LIVER TRANSPLANTATION
Selection, Listing Criteria, and Preoperative Management

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In 1997, liver disease was implicated in more than 25,000 deaths and was the 10th leading cause of mortality in the United States. In addition to decreased life expectancy, advanced liver disease also results in a diminished quality of life. Therapy for decompensated liver disease has, until recently, been merely supportive. Orthotopic liver transplantation (OLT) now offers definitive therapy for decompensated liver disease. Whereas the one-year survival for patients with decompensated cirrhosis is less than 10%, OLT offers overall 5-year survival rates of greater than 60% to 70%. Orthotopic liver transplantation is limited, however, by the number of available donor organs. Since 1988, the number of individuals on the waiting list for OLT has grown from 616 to just over 12,000 (United Network of Organ Sharing [UNOS] data) in the United States). The timing of referral for OLT is a difficult decision in the care of patients with liver disease. Fortunately, the American Association for the Study of Liver Diseases has recently developed practice guidelines that address when patients should be referred and perioperative risks.

Although innovations such as split-liver transplants and living related donations (see article by Drs. Ghobrial and Busuttill) will likely expand the donor pool, the donor shortage will likely remain critical for the foreseeable future.

Patients listed for OLT usually have a protracted wait and are at risk of potentially lethal complications of liver disease. The prolonged waiting period is reflected in the increased disease severity of patients undergoing OLT. An increasing number of recipients are sent to transplant surgery from intensive care unit beds. Between 1988 and 1997, the percentage of patients waiting more than 6 and 12 months has increased from 36% to 69% and from 22% to 48.3%, respectively. Two important factors associated with prolonged waiting times are older age of entry (50 to 64 years) and blood type B.

MINIMAL LISTING CRITERIA

The most controversial issue in OLT is organ allocation, which is determined by guidelines developed by UNOS. The discrepancy between potential recipients and available donor organs has resulted in an increasing attrition rate of patients listed for OLT. The waiting time for OLT varies among the 11 UNOS regions. This variation has resulted in a number of initiatives to create more equal access to donor organs for OLT recipients.

In 1997, UNOS definitions were revisited to ensure prompt transplant of patients with acute liver failure. Status 1 criteria became clearly defined, and status 2 urgency was revised to include patients with chronic liver failure with a life expectancy of less than 7 days. Changes were also made in donor allocation. In an effort to further decrease waiting times for critically ill patients, organ distribution was again altered in August 1999 with donor organs allocated in the following order: local status 1, regional status 1, local status 2a, local status 2b, local status 3,
regional status 2a, regional status 2b, regional status 3, and then nationally in descending urgency of medical status (currently on hold pending further discussion). Before this revision, livers were allocated first locally, then regionally, and then nationally in descending urgency of medical status. Livers were first offered to patients locally, then regionally, regardless of medical status. Local areas are served by one of 62 national organ procurement organizations, distributed among the 11 regions. Although the goal of each of the UNOS criteria revisions for organ distribution has been to achieve a more equitable system, controversy is likely to persist. For example, expanded distribution of organs outside the local region for status 1 patients may result in longer cold ischemia times with decreased graft viability, especially of marginal grafts.\[130\]

To address concerns about inequities in organ allocation, a meeting of hepatologists and surgeons was held under the auspices of the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases to develop clinically relevant listing criteria for OLT.\[80\] The minimal listing criteria include both specific criteria for all forms of cirrhosis and nonspecific criteria that apply to all causes of cirrhosis and require a minimum Child-Pugh score of 7, based on a 1-year survival of less than 90%. Disease-specific criteria were developed for conditions in which survival and outcome may be inadequately represented by the Child-Pugh score, such as malignancy, and cholestatic liver diseases, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). For PBC and PSC the Mayo mathematic model and the Mayo Risk Score, respectively, have been shown to more accurately predict survival than the Child-Pugh score. Patients with PBC and PSC should be referred if their risk score predicts a less than 95% 1-year survival. The Mayo model for PBC takes into account bilirubin, albumin, age, prothrombin time, and the presence of edema. The Mayo PSC model also includes bilirubin and age, but uses splenomegaly instead of albumin and edema to predict survival. Other disease-specific criteria include at least 6 months of abstinence from alcohol in patients with alcohol-related liver disease. The article by Dr. Bruix and colleagues discusses a subset of patients with hepatocellular carcinoma (HCC) who can be cured by OLT. Generally accepted criteria for OLT include solitary tumors of less than 5 cm in diameter or 3 or less tumors with the largest lesion measuring less than 3 cm in diameter without metastases. Reasons for removal from the OLT waiting list are depicted subsequently.

