cells may be necessary to replace blood loss in patients with

gastrointenstinal bleeding, such as from gastroesophageal varices. While hypoprothrombinemia may usually be treated with vitamin K, this treatment is ineffective when synthesis of coagulation factors is impaired because of severe hepatic disease. In such cases, correcting the prolonged prothrombin time requires large volumes of fresh frozen plasma. Because the effect is transient, plasma infusions are not indicated except for active bleeding or before an invasive procedure. Use of recombinant factor VII may be an alternative [8]. Severe thrombocytopenia, especially when associated with life-threatening bleeding episodes, should be treated with platelet transfusions.

Another significant complication of cirrhosis is the increased risk for the development of hepatocellular carcinoma. Cirrhosis is considered a major clinical and histopathologic precursor for the development of hepatocellular carcinoma regardless of its underlying etiology, but especially in cirrhosis related to chronic infection with hepatitis B virus or hepatitis C virus. Up to 5% of patients with cirrhosis are at risk to develop hepatocellular carcinoma annually [53]. In one analysis of four major studies involving 91,666 autopsies, the prevalence of hepatocellular carcinoma in patients with cirrhosis ranged from 7.4% to 23%, compared with $<0.3\%$ in patients without cirrhosis [54]. Treatment options for hepatocellular carcinoma include total surgical resection (of a solitary tumor or tumors localized to one lobe), systemic chemotherapy, radiation therapy, and liver transplantation (in cases of localized disease without extrahepatic manifestations). Hepatic arterial chemoembolization, cryosurgery, percutaneous ethanol injection, or radiofrequency ablation can be considered for small (typically <4–5 cm), localized, unresectable tumors [8].

Liver transplantation

Orthotopic liver transplantation (LT) is indicated in selected cases of irreversible, progressive chronic liver disease, such as in cirrhosis. The cardinal indications for LT are based on disease severity that reflects hepatocellular failure, such as coagulopathy and jaundice; complications of portal hypertension, such as refractory ascites and recurrent variceal bleeding; or the combination of portosystemic shunting and diminished hepatocellular function, as in hepatic encephalopathy [55].

Contraindications to LT include, but are not limited to, active alcoholism or substance abuse, AIDS, extrahepatic malignancy, uncontrolled sepsis, cholangiocarcinoma, hemangiosarcoma, advanced cardiac or pulmonary disease, and a Child–Turcotte–Pugh score <7 (see Table 3). Hepatocellular carcinoma, hepatitis B and C, some cases of Budd–Chiari syndrome, and autoimmune liver disease may recur in the transplanted liver.

The majority of organs used for LT are obtained from cadaveric donors, and the major impediment to more widespread use of LT is a shortage of

donor organs. Currently, more than 17,000 patients in the United States are on the LT waiting list, and slightly more than 5600 cadaveric liver donors were recovered during 2005, according to data from the Organ Procurement and Transplantation Network, United Network for Organ Sharing (UNOS) [56]. Increasingly, adult living donor liver transplantation (LDLT) is an option for some patients. In LDLT, part of the liver from a living donor (usually a healthy relative of the recipient) is resected and transplanted into a recipient. LDLT in adults has expanded in recent years after becoming the standard of care for children in many transplant centers. In 2005, a total of 277 LDLTs were performed in the United States with 225 LDLTs recipients (81.2%) being adults according to UNOS data. Five-year survival rates as high as 80% are now reported [55].

Since February 2002, a new nationwide system has been used to rank patients waiting for LT. Called the Model for End-Stage Liver Disease (MELD), it replaces the previous Status 2A, 2B, and 3 UNOS categories [57]. The MELD system numerically ranks each patient waiting for LT from 6 (less ill) to 40 (gravely ill) based on three biochemical variables: serum creatinine (SCR), total bilirubin (TB), and prothrombin time expressed by international normalized ratio (INR). The MELD score is calculated from the formula in Box 1.

A system similar to MELD has also been established for patients <18 years old. This is called the Pediatric End-Stage Liver Disease (PELD) survival model.

