Liver transplantation (LT) has grown dramatically over last 2 decades and the hepatologist has had to assume a larger role in managing the potential candidate awaiting surgery. In part 1 of this review, we described the pre-LT evaluation process, contraindications of LT, general care, and treatment of various etiologies of liver disease prior to LT. In this part, we review the management of liver-specific complications that are responsible for significant morbidity and waitlist mortality of LT candidates.

Liver-Specific Complications

Portal Hypertension

Portal hypertension is the main complication of liver cirrhosis. This syndrome develops in the majority of patients with cirrhosis and is responsible for most life-threatening complications of cirrhosis, including gastrointestinal bleeding from ruptured gastroesophageal varices, hepatorenal syndrome, and hepatic encephalopathy.

Prophylaxis of Esophageal Variceal Bleeding

The average lifetime risk of variceal bleeding in patients with cirrhosis who have had no previous bleeding is 30%.1 Each bleeding episode bears a mortality risk of 30 to 50%.2 In prospective studies, advanced Child-Turcotte-Pugh stage, large esophageal varices, and red wale markings are independent risk factors for 1st variceal bleed.3–5 The modalities available for primary prophylaxis are nonselective β-blockers, endoscopic therapy, and transjugular intrahepatic portosystemic shunt (TIPS). Nonselective β-blockers decrease portal pressure and collateral flow through a combination of decreased cardiac output and unopposed alpha-mediated splanchnic vasoconstriction, resulting in decreased effective splanchnic blood flow, thereby reducing the risk of initial variceal bleeding and a trend toward decreased mortality.6–8 β-blockers should be considered in all patients with large varices and red markings.7 Propranolol or nadolol can be used and the dose should be titrated weekly to decrease the resting heart rate by 25% and the systolic blood pressure to no lower than 90 mm of Hg.9 The risk reduction with β-blockade averages less than 50% and the maximum benefit is seen in patients with Child-Turcotte-Pugh A and B cirrhosis. More than 30% of patients have no decrease in portal pressure despite adequate β-blockade.10 The addition of long-acting nitrates to nonselective β-blockers has been shown to enhance their hemodynamic effect and reduce the risk of bleeding from esophageal varices and therefore should be considered in patients who do not respond ideally to β-blockers.11 Poorer results compared with pharmacotherapy have led to the discontinuation of endoscopic variceal sclerotherapy as primary prophylaxis for variceal bleeding.12–14 Sarin et al.15 showed that endoscopic variceal band ligation is safer and more effective than propranolol for the primary prevention of variceal bleeding. However, in a recent randomized controlled multicenter trial that evaluated primary prophylaxis of variceal bleeding, variceal band ligation and propranolol were similarly effective.16 Despite effectiveness in the arrest of bleeding, TIPS cannot be recommended as a 1st-line approach to manage variceal bleeding or for primary prophylaxis because of increase incidence of hepatic encephalopathy and expense related to the management of TIPS malfunction.17,18

Gastric Variceal Bleeding

No specific measures are available to prevent 1st bleeding from gastric varices. Most of the current regimens to treat gastric varices are derived from anecdotal evidence.
or are extrapolated from trials of esophageal varices.\textsuperscript{14,19} TIPS is very effective with a success rate of 90% for initial hemostasis. The rate of early rebleeding after TIPS procedure is 20% and often the source of such bleeding is nonvariceal, i.e., ulcer secondary to banding or sclerosis.\textsuperscript{18}