Contraindications/Reasons for Removal from Orthotopic Liver Transplant List \[21\] \[80\]

1. Well-compensated cirrhosis, without a history of complications such as variceal hemorrhage or spontaneous bacterial peritonitis
2. Alcohol use in the previous 6 months by a patient with a diagnosis of alcohol abuse or dependence
3. Illicit drug use in previous 6 months by a patient with a diagnosis of substance abuse
4. Extra hepatic malignancy other than skin cancer
5. Systemic sepsis
6. HIV positive status

GENERAL CONSIDERATIONS

Although the diagnosis of cirrhosis implies the potential for major complications of liver disease, the prognosis of well-compensated cirrhosis is actually quite good. Fattovich et al observed that in well-compensated cirrhosis the development of decompensated liver disease such as ascites and variceal hemorrhage over a mean period of 10 years was quite low.\[32\] The diagnosis of cirrhosis is not an indication to advise on OLT, but does introduce a need for meticulous follow-up to anticipate potential complications, such as HCC or the onset of ascites, that might indicate a need for referral to a transplant program.

The goals of preoperative care of the OLT candidate include proactive management of decompensated liver disease with interventions, such as antibiotic prophylaxis against
spontaneous bacterial peritonitis (SBP), the use of beta-blockers or banding for the primary or secondary prophylaxis of variceal bleeding, and therapeutic paracentesis for refractory ascites. Because the complications of cirrhosis can be life threatening, the patient’s clinical status must be assessed frequently.

As a patient’s priority for OLT in the UNOS system increases according to severity of liver disease, it is crucial that the transplant center is apprised of new developments in the transplant candidate’s clinical status. In addition to managing the manifestations of decompensated liver disease, attention to standard medical care should not be neglected. Patients should be screened for colorectal, breast, and cervical cancer. Smoking is unequivocally prohibited. If alcohol abuse has been a factor in the patients’ liver disease, continued involvement with some form of alcohol rehabilitation program such as Alcoholic Anonymous is mandated by many transplant programs. Random drug and alcohol screens may be necessary if there are concerns about patient abstinence. Patients should be vaccinated against pneumococcus and tetanus and diptheria[23] (Table 3). It has been recently reported that influenza A infection can lead to hepatic decompensation in patients with chronic liver disease,[29] so it is reasonable to recommend a yearly influenza vaccine. Susceptible individuals are increasingly being immunized against hepatitis A and B because of concerns about increased severity of acute viral hepatitis in patients with pre-existing liver disease.[63][131] The hepatitis A vaccination is safe and immunogenic in patients with chronic liver disease.[64]

### Table 3 -- Immunization for Adults with Chronic Liver Disease

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Target Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>All patients</td>
</tr>
<tr>
<td>Measles-mump-rubella (booster if primary schedule given)</td>
<td>All patients</td>
</tr>
<tr>
<td>Pneumococcus (revaccinate after 6 years)</td>
<td>All patients</td>
</tr>
<tr>
<td>Tetanus-diphtheria (booster if primary schedule given)</td>
<td>All patients</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Susceptible patients</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Susceptible patients</td>
</tr>
</tbody>
</table>

Routine blood work should be updated every 2 to 3 months and include standard tests of liver and kidney function. Alpha-fetoprotein (AFP) should be checked every 6 months to screen for hepatocellular carcinoma, and annual ultrasounds should be obtained to assess portal vein patency. Patients should avoid raw and improperly cooked foods because of the risk of *Vibrio vulnificus* infection, which has a high case-fatality rate in patients with chronic liver disease.[66][75][98]

Because of the unpredictability long waiting times for OLT and the significant risk associated with worsening liver disease, patients and their families need frequent reassurance and education. Attendance at patient support groups should be encouraged.