Within any region of the country, a donor organ in a particular ABO blood group is allocated to the cirrhotic patient within the same blood group who has the highest MELD or PELD score. Special rules have been developed to address potentially life-threatening liver disease complications, such as hepatocellular carcinoma and hepatopulmonary syndrome. Patients with these conditions, as well as other exceptional cases, can receive a higher MELD or PELD score than that calculated from creatinine, bilirubin, and INR alone.

Box 1. Model End Stage Liver Disease (MELD) score for adults*

$$\text{MELD Score} = 10 \times [0.957 \times \log(\text{SCR}) + 0.378 \log(\text{TB}) + 1.12 \times \log(\text{INR}) + 0.643]$$

SCR = serum creatinine (mg/dL); TB = total bilirubin (mg/dL); INR = international normalized ratio

* Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33(2):464–70.

Prognosis

The prognosis of cirrhosis has shown little change over the years. The course after diagnosis of cirrhosis is typically 5 to 20 years of asymptomatic disease. Once complications start to occur, death within 5 years without LT occurs with most patients. Factors determining progression and overall prognosis of the disease include the ability to remove or alleviate the underlying cause of cirrhosis (if possible). If the etiology of cirrhosis cannot be removed, the course of the disease is more rapid. For example, in patients with alcoholic cirrhosis, survival is affected by alcohol ingestion. Five-year survival is 60% to 85% in those who abstain, compared with 40% to 60% for those who continue to drink alcohol.

LT has markedly improved the outlook for patients who are acceptable candidates and are referred for evaluation early. The likely 1-year survival rate for patients with decompensated cirrhosis is $<10\%$ without LT, but approximately 85% to 90% at 1 year and 75% at 5 years after LT for most indications [58]. Hematemesis, jaundice, and ascites are unfavorable prognostic signs in cirrhosis. In established cases with severe hepatic dysfunction (serum albumin <3 g/dL, bilirubin >3 mg/dL, ascites, encephalopathy, cachexia, and upper gastrointestinal bleeding), only 50% survive 6 months. The risk of death in this subgroup of patients with advanced cirrhosis is associated with renal insufficiency, cognitive dysfunction, ventilatory insufficiency, age ≥ 65 years, and prothrombin time ≥ 16 seconds. Obesity appears to be a risk factor for cirrhosis-related death or hospitalization in nonalcoholic patients [8].

The Child–Turcotte–Pugh classification (also called the Child–Pugh classification) (see Table 3) is widely used to assess the prognosis of chronic liver disease, mainly cirrhosis [59,60]. The Child–Turcotte–Pugh classification was originally used to predict mortality during surgery in patients with chronic liver disease. It is now used primarily to determine the prognosis of chronic liver disease, as well as the necessity for LT. However, as previously noted, the MELD and PELD scores are currently the major determinants used for prioritizing the need for LT and the allocation of donor organs. More than one third of the patients with Child–Turcotte–Pugh scores of 10 to 15 (class C) can be expected to die within a year without LT. In contrast, patients with Child–Turcotte–Pugh scores of 7 to 9 (class B) have an 80% chance of surviving 5 years without LT, and those with Child–Turcotte–Pugh scores of 5 to 6 (class A) have a 90% chance of surviving >5 years without LT [61].

Dental management and dental treatment of the patient with cirrhosis

Cirrhosis has a number of significant implications for a patient receiving dental treatment. Major considerations include:

- Unpredictable hepatic metabolism of drugs administered or prescribed in dental treatment,

- Potential for impaired hemostasis and bleeding diathesis due to thrombocytopenia or reduced hepatic synthesis of coagulation factors, and
- Increased risk of infection, or spread of infection, including SBP.

Consequently, consultation with the patient's physician is essential to the proper management of the dental patient with cirrhosis [62].