**Treatment of Acute Variceal Bleeding**

Patients suspected of acute variceal bleeding should be managed in the intensive care setting. General principles of resuscitation should be followed, which include protection of airway, insertion of 2 large-bore intravenous cannulas, blood volume resuscitation with packed erythrocytes, correction of coagulopathy with fresh frozen plasma, and platelet transfusion if they are below 30,000/mm\textsuperscript{3}. Care must be taken not to overexpand plasma volume, which may increase portal pressure and result in exacerbation of variceal bleeding and ascites. Antibiotics should be administered prophylactically, especially in patients with ascites, to prevent spontaneous bacterial peritonitis.\textsuperscript{20,21} Emergency endoscopy of the upper gastrointestinal tract can then be performed and the most appropriate treatment modality should be chosen at that point. The drug classes that have been extensively studied in acute variceal bleeding are vasopressin and somatostatin and their analogs. Both somatostatin and vasopressin arrest variceal bleeding by causing splanchnic vasoconstriction and thereby decreasing the portal pressure, but this has no effect on mortality.\textsuperscript{19} There is an increased association between myocardial infarction and arrhythmias and the use of vasopressin. Furthermore, bowel ischemia, cerebrovascular ischemia, and peripheral tissue necrosis have been reported. The severity of complications such as myocardial ischemia has led to discontinuation of the use of vasopressin.\textsuperscript{14}

Terlipressin is a longer acting analog of vasopressin and can be given as bolus-infusion every 4 hours. Its efficacy is similar to vasopressin in controlling the acute variceal bleeding and is associated with fewer side effects.\textsuperscript{22} The ease of administration has allowed for paramedic administration in the field with arrest of bleeding prior to arrival at the hospital. Terlipressin is not yet approved for use in the United States.

Somatostatin is superior to vasopressin for immediate control of bleeding and has less severe side effects than vasopressin, although survival improvement has not been seen with somatostatin.\textsuperscript{19}

Octreotide is a synthetic analog of somatostatin. When compared with other vasoactive drugs, octreotide was better than vasopressin and equivalent to terlipressin for controlling bleeding. The side effects were less frequent and less severe with octreotide than with either vasopressin or terlipressin. However, the efficacy of octreotide as a single therapy is controversial. Results from a recent meta-analysis suggest that octreotide may improve the results of endoscopic therapy but has no or little effect if used alone.\textsuperscript{19}

Endoscopic sclerotherapy controls active hemorrhage in 80 to 90% of patients. However, a skilled endoscopist must be readily available, and the procedure is associated with serious complications in 10 to 20% of patients, with an overall mortality of 2%.\textsuperscript{19} The combination of sclerotherapy with somatostatin, octreotide, and vaptreotide has been reported to be superior to sclerotherapy alone in terms of control of bleeding and reduction of treatment failures within 5 days.\textsuperscript{23,24}

The 6-week survival of the combination of sclerotherapy and drugs was similar to sclerotherapy alone. Variceal band ligation was shown to be better than endoscopic sclerotherapy in controlling the acute bleed and mortality.\textsuperscript{25} The banding may be more challenging during active bleeding due to reduction in the field of vision by as much as 30% with the addition of banding device to the endoscope. The choice of procedure depends on the available expertise in the center managing the patient; variceal banding has become the procedure of choice in the management of variceal bleeding.

Balloon tamponade is a useful temporary measure to control acute variceal bleeding and to stabilize the patient while more definitive procedures are being accomplished. Control of bleeding is successful in as many as 80 to 90% of cases, but rebleeding occurs in up to 50% when the balloon(s) are deflated. Furthermore, significant perforation risk is present that may lead to high mortality if the balloons are inflated for prolonged periods of time.\textsuperscript{7}

Rebleeding is a very common and usually occurs within 6 weeks of the index episode. The recurrence reported as high as 70% in patients who have had at least 1 prior bleeding episode.\textsuperscript{21} The use of β-blockers (with and without variceal band ligation) is the most accepted approach to manage these patients. There is still debate about the cost-effectiveness of this pharmacological approach combined with endoscopy.

In approximately 10% of patients in whom rebleeding cannot be controlled with 2 endoscopic therapeutic sessions within 24 hours, either surgery or TIPS should be planned. At the most recent American Association for the Study of Liver Diseases meeting, Henderson et al.\textsuperscript{26} presented the 1st analysis of the multicenter study of distal splenorenal shunt vs. TIPS for refractory variceal bleeding. This study found that both modali-
ties were equally effective in preventing rebleeding, and encephalopathy and survival were similar. TIPS can be used in patients with Child-Turcotte-Pugh class B or C cirrhosis as a salvage therapy and preferably as a bridge to transplant. Worsening of hepatic encephalopathy after TIPS procedure may impair the outcome compared to Child-Turcotte-Pugh A patients.