### ASCITES

Ascites is one of the cardinal features of decompensated cirrhosis and it is one of the most difficult management problems in OLT candidates. Every patient with ascites should have a diagnostic paracentesis to characterize the fluid.[104] Pertinent tests include measurement of the serum-ascites albumin gradient to confirm portal hypertensive ascites and ascitic fluid cell count to exclude SBP, which may be asymptomatic in cirrhotic patients.[94][105]

The initial treatment of cirrhotic ascites is salt restriction, but salt restriction is efficacious in less than 20% of patients and diuretic use becomes necessary.[6] Fluid restriction is recommended only if the serum sodium is less than 120 mEq/L.[6][108] Rapid correction of
hyponatremia should be avoided because it has been implicated in the pathogenesis of central pontine myelinolysis after OLT.

Spironolactone is frequently used alone or in conjunction with furosemide, with initial doses of 100 mg spironolactone and 40 mg furosemide. Dosages can be titrated up as necessary to achieve adequate natriuresis. Patients without peripheral edema can safely lose up to 300 to 500 g of weight per day. Patients with peripheral edema can lose between 1000 and 2000 g of weight per day because peripheral edema has a renal protective effect. Some patients may continue to have significant ascites despite large doses of spironolactone and furosemide. Addition of hydrochlorothiazide (25 mg/day starting dose) may help induce a diuresis in these patients. Electrolytes, blood urea nitrogen, and serum creatinine should be monitored while the patient is on diuretic therapy. Diuretics should be discontinued if serum sodium falls below 120 mEq/L or if the creatinine rises above 2 mg/dL. The hyponatremia reflects an excess of free water and should not be managed with hypertonic saline infusion.

If tender gynecomastia develops with aldactone, alternative diuretics include amiloride or triamterene. The shorter half-lives (approximately 10 hours) of amiloride and triamterene facilitate their dose titration, in contrast to the longer half-life of spironolactone (4 to 5 days). Muscle cramps can accompany the use of furosemide and other diuretics. Although the exact mechanism is unknown, calcium channel blockers, quinine sulfate, and benzodiazepines can be helpful in relieving these cramps. In patients who have sulfa allergies, ethacrynic acid may be used instead of furosemide. Aggressive intravenous diuresis or abrupt changes in dosages should be avoided because these can be associated with electrolyte abnormalities, hepatorenal syndrome, and encephalopathy.

Refractory Ascites

Refractory ascites is defined as the inability to effectively diurese a patient despite salt restriction and high-dose diuretics because of electrolyte abnormalities or renal insufficiency; refractory ascites occurs in less than 10% of cirrhotic patients with ascites. It is important to exclude other causes of renal dysfunction, such as concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs). A 24-hour urine collection should be performed to confirm salt restriction and efficacy of diuretic therapy. Continuing weight gain in a patient excreting greater than 78 mEq/L of urinary sodium in a 24-hour period suggests dietary noncompliance.

Repetitive paracentesis is time consuming, cumbersome, and may lead to excessive protein loss. Good compliance, however, with dietary sodium intake and diuretic therapy, can allow the time between repeated large-volume paracentesis to be extended to every 2 or 3 weeks. The need for more frequent paracentesis suggests medical or dietary noncompliance. There is currently little data supporting the use of volume expanders in patients undergoing paracentesis. No study has shown a difference in mortality or morbidity between the groups who did or did not receive volume expanders.

The popularity of the transjugular intrahepatic portosystemic shunt (TIPS) has led to its increasing use in patients with refractory ascites. Insertion of a TIPS device may result in a significant decrease in ascites volume with a corresponding reduction in diuretic requirements or the need for frequent large-volume paracentesis. An intrahepatic portosystemic shunt, however, is equivalent to a nonselective portosystemic shunt and may lead to a significant reduction in hepatocellular reserve. Intrahepatic portosystemic shunts cannot be routinely recommended in all cirrhotic patients because morbidity and mortality may actually be increased in Child-Pugh class C patients treated with TIPS as compared with the morbidity and mortality of repeated paracentesis in Child-Pugh class C patients. Hepatic encephalopathy, in particular, may become intractable. Absolute and relative contraindications are listed below. After TIPS placement regular surveillance for shunt stenosis with doppler ultrasound is recommended. Most shunt occlusions can be revised radiographically, with less than half requiring restenting.
Contraindications to Transjugular Intrahepatic Portosystemic Shunt  

Relative

Systemic sepsis

Advance encephalopathy not precipitated by gastrointestinal bleeding

Hepatic neoplasms

Portal vein thrombosis

Absolute

Right-sided cardiac failure

Polycystic liver disease

Severe hepatic failure

Hepatic neoplasms (if between hepatic and portal vein tract)

Peritoneovenous shunting has been attempted with the LeVeen and Denver shunts. The shunts function by drawing ascitic fluid through subcutaneous tubes into the intrathoracic vascular space. The Denver shunt has a pump chamber to aid in the fluid flow. Significant limitations include a high rate of shunt occlusion, disseminated intravascular coagulation, and a perioperative mortality that is as high as 5% to 30%. The low overall efficacy of peritoneovenous shunts and the availability of TIPS has led to the diminished popularity of the Denver shunt.