When considering dental treatment for a patient with cirrhosis, thorough medical and dental histories are essential with a focus on establishing the patient's current degree of hepatic functional impairment. The dentist also should know about the history and presence of any complications of cirrhosis, the severity of such complications, and the treatment for those complications. Such complications include portal hypertension, ascites, HE, SBP, coagulopathy, and HRS, as well as concomitant cardiovascular disease. In gathering additional pertinent information in the evaluation of the patient with cirrhosis before dental treatment, the dentist should establish the underlying etiology of cirrhosis (if known) and determine the presence of continued risk factors for cirrhosis (eg, alcohol use). In addition, the dentist should review current laboratory test results, including:

- serum bilirubin
- serum albumin
- AST
- ALT
- serum gamma-glutamyl transpeptidase
- complete blood count with differential (including platelet count)
- partial thromboplastin time
- prothrombin time (PT) or INR

Cirrhosis (and liver disease in general) may have complex effects on drug clearance, biotransformation, and pharmacokinetics. Pathogenetic factors include alterations in absorption, plasma protein binding, intrinsic clearance and hepatic extraction ratio, liver blood flow and vascular shunting, biliary excretion, enterohepatic circulation, and renal clearance.

Patients with cirrhosis may have an unpredictable hepatic metabolism of drugs that can lead to atypical effects of administered or prescribed dental medications. However, the hepatic reserve appears to be large and liver disease has to be severe before important changes in drug metabolism take place. The ability to eliminate a specific drug may or may not correlate with liver's synthetic capacity for substances such as albumin or clotting factors, which tends to decrease as hepatic function declines.

Unlike renal disease, where estimates of renal function based on creatinine clearance correlate with parameters of drug elimination such as clearance and half-life, routine liver function tests do not reflect actual liver function but are rather markers of liver-cell damage. Therefore, no general rules are available for modifying dosage in patients with liver disease. However, as a general guideline, a dosage reduction of drugs metabolized

by the liver should be considered if one (or more) of the following are present [11]:

- AST or ALT levels elevated >4 times normal;
- serum bilirubin elevated above 2.0 mg/dL;
- serum albumin <3.5 g/dL;
- signs of ascites or encephalopathy attributable to hepatic failure.

Patients with cirrhosis may demonstrate a significant decrease in hepatic drug metabolism resulting in an increased or unpredictable effect at normal doses. Therefore, the clinician should be careful to avoid or reduce the use of hepatically metabolized drugs used or prescribed in dental treatment as outlined in Table 4 [44,63–65]. It has also been suggested that patients with cirrhosis should be given only half the initial dose of an oxidized drug (eg, drugs that would be inactivated by a normal microsomal enzyme system) and adjustment should be made according to therapeutic response or side effects [66].

The medical management of coagulopathy and thrombocytopenia as a complication secondary to cirrhosis (ie, with fresh frozen plasma, recombinant factor VII, platelet replacement) has been previously discussed. Local hemostatic measures (eg, pressure, absorbable gelatin sponges, oxidized cellulose, microfibrillar collagen, topical thrombin, epsilon-aminocaproic acid used as an oral irrigant, sutures, surgical splints and stents) may also prove useful in controlling bleeding associated with dental procedures in patients with cirrhosis.

If any significantly abnormal result in platelet count, PT or INR, partial thromboplastin time, or other coagulation test is detected in a patient with cirrhosis, consultation with a hematologist or hepatologist is recommended before beginning dental treatment. Consultation with a hematologist or hepatologist is also recommended in cases where the patient shows clinical signs of jaundice, ascites, or clubbing of fingers, or is classified as Child–Turcotte–Pugh class B or C [11]. If oral surgical procedures are required, special attention should be paid to the meticulous surgical technique and minimization of unnecessary tissue trauma to the patient. Advanced oral surgical procedures, or any major invasive or traumatic dental procedures with the potential to cause bleeding performed on a patient with multiple or a severe single coagulopathy may need to be provided in a hospital setting [9].