**Ascites**

Ascites is the most common major complication of portal hypertension. The initial evaluation of a patient with ascites should include a history, physical evaluation, and abdominal paracentesis with ascitic fluid analysis. Bleeding is sufficiently uncommon so as to obviate the routine requirement for fresh frozen plasma or platelets prior to a diagnostic paracentesis. The initial ascitic fluid analysis should include a cell count and differential and serum-ascites albumin gradient. The culture yield increases to 80% when ascitic fluid with a polymorphonuclear count >250 cells/mm³ is inoculated directly into blood culture bottles at the bedside.

The mainstay of treatment of patients with ascites includes education regarding dietary sodium restriction (2,000 mg/day or 88 mmol/day) and oral diuretic therapy that has been shown to be effective in 90% of patients. Chronic hyponatremia is commonly seen in cirrhotic patients and is seldom morbid, although recent data has shown that hyponatremia is an independent risk factor for death while awaiting LT. Rapid attempts to correct hyponatremia can lead to more complications, such as central pontine myelinolysis, than hyponatremia itself, although severe hyponatremia will increase the risk of posttransplant neurological complications. Severe hyponatremia (serum sodium <120 mmol/L) requires fluid restriction in cirrhotic patients with ascites. Cirrhotic patients do not usually have symptoms from hyponatremia until their sodium levels fall below 110 mmol/L, or unless the decline in sodium is very rapid. Recently, Gerbes et al. showed that VPA-985, an orally active vasopressin 2 receptor antagonist, can correct severe hyponatremia in patients with cirrhosis and ascites, its clinical utility remains to be determined.

The usual diuretic therapy consists of single morning doses of oral spironolactone and furosemide, beginning with 100 and 40 mg, respectively. Single-agent furosemide has been shown to be less efficacious than spironolactone in a randomized controlled trial. The dose of both oral diuretics can be increased simultaneously, maintaining the 100 mg / 40 mg ratio, with a maximum of 400 mg/day / 160mg/day, if weight loss and natriuresis are inadequate on lower doses. In general, this ratio maintains normokalemia. Furosemide can be temporarily withheld in patients presenting with hypokalemia. Single morning dosing tends to increase compliance and is recommended. The antiandrogenic effects of spironolactone, such as decreased libido, impotence, and gynecomastia in men may require dose reduction or discontinuation of the medicine. Amiloride can be substituted for spironolactone, but it is more expensive and has been shown to be less effective in a randomized control trial.

The etiology of nocturnal muscle cramps is not well understood and may respond to magnesium supplementation or the oral administration of quinine sulfate at a dose of 325 mg in the evening. Serum sodium less than 120 mmol/day despite fluid restriction and serum creatinine >2.0 mg/dL should result in the cessation of diuretic therapy, reassessment of the situation and consideration of 2nd-line options. These patients should be monitored for daily weight, orthostatic symptoms, and periodic serum electrolytes, blood urea nitrogen, and creatinine. Random urine sodium concentration is measured if the weight loss is not adequate. The frequency of follow-up is determined by response to treatment and by patient stability.

Refractory ascites is defined as ascites that is not responsive to sodium-restricted diet and high-dose diuretic treatment in the absence of prostaglandin inhibitors such as nonsteroidal antiinflammatory drugs. Serial therapeutic paracentesis are effective in controlling ascites. Serial therapeutic paracentesis should be performed as needed, approximately every 2 weeks. The postparacentesis albumin infusion is expensive and unproven to be necessary for paracentesis of <5 L. For larger volume paracentesis, an albumin infusion of 5–8 g/L of ascitic fluid removed can be considered.