Spontaneous Bacterial Peritonitis: Treatment

Spontaneous bacterial peritonitis must be considered in any cirrhotic patient with ascites who presents with acute clinical deterioration because the classical signs of peritonitis such as fever, chills, and abdominal pain may be absent. Therapy should be instituted as soon as a diagnostic paracentesis confirms the diagnosis of spontaneous bacterial peritonitis, defined as an absolute neutrophil count (ANC) greater than 250/mm³. An increased microbiologic yield is obtained by inoculating the culture bottles at the bedside, instead of sending the specimen to the laboratory. Empiric therapy should consist of a third-generation cephalosporin. Aminoglycosides are contraindicated because of an enhanced risk of nephrotoxicity in decompensated cirrhosis. Antibiotic therapy should be tailored depending on the susceptibility profile of the infecting organism. The recommended duration of therapy is 5 days. Follow-up paracentesis is necessary if the patient does not seem to be responding to antibiotic therapy; followup paracentesis is also necessary to document a decrease in neutrophil count, particularly in patients with culture-negative neutrocytic ascites (i.e., ANC >250/mm³ and
ascitic culture negative). Secondary peritonitis, such as peritonitis caused by perforated viscus, should be suspected if the ascitic fluid gram stain shows a polymicrobial flora, a neutrophil count greater than 10,000/mm$^3$, a brownish color (gall bladder rupture), glucose less than 50 mg/dL, lactate dehydrogenase greater than 225 IU/L (or greater than serum), or protein greater than 1.0 mg/dL.$^{[1]}$ $^{[10]}$

The mortality caused by SBP has fallen dramatically with prompt therapy.$^{[11]}$ $^{[12]}$ Overall mortality, however, remains elevated reflecting the severity of the underlying liver disease and the association with hepatorenal syndrome. One recent study has reported that infusion of albumin during paracentesis of cirrhotic patients with SBP reduced the incidence of HRS and improved survival, although its use is not routinely recommended in noninfected patients.$^{[10]}$ $^{[23]}$

**Spontaneous Bacterial Peritonitis: Prophylaxis**

Patients with a total ascitic protein of less than 1 g/dL, previous episodes of SBP, or recent upper gastrointestinal bleeding are at increased risk of developing spontaneous bacterial peritonitis and should receive prophylactic antibiotics (Table 4).$^{[5]}$ $^{[11]}$ $^{[78]}$ $^{[93]}$ $^{[122]}$ $^{[126]}$ $^{[132]}$

Prophylactic antibiotic therapy is effective in reducing the incidence of SBP and is also cost-effective.$^{[55]}$ $^{[135]}$ Although there has been concern about the selection of resistant organisms with prophylactic antibiotic use, the clinical significance is unknown.$^{[30]}$

**TABLE 4 -- ANTIBIOTICS USED IN THE PROPHYLAXIS OF SPONTANEOUS BACTERIAL PERITONITIS**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage (Oral)</th>
</tr>
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<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>750 mg weekly</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (double strength)</td>
<td>Tablet 5 times a week</td>
</tr>
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*Data from references $^{[44]}$ $^{[46]}$ $^{[79]}$ $^{[90]}$ $^{[102]}$.*

**Hepatorenal Syndrome**

Hepatorenal syndrome (HRS) occurs in approximately 10% of hospitalized cirrhotic patients.$^{[5]}$ $^{[101]}$ Diagnostic criteria for hepatorenal syndrome are shown below. Currently, two distinct forms of hepatorenal syndrome are recognized. Type I HRS is defined as a rapid deterioration in renal function with virtually all patients expiring within 10 weeks of onset. In contrast, type II HRS is insidious with a life expectancy of several months. The major clinical consequence of HRS type II is the development of refractory ascites.