As previously discussed, patients with cirrhosis demonstrate an increased susceptibility to infection due to a number of contributory and predisposing factors. Any orodental infection in a patient with cirrhosis should be treated aggressively with appropriate antibiotic therapy. Concern also exists regarding the potential for the increased risk of infections occurring after invasive dental and oral surgical procedures in patients with cirrhosis. Currently, there is no evidence-based data to support the recommendation that patients with advanced liver disease or cirrhosis should have antibiotic prophylaxis before routine dental procedures. However, some sources recommend that

Table 4
Drug use in patients with cirrhosis

Drug	Use in patients with cirrhosis	Comments
Acetaminophen	Yes, with modifications	Acetaminophen can be given to adults with cirrhosis in divided doses of no more than 4.0 gm per day for up to 2 weeks without adverse hepatic effects. Patients should be strongly advised not to take alcohol during the period when they are using acetaminophen.
Amide local anesthetics (eg, lidocaine, mepivacaine)	Yes, with caution	Most amide local anesthetics (eg, lidocaine, mepivacaine) are primarily metabolized (~90%) in the liver. Articaine is metabolized primarily (90–95%) in the plasma, while prilocaine is metabolized in the liver and kidneys. The serum-elimination phase of lidocaine, and of amides in general, is significantly increased when there has been severe destruction of hepatic tissue. However, lidocaine has a large and rapid volume of distribution. Once lidocaine has become distributed, only 6% of that volume is present in the blood. Changes in hepatic metabolic function, and subsequently lidocaine's elimination half-life, cause only a minimal elevation of the peak blood concentrations after single-dose use, such as in local anesthesia, and are usually clinically insignificant. Therefore, amide local anesthetics can be used with relative safety in the treatment of patients with cirrhosis. However, caution should still be exercised since they are at still at some degree of increased risk of developing toxic plasma concentrations. The minimum dose necessary to achieve adequate local anesthesia should be administered.
Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)	Avoid	The clearance of aspirin and NSAIDs is relatively normal in patients with chronic liver disease, but these drugs are protein bound. A decrease in serum protein concentrations may result in enhanced toxicity inasmuch as more free drug will be available. The antiplatelet effect of both aspirin and NSAIDs in patients already susceptible to bleeding makes their use hazardous. In addition, esophageal varices, hemorrhagic gastritis, and peptic ulcers are commonly found in patients with portal hypertension. The tendency of these drugs to cause erosive lesions of the stomach and esophagus is well known, and they pose a particular threat to these patients. Prophylaxis with an antacid or histamine receptor antagonist may be considered to prevent gastritis and gastrointestinal bleeding associated with the hepatic dysfunction. However, the use of aspirin and NSAIDs in patients with cirrhosis should be avoided if at all possible.

Benzodiazepines	Yes, with modifications	In patients with cirrhosis, hydrolytic reactions are impaired. This causes a decrease in metabolism, with a subsequent accumulation of benzodiazepines (and any active metabolites if produced) leading to excess sedation with repeated doses. It has also been suggested that, in the patient with cirrhosis, benzodiazepine receptors in the brain are more sensitive to this class of drug, which may lead to or exacerbate hepatic encephalopathy independent of limitations in drug elimination and accumulation. If a benzodiazepine is to be used, the dosage should be decreased and given at less frequent intervals. Also, benzodiazepines without significant active metabolites (eg, alprazolam, lorazepam) are preferable over those with active metabolites (eg, diazepam).
Beta lactam antibiotics (eg, penicillin, amoxicillin)	Yes	In general, antibiotics of the beta-lactam group (including first-generation cephalosporins) can be used, inasmuch as their means of elimination are predominantly renal filtration and tubular excretion. Penicillin, ampicillin, amoxicillin, cephalexin, and cefazolin are generally well tolerated in patients with cirrhosis.
Clindamycin	Avoid	The metabolism of clindamycin is prolonged in patients with chronic liver disease. There have been reports of progressive liver disease in patients receiving clindamycin, and there is evidence suggesting that the drug contributed to the damage. Clindamycin should be avoided in patients with cirrhosis.
Macrolide antibiotics: azithromycin	Yes, with caution	Azithromycin is principally eliminated via the liver. Therefore, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Abnormal liver function, including cholestatic jaundice, and hepatitis, and pancreatitis have been reported infrequently in clinical trials or during postmarketing studies with azithromycin. Hepatic necrosis and hepatic failure, sometimes resulting in death, have occurred rarely.
Macrolide antibiotics: clarithromycin	Yes, with caution	Liver function impairment alters the pharmacokinetics of clarithromycin by decreasing the amount of metabolites formed and increasing the renal clearance of the parent drug; however, steady-state concentrations in patients with mild to severe hepatic function impairment do not differ from those in patients with normal hepatic function, unless there is also concurrent severe renal function impairment; no dosage adjustment is necessary in patients with hepatic function impairment if renal function is normal.