LeVeen or Denver shunts were popularized in the 1970s as a physiologic treatment of ascites. Shunt placement has been shown in controlled trials to decrease the duration of hospitalization, the number of hospitalizations and the dose of diuretics. However, their poor long-term patency, significant complication profile, and lack of survival advantage compared with medical therapy in controlled trials have led to near abandonment of these devices. Shunt-related fibrous adhesions can make subsequent LT difficult.

TIPS is physiologically equivalent to a side-to-side portocaval shunt that is placed by an interventional radiologist. Five randomized trials comparing TIPS and large volume paracentesis have demonstrated
that TIPS is effective in minimizing ascites and in reducing the need for paracentesis. However, whether the TIPS procedure improved survival of the patients with cirrhosis and refractory ascites is still debated; the trials have reported the discordant results of the effect of TIPS on survival. Rossle et al. and Salerno et al. showed that TIPS was independently associated survival without LT. Salerno et al. observed the relative risk of dying was 2.95 times greater in patients assigned to the paracentesis group, according to the multivariate analysis. The results from the North American Study for the Treatment of Refractory Ascites and a randomized trial from the University of Barcelona, Spain showed that TIPS is substantially superior to conventional medical therapy but does not improve the survival or quality of life. The reasons why randomized trials have not demonstrated a survival benefit are unclear. However, the Child-Turcotte-Pugh class or its component was similar among the trials. Factors associated with increased mortality after TIPS include Child-Turcotte-Pugh class C, renal insufficiency, hyperbilirubinemia, marked coagulopathy, and advanced age. Before recommending TIPS to LT candidates, the risks and benefits should be carefully assessed to avoid a potentially catastrophic outcome.

**Spontaneous Bacterial Peritonitis**

Spontaneous bacterial peritonitis (SBP) is a particularly important complication because the presence of infection usually removes a patient from consideration of transplantation until the infection is cleared. A diagnostic abdominal paracentesis must be performed and the ascitic fluid must be analyzed for cell count and bacterial culture before a confident diagnosis of ascitic fluid infection is made. The diagnosis of SBP is made when there are >250 polymorphonuclear cells per milliliter and/or positive ascitic fluid bacterial culture without an evident intra-abdominal or surgically correctable source. These patients should receive empiric treatment with broad-spectrum antibiotics. Delaying treatment until the ascitic fluid culture grows bacteria may result in the patients’ death from overwhelming infection. Cefotaxime, a 3rd generation cephalosporin, has been shown to be superior to ampicillin in combination with tobramycin in a controlled trial. In a randomized controlled trial involving 100 patients, it has been reported that 5 days of treatment is as efficacious as 10 days of treatment in the treatment of carefully characterized patients with SBP. Patients with less than 250 polymorphonuclear cells in ascitic fluid and signs or symptoms of infection should also receive empiric antibiotic therapy.

Oral ofloxacin has been reported in a randomized controlled trial to be as effective as parenteral cefotaxime in the treatment of SBP in patients who are not vomiting and are not in shock. Repeat paracentesis should be performed to document cultures sterility and decrease in polymorphonuclear cell count in patients with SBP; this step is particularly important in cases in which clinical improvement is not apparent after the 1st 3 days of antibiotic therapy.

**Hepatic Encephalopathy**

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that may complicate acute or chronic liver failure. It is characterized by changes in mental state, including a wide range of neuropsychiatric symptoms ranging from minor signs of altered brain function to deep coma. Most theories explaining the pathogenesis of HE accept that nitrogenous substances derived from the gut adversely affect brain function. These compounds gain access to the systemic circulation as a result of decreased hepatic function or portosystemic shunts and may produce alterations of neurotransmission that affect consciousness and behavior. Abnormalities in glutaminergic, serotoninergic and gamma-aminobutyric acidic, and catecholamine pathways, among others, have been described in experimental HE. A large body of work points towards ammonia as a key factor in the pathogenesis of HE.