**Diagnostic Criteria for Hepatorenal Syndrome $^{[5]}$ $^{[7]}$**

Principal

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension
2. Serum creatinine > 1.5 mg/dL or 24 hour creatinine clearance of <40 mL/min
3. Absence of shock, ongoing bacterial infection, use of nephrotoxic drugs
4. No sustained improvement with diuretic withdrawal and expansion of plasma volume with 1.5 L isotonic saline
5. No obstructive uropathy or parenchymal renal disease
Supporting

1. Urine volume <500 mL/d
2. Urine sodium <10 mEq/L
3. Unremarkable urine sediment
4. Fractional excretion of sodium <1%

Before a diagnosis of HRS type I can be established, other specific causes of renal dysfunction must be excluded including obstruction, volume depletion, glomerulonephritis, acute tubular necrosis, and drug-induced nephrotoxicity.\textsuperscript{5} \textsuperscript{7} A urinary catheter and renal ultrasound are necessary to exclude urinary obstruction. A fluid challenge of 1.5 L of isotonic saline should be administered to exclude volume depletion. Nephrotoxic drug use such as NSAIDs and aminoglycosides should be excluded. Patients with advanced portal hypertension have decreased effective intravascular volume, so renal perfusion is dependent upon prostaglandin-mediated vasodilation. The use of NSAIDs may lead to decreased renal blood flow and subsequent acute renal failure.\textsuperscript{18} \textsuperscript{136} \textsuperscript{137} Factors predisposing to the development of HRS include hyponatremia, marked activation of the renin-angiotensin-aldosterone axis and sympathetic nervous system, low mean arterial pressure,\textsuperscript{42} SBP, and overzealous diuresis.

The treatment of HRS has been disappointing. Renal vasodilators (dopamine, prostaglandins, prostaglandin analogues), systemic vasoconstrictors (norepinephrine, octapressin), and antagonists of renal vasoconstriction (angiotensin II receptor antagonists, intrarenal phentolamine) have all been generally unsuccessful in reversing HRS.\textsuperscript{7} Preliminary data, however, suggests that the combination of volume expansion and systemic vasoconstrictors may help reverse HRS.\textsuperscript{50} Other modes of nonpharmacologic therapy, such as peritoneovenous shunting, portacaval shunts, and dialysis have not been found to improve survival. Although the successful use of TIPS in the treatment of HRS has been described in case reports and small case series, its role remains to be defined for this indication.\textsuperscript{49}

ENCEPHALOPATHY

Between 30\% and 70\% of patients have some degree of clinically obvious encephalopathy, which can range from subtle neurologic dysfunction to frank coma.\textsuperscript{2} \textsuperscript{12} \textsuperscript{100} The onset of encephalopathy requires a rigorous approach to identify potential precipitants, notably recent constipation, dehydration, gastrointestinal bleeding, infection, medication noncompliance, the use of sedatives or tranquilizers, or excessive dietary protein ingestion.\textsuperscript{26} \textsuperscript{34} Serum electrolytes, blood urea nitrogen, serum creatinine and a complete blood count should be obtained to look for evidence of sepsis or blood loss. A urine toxicology test should be performed if there is clinical suspicion of illicit drug use, and ascites should be tapped to exclude spontaneous bacterial peritonitis. Usually, hepatic encephalopathy responds to catharsis within 48 hours. Failure to respond should prompt a search for alternative causes of intractable encephalopathy such as portal vein thrombosis, spontaneous splenorenal shunt, or occult hepatocellular carcinoma. The widespread use of TIPS in patients with decompensated cirrhosis has increased the frequency of severe encephalopathy. Revision of the stent with reduction of its diameter may lessen portosystemic shunting and improve neurologic function.

Treatment

Treatment revolves around identifying and correcting any precipitants; upper gastrointestinal hemorrhage, medications, and dehydration are the most commonly implicated...
precipitants. Cooperative patients can be given lactulose orally, but lactulose enemas or nasogastric tube administration may be needed for comatose or stuporous patients. The usual starting dose of lactulose when given orally is 15 mL to 30 mL every 6 to 8 hours, or 300 mL when given as an enema. The dose is titrated to achieve 2 to 4 soft bowel movements daily and mental status improvement. The effect of lactulose is generally seen within a day of initiating therapy. If a patient continues to have encephalopathy despite correction of the precipitating event and administration of lactulose, neomycin may be added. Although neomycin has been found to be as effective as lactulose in clinical trials, its potential nephrotoxicity and ototoxicity limit its use as a single agent. The usual daily dose is 2 to 8 g given orally in four divided doses.