(*continued on next page*)

Table 4 (*continued*)

Drug	Use in patients with cirrhosis	Comments
Macrolide antibiotics: erythromycin	Yes, with caution	Erythromycin is principally excreted by the liver. The elimination half-life of both orally and parenterally administered erythromycin has been shown to be increased in patients with impaired hepatic function due to alcoholic liver disease. Additionally, there have been reports of hepatic dysfunction, including increased liver enzymes, hepatitis hepatocellular and cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral or parenteral erythromycin products. Therefore, caution should be exercised when erythromycin is administered to patients with impaired hepatic function.
Metronidazole	Yes, with modifications	Obstructive liver disease affects metronidazole metabolism to a greater extent than does hepatocellular liver disease. It has been recommended that if this drug is used for the patient with end-stage liver disease, 500 mg be given on a 12-hour regimen instead of the usual 6-hour regimen.
Narcotic analgesics	Yes, with modifications	Like all drugs that depress the central nervous system, narcotic analgesics may trigger or aggravate hepatic encephalopathy when used in patients with end-stage liver disease; the mechanism is not clear. Codeine is readily absorbed from the gastrointestinal tract, is rapidly distributed to body tissues, and is preferentially deposited in such organs as the spleen, kidney, and liver. Codeine (and presumably its derivatives, such as oxycodone and hydrocodone) can be used in patients with cirrhosis, but the dosage intervals need to be increased. Chronic use should be avoided. These drugs should be used with caution in combination with other drugs, such as acetaminophen, that may compete with glucuronic conjugation pathways. This system may become rapidly depleted, which can lead to the formation of hepatotoxic metabolites that may cause further injury to the already compromised liver.

Data from Refs. [43,62–64].

dentists consult with the patient's physician regarding the use of prophylactic antibiotics to prevent postoperative infections in patients likely to respond poorly to invasive procedures and infections, such as those with moderate to severe cirrhosis (eg, Child–Turcotte–Pugh class B or C), or those with history of bacterial infections (eg, SBP, pneumonia, bacteremia) [11].

Another area of concern in the patient with cirrhosis involves the potential for bacteremias occurring as a result of invasive dental and oral surgical procedures increasing the risk of SBP in these patients. These concerns are primarily based upon reports of SBP occurring in patients with cirrhosis due to bacteremias that resulted from other procedures, such as endoscopy [67,68]. Based on these reports, at least one source [44] recommends that the clinician should consider antibiotic prophylaxis before invasive dental treatment with the pre-LT patient who has cirrhosis and a history of SBP, or with a patient demonstrating LT rejection, as well as with any patient with cirrhosis who has ascites, or whose medical condition would drastically deteriorate should SBP develop. When antibiotic premedication is indicated to prevent SBP, the authors recommend oral administration of 2 g of amoxicillin in addition to 500 mg of metronidazole 1 hour before the procedure.

Conversely, a review of the literature failed to find any evidence of SBP occurring as a result of, or attributed to, dental treatment procedures. At least one case of SBP due to infection by *Streptococcus salivarius* in a patient with cirrhosis has been reported [69]. However, dental treatment, oral infection, or ''poor teeth'' were not implicated as source of the infection.

An additional consideration in the dental management of the patient with cirrhosis with ascites involves that potential for discomfort to the patient while in the reclined position because of increased abdominal size and weight, which would place excessive pressure on the abdominal blood vessels. The upright or semireclined position is recommended. If the clinician is uncertain which is best, the patient should be asked which position is most comfortable. Long appointments should be avoided for the same reason [70].

See the article by Goldman about dental management of the post-LT patient elsewhere in this issue.

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