The approach to HE has not changed significantly in recent years. HE is a diagnosis of exclusion and is mainly clinical. The suspicion of HE in patients with chronic liver disease should prompt the search for the precipitating factors that include gastrointestinal bleeding, electrolyte abnormalities, renal failure, infection, recent placement of TIPS shunt, use of sedatives / hypnotics, development of hepatocellular carcinoma, and constipation. However, the other causes of change in mental status such as intracranial bleed or masses, hypoglycemia, and a postictal state should be ruled out. Although hyperammonemia is associated with HE, ammonia levels do not correlate with the level of encephalopathy.
The treatment goals for HE are provision of supportive care, identification and removal of precipitating factors, and reducing the production and absorption of nitrogenous load from the gut. Ultimately, assessment of the need for long-term therapy is very important.

There is no good clinical evidence supporting protein restriction in patients with acute hepatic encephalopathy. The only randomized trial, reported only in abstract form, found no difference between moderate (.8 gm/kg per day) and more aggressive protein restriction. Zinc, a cofactor of urea cycle enzymes, may be deficient in cirrhotic patients, especially if associated with malnutrition. Zinc supplementation improves the activity of the urea cycle in experimental models of cirrhosis. One trial has evaluated the effects of zinc over a short period (up to a week), without major improvement. Another nonrandomized study reported positive results with administration of zinc for 3 months. However, this anecdotal report has not been confirmed in larger studies.

Nonabsorbable disaccharides such as lactulose are routinely used to decrease ammonia production in the gut. Lactulose increases fecal nitrogen excretion by facilitation of the incorporation of ammonia into bacteria as well as by its cathartic effect. Lactulose administered orally reaches the cecum, where it is metabolized by the enteric bacteria, causing a fall in pH. This drop in pH leads to metabolic shift in bacteria favoring uptake of ammonia. The dose is adjusted to produce 2 or 3 soft bowel movements daily. A systematic review found that lactulose or lactitol were more effective than placebo in improving hepatic encephalopathy but had no significant benefit on mortality. However, the benefit on encephalopathy no longer reached statistical significance when the analysis was confined to studies with the highest methodologic quality. The authors also found that antibiotics appeared to be relatively more effective.

Antibiotics such as neomycin, low dose metronidazole, vancomycin, and rifaximin are also useful for lowering blood ammonia, mainly by an effect on ammonia production by intestinal bacteria. However, antibiotic therapy may be associated with significant toxic side effects (e.g., renal failure, ototoxicity, and peripheral neuropathy).

An alternate strategy for lowering of blood ammonia is the stimulation of ammonia fixation. Under normal physiological conditions, ammonia is removed by the formation of urea in periportal hepatocytes and by glutamine synthesis in perivenous hepatocytes, skeletal muscle, and brain. In cirrhosis, both urea cycle enzymes and glutamine synthetase activity are decreased in the liver. Strategies to stimulate residual urea cycle activities and/or glutamine synthesis have been tried over the last 20 years. One of the most successful agents to be used so far is L-ornithine L-aspartate. Randomized controlled clinical trials with L-ornithine L-aspartate demonstrate significant ammonia lowering and concomitant improvement in psychometric testing.

Benzoate is also effective in reducing blood ammonia both in patients with inherited urea cycle disorders and in cirrhotic patients. In a randomized controlled clinical trial with sodium benzoate vs. lactulose, improvement in neuropsychiatric performance was found to be comparable.

Several controlled clinical trials have been performed to assess the efficacy of the benzodiazepine receptor antagonist flumazenil in cirrhotic patients with various degree of severity of HE. Spectacular improvements in neuropsychiatric status were recorded in a subset of patients receiving flumazenil. However, the possible confounding effects of prior exposure to benzodiazepines, possibility of seizures, and lack of correlation between the clinical response and blood levels of diazepines have tempered enthusiasm for the use of benzodiazepine receptor agonist in these patients.