Sufficient benefit has not been established for agents that stimulate metabolic ammonia fixation (ornithine-aspartate, sodium benzoate, and L-carnitine) in the treatment of hepatic encephalopathy. Conflicting results on the use of branched-chain amino acids has lead to skepticism about their use. In a prospective study in which postoperative cirrhotic patients were randomized to branched-chain amino acids and standard amino acid infusion, no difference in clinical outcome was observed. The clinical role of flumazenil, a benzodiazepine antagonist, is not yet defined. Flumazenil may be helpful in improving the neurologic score in cirrhotic patients with grade III or IV encephalopathy, providing prognostic information, and helping with the differential of hepatic encephalopathy. Effects, however, are not usually sustained and recovery to baseline mental status is uncommon. Flumazenil is costly and requires parenteral administration. No benefit has been demonstrated with subclinical or mild encephalopathy.

HEPATOCELLULAR CARCINOMA SCREENING

Hepatocellular carcinoma can complicate all common causes of cirrhosis, but occurs more frequently in cirrhosis caused by chronic viral hepatitis, especially with concomitant alcohol use, than in other forms of cirrhosis such as PBC. Dr. Bruix addresses the management of HCC in detail in another article.

Screening for HCC has become part of the management of cirrhotic patients, including OLT candidates. Although the cost-effectiveness and optimal strategy for HCC screening in patients with cirrhosis remain undefined, HCC detection has important implications in the OLT candidate. Under current UNOS rules, a patient with HCC may qualify for status 2b if certain criteria are met: the tumor diameter is less than or equal to 5 cm if single, or the largest tumor diameter is less than or equal to 3 cm if 3 or fewer lesions are present.

Screening for HCC is controversial because it has been difficult to establish that it leads to decreased mortality. One of the reasons that mortality may not be affected is that effective therapy for HCC remains elusive for most patients. A recent preliminary report by McMahan et al in a study of Alaska natives suggests early detection improves survival.

The most common test used for HCC screening is serum AFP. Up to 40% of patients with HCC do not have elevated AFP values. The sensitivity and specificity of AFP for the diagnosis of HCC is strongly dependent on the threshold value used to trigger further investigation. The most commonly used AFP value for screening is 20 mg/mL, which has a sensitivity of 64% and specificity of 91% for cancer detection. The specificity is frequently limited by frequent nonspecific elevations caused by chronic hepatitis flares and cirrhosis. Based on a median doubling time of 3 to 4 months for HCC, it seems reasonable to check a serum AFP twice yearly. Ultrasound is commonly used for screening because it is inexpensive, readily available, and noninvasive. Ultrasound, however, cannot conclusively differentiate between malignant and benign lesions in the liver. Nonetheless, some investigators recommend obtaining an ultrasound once to twice yearly. Ultrasound can detect lesions
as small as 0.5 to 1 cm in diameter. The sensitivity and specificity for this use of ultrasound has been estimated to be 79% and 94%, respectively.

The discovery of a liver mass in a cirrhotic patient strongly suggests HCC, particularly if the serum AFP is elevated. A mass found by ultrasound should prompt further radiographic imaging to characterize the lesion, to assess for satellite lesions and vascular and local invasion. On computerized tomography (CT) scan without intravenous contrast, a hypodense mass with central areas of lower density is characteristic of HCC. With the addition of intravenous contrast, HCC appears hyperdense. On magnetic resonance imaging HCC appears as a heterogeneous mass with high signal intensity on T2 and low signal intensity on T1. Liver biopsy is often discouraged because of the possibility of tumor spread. If a liver biopsy is deemed necessary, it should be performed by ultrasound or CT guidance.

Additional radiographic imaging is essential if there is an interval increase in serial AFP levels. If a diagnosis of HCC is made, the management should be reviewed with the transplant center and the patient's UNOS status adjusted accordingly.