**Renal Insufficiency and Hepatorenal Syndrome**

Acute renal failure is thought to be common in patients with cirrhosis, but its exact incidence is variable. Patients with cirrhosis are predisposed to acute renal failure following complications such as variceal bleeding or administration of nephrotoxic drugs such as nonsteroidal antiinflammatory drugs, antibiotics, diltiazem, etc. The cause of renal insufficiency could be prerenal, intrarenal, or hepatorenal. The management of renal insufficiency in patients awaiting LT focuses on prevention of additional injury and optimization of existing renal function. Nonsteroidal antiinflammatory drugs should be used only with close follow-up, because the subsequent decrease in renal prostaglandin may precipitate acute renal failure. Radiographic imaging studies using intravenous contrast dye also need to be approached with caution because of the known risk of renal injury. The use of acetylcysteine together with hydration is the treatment of choice to protect against radiographic contrast media-induced nephropathy. Large volume paracentesis followed by intravenous albumin infusion decreases the risk of acute renal failure after paracentesis. The results of albumin use in this clinical setting are better than other volume expanders such as dextran. In a recent study comparing normal saline and albumin, albumin was more effective...
than saline in the prevention of paracentesis-induced circulatory dysfunction.\textsuperscript{67} Saline is a valid alternative to albumin when less than 5 L of ascitic fluid is evacuated.

Moreover, patients with cirrhosis may develop a specific acute renal failure called hepatorenal syndrome (HRS). It is a diagnosis of exclusion. HRS is an ominous complication of end-stage liver disease. Retrospective studies indicate that HRS is present in \(~17\%) of patients admitted to the hospital with ascites and in \(>50\%) of cirrhotic patients who die from liver failure. The hallmarks of HRS are reversible renal constriction and mild systemic hypotension.\textsuperscript{68} The kidneys are structurally normal and at least in the early part of the syndrome, tubular function is intact, as reflected by avid sodium retention and oliguria. The cause of renal vasoconstriction is unknown, but its pathogenesis may predominantly involve both increased vasoconstrictor and decreased vasodilator factors. Two patterns of HRS are observed in clinical practice: type 1 and type 2. Type 1 HRS is an acute form of HRS in severe liver disease and is progressive. It is associated with poor prognosis with 80\% mortality at 2 weeks. Type 2 HRS occurs in patients with diuretic-resistant ascites. The course of renal failure is slow. It is also associated with poor prognosis, although the survival time is longer than that of patients with type 1 HRS. The definition of HRS was proposed by the International Ascites Club.\textsuperscript{36}

Although the best treatment for HRS is LT, patients with HRS who are transplanted have more complications and a higher in-hospital mortality rate than those without HRS.\textsuperscript{69} It has been suggested that systemic vasoconstrictor therapy may improve renal function in patients with HRS by increasing the effective arterial blood volume. A nonrandomized retrospective study in a large series of patients with HRS suggests that the vasopressin analog terlipressin is an effective treatment of renal failure.\textsuperscript{70} Other nonrandomized studies suggest that vasoconstrictive therapy with noradrenaline\textsuperscript{71} or midodrine combined with octreotide\textsuperscript{72} may improve renal function in these patients. TIPS has previously been shown to have beneficial effect on renal function in HRS.\textsuperscript{73} In a recent study by Wong et al.,\textsuperscript{74} TIPS was associated with further improvement in the renal function as well as circulatory function, with normalization of effective arterial blood volume in selected type 1 HRS patients (international normalized ratio less than 2, bilirubin less than 5 mg/dL, and Child-Turcotte-Pugh lower than 12), following administration of combination therapy with midodrine, octreotide, and albumin.\textsuperscript{74} A randomized study in a small series of patients, comparing the molecular adsorbent recirculating system combined with intermittent venovenous hemofiltration vs. intermittent venovenous hemofiltration alone, suggests that the molecular adsorbent recirculating system may improve survival in HRS.\textsuperscript{75}

**Hepatopulmonary Syndrome**

Hepatopulmonary syndrome (HPS) is a progressive, debilitating complication of end-stage liver disease that occurs in 4 to 25\% of liver transplant candidates.\textsuperscript{76–78} The diagnosis of HPS rests on the triad of cirrhosis, hypoxemia, and intrapulmonary vascular dilation. Pulmonary features include digital clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia.

LT candidates with hypoxemia (PaO\textsubscript{2} < 70 mm of Hg or arteriolar–aerolar gradient >20) in the absence of any pulmonary dysfunction, should be screened for HPS since the syndrome appears to resolve after orthotopic LT. Further work-up should include an arterial blood gas on 100\% oxygen, double contrast echo or 99mTc macro-aggregated albumin brain perfusion scan to establish the presence of intrapulmonary vascular dilatation. The presence of microbubbles in the left cardiac chambers between 3 and 6 heartbeats after the visualization in the right chambers and a shunt fraction of more than 6\% is considered as a positive test for the presence of intrapulmonary vascular dilatation and thus confirms the diagnosis.\textsuperscript{79,80} Figure 1 illustrates the work for HPS.

Patients with HPS awaiting LT get a priority over other patients. Complete resolution after orthotopic LT even in the setting of severe hypoxemia has been well documented.\textsuperscript{59,77} However, PaO\textsubscript{2} less than 50 mm of Hg and 99mTc macro-aggregated albumin brain uptake >20\% are the pretransplantation risk factors for increased mortality.

Efforts have to be made to rule out intrapulmonic shunting. Pharmacologic approaches have been disappointing in providing consistent and reproducible improvement in hypoxemia.\textsuperscript{81} The placement of TIPS to improve hypoxemia due to HPS remains controversial and cannot be advised without further prospective study.\textsuperscript{82} Coil embolization to occlude discrete arteriovenous communications in patients with severe hypoxemia and HPS has resulted in significant improvement in PaO\textsubscript{2} in 2 adults.\textsuperscript{83} Embolotherapy is an accepted approach to the management of severe hypoxemia associated with discrete arteriovenous malformation,\textsuperscript{84} but is not effective in HPS due to capillary dilation without discrete anatomic shunting.
Portopulmonary Hypertension

Portopulmonary hypertension (PPH) refers to the development of pulmonary arterial hypertension in the setting of portal hypertension with or without liver disease. It is defined as mean pulmonary artery pressure (PAP) >25, with a normal pulmonary capillary wedge pressure, an elevated pulmonary vascular resistance >125 dynes/second/cm⁻⁵, or increased trans pulmonary gradient (mean PAP / pulmonary capillary wedge pressure >10 mm of Hg). Candidates with PAP greater than or equal to 40 mm of Hg on echocardiography should undergo a right heart catheterization to confirm the diagnosis of PPH. Figure 2 illustrates the work-up for PPH. It has been estimated that in patients who undergo LT with a mean PAP between 35 and 49 mm of Hg and pulmonary vascular resistance >250 dynes/second/cm⁻⁵ or greater, the mortality is 50%. Patients with a mean PAP of 50 mm of Hg or greater have a cardiopulmonary mortality rate of 100%. It is therefore recommended that moderate to severe PPH and significant right ventricle dysfunction should be considered contraindications to LT.

However, preoperative therapy to reduce PPH and right ventricular dysfunction may improve clinical status and make LT feasible. Continuous intravenous epoprostenol (prostacyclin, or prostaglandin I₂) is a potent vasodilator shown to improve exercise tolerance, reduce pulmonary vascular resistance, and improve mortality in patients with primary pulmonary hypertension. Similar hemodynamic improvements have been achieved before LT in patients with PPH. Kuo et al. treated 4 patients with 10–28 ng/kg/minute of epoprostenol over 6 to 14 months and reported a 29 to 46% decrease in mean PAP, a 22 to 71% decrease in pulmonary vascular resistance, and a 25 to 75% increase in cardiac output. Krowka et al. treated 10 patients with mean PAP of 35 mm of Hg and higher for 8 days to 30 months. Six patients showing improvements in pulmonary vascular resistance, mean PAP, and cardiac output after 1 hour had further reduction of pulmonary vascular resistance when treated with continuous therapy. Not enough data exist regarding the long term benefit of epoprostenol therapy or regarding the lasting effect after the cessation of therapy to make any recommendations. However, epoprostenol therapy is most appropriate for the cirrhotic patient who except for moderate to severe PPH has no other contraindication for LT.

Hepatic Hydrothorax

Hepatic hydrothorax is defined as the accumulation of fluid in the pleural space as a consequence of liver disease. The most common symptom is dyspnea without chest pain. It can be detected with chest radiographs in as many as 13% of patients with cirrhosis. Right-sided pleural effusion is seen in 66% of the patients with hepatic hydrothorax. The management options for hepatic hydrothorax include medical management of ascites, and therapeutic thoracocentesis for the control of shortness of breath. The pleural fluid usually has the characteristics of a transudate. However, an occasional patient with hepatic hydrothorax may develop “spontaneous bacterial pleuritis.” They should be treated as for SBP; insertion of chest tube is contraindicated in these patients. TIPS has been successfully used to manage the symptoms of hepatic hydrothorax in the setting of marked ascites. Pleurodesis of the pleural space with chemical means such as talc, antibiotics, or chemotherapeutic agents usually fails. Video thoracoscopy with the repair of presumed diaphragmatic defects has been described in the literature.

Pruritus

Pruritus is a common symptom of chronic cholestatic liver diseases, particularly primary biliary cirrhosis. The 1st line of treatment is cholestyramine, an anion
exchange resin. It should be administered at least 4 hours before or after taking the other medications, as it binds many drugs. Side effects include bloating, constipation, and sometimes diarrhea. The 2nd line of medication is rifampin. The mechanism of action is unclear but it is effective in controlling pruritus in 50% of the patients with primary biliary cirrhosis. Dosage is 150 mg twice a day and it is effective within 6 weeks of therapy. The drug should be taken regularly for the effectiveness of treatment. These patients should be monitored closely for the possibility of drug hepatotoxicity. Several studies have demonstrated the effectiveness of opioid receptor antagonists (nalmefene, naloxone, and naltrexone) in the control of pruritus. The major side effects are the symptoms of opioid withdrawal. The treatment should be started slowly, preferably in a hospital setting.

Management of Osteopenia and Osteoporosis

Osteoporosis and fractures are more common in cirrhotic patients than in the general population in the absence of confounding risk factors such as female gender, cholestasis, and excess alcohol intake. The role of osteopenia and osteoporosis...
of calcium and vitamin D in preventing osteoporosis is unclear. According to recently published guidelines on the management of osteoporosis associated with chronic liver disease, patients with cirrhosis or severe cholestasis should have a baseline bone mineral densitometry. If the T score is more than –1.5 or between –1.5 and –2.5, no treatment is recommended. These patients should be followed up with bone mineral densitometry every 2 years. The work-up for the patients with bone mineral densitometry less than –2.5 should include thyroid function tests, serum calcium, phosphate, estradiol, follicle stimulating hormone, luteinizing hormone, testosterone, and sex hormone binding globulin levels. The optimum duration of therapy has not been established.

The current recommendation is that the treatment should be given for a minimum of 5 years and the bone mineral densitometry repeated after 2 years and at the end of treatment. In women, hormone replacement therapy with estrogen and progesterone should be offered to premenopausal females. For men, transdermal testosterone can be given to hypogonadal males.

The treatment recommendation for patients unable to take hormone replacement therapy / testosterone or eugonadal is bisphosphonates. Calcitriol or calcitonin should be considered in those patients with osteoporosis who are either intolerant of hormone replacement therapy and bisphosphonates or whose bone mineral densitometry worsens despite either the use of bisphosphonates or treatment of hypogonadism.

In the absence of larger studies on the effect of vitamin D supplementation on bone mineral densitometry, it seems reasonable to recommend correction of vitamin D deficiency with an oral daily dose of 800 IU of vitamin D, and 1–2 gm of elemental calcium supplementation.

Conclusion

The care and monitoring of pre-LT candidates is very challenging. Careful management of liver-specific complications can maximize their survival on the waiting list.

References

20. Bernard B, Grange JD, Khac EN, Amitox N, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infec-