HEPATOPULMONARY SYNDROME

Patients who complain of symptoms of dyspnea at rest or exertion, platypnea, or are found to have low hemoglobin saturation on a pulse oximeter should be evaluated for hepatopulmonary syndrome. The incidence of hepatopulmonary syndrome is estimated to be between 13% and 15% in patients with chronic liver disease. Notably, oxygenation in hepatopulmonary syndrome can deteriorate with stable liver function. The triad of chronic liver disease, intrapulmonary vascular dilatation, and increased alveolar-arterial gradient characterizes hepatopulmonary syndrome. The diagnosis is important to make because associated mortality has been estimated in one study to be 41% in patients followed for a mean of 2.5 years.

Initial evaluation of suspected hepatopulmonary syndrome includes an arterial blood gas to measure PaO2, performed with the patient in a supine position. A value of less than 70 mm Hg is consistent with hepatopulmonary syndrome. Pulmonary function tests should be performed to help exclude functional defects, and a chest roentgenogram can help exclude parenchymal disease, such as infiltrates or pleural effusions that can contribute to hypoxemia. The diagnosis of hepatopulmonary syndrome requires the demonstration of intrapulmonary vascular dilatation by perfusion lung scanning with technetium 99m-labeled macroaggregated albumin, pulmonary arteriography, or contrast-enhanced echocardiography. Contrast-enhanced echocardiography is believed to be the most sensitive modality to detect intrapulmonary vascular dilatation. The appearance of contrast (bubbles or dye) in the left heart several beats after its appearance in the right atrium indicates intrapulmonary shunting.

Medical management of hepatopulmonary syndrome has been generally disappointing. Successes described in case reports and small case series have not been reproduced in larger studies. Increasingly, OLT has been advocated for reversal of hepatopulmonary syndrome. Predictors of reversibility include young age, degree of preoperative hypoxemia, normal to finely diffuse vascular abnormality on angiography, and good response to 100% oxygen (PaO2 >200 mm Hg). Up to 82% of patients have resolution of their hypoxemia within 15 months of their OLT. Patients with hepatopulmonary syndrome have been noted to require more ventilatory support and longer duration in the intensive care unit. Because a candidate's perioperative risk worsens with deteriorating oxygenation, the transplant center should be immediately notified of the diagnosis.
OSTEOPOROSIS

Osteoporosis is associated with serious consequences before and after OLT. Hip fractures have significant associated mortality, and vertebral fractures can lead to deformity and pain. Patients with chronic liver disease are at an increased risk of developing osteoporosis for a variety of reasons including the effect of alcohol on bone mass, malnutrition, vitamin malabsorption, sedentary lifestyle, and use of corticosteroids. Women with clinically evident cirrhosis are more likely to have early menopause and an increased risk of osteoporosis. Tobacco use also increases the risk of osteoporosis.

All patients considered at risk for osteoporosis should be evaluated with bone densitometry. Patients found to have osteoporosis should be treated with calcium supplements. Perimenopausal and postmenopausal women should receive hormonal replacement, if not contraindicated. Men should be evaluated for hypogonadism. Corticosteroid use should be kept to a minimum, and exercise should be encouraged in both men and women. The role of bisphosphonates in patients with decompensated liver disease and osteoporosis is under evaluation. Alendronate is contraindicated in patients with esophageal varices because of the risk of esophageal ulceration.

PRURITUS

Although pruritus is most typically associated with cholestatic liver diseases, it is also frequent in decompensated cirrhosis of other origins, most notably hepatitis C virus (HCV).

Two mechanisms have been proposed for pruritus. The subjective improvement of pruritus with bile acid binding agents such as cholestyramine has implicated these substances in the pathogenesis. More recent evidence, however, has suggested opiate-mediated mechanisms based on (1) a poor correlation between pruritus and levels of serum and cutaneous bile acids; (2) cholestyramine, which is effective in most patients with pruritus, interferes with the absorption of compounds in addition to bile acids; (3) the central administration of opiates causes pruritus in animals; (4) pruritus caused by plasma extracts from patients with cholestasis is blocked with opiate antagonists; and (5) opiate antagonists have shown efficacy against pruritus in clinical human trials.

Specific bile-acid lowering treatment usually begins with cholestyramine. Fortunately, 90% of patients respond to this first line of therapy. The starting dose is 4 g 30 minutes before each meal. An additional 4 grams should be taken after breakfast. If there is no relief after 3 to 4 days, the daily dose is increased by 4 g. Although cholestyramine is efficacious in most patients with pruritus, many patients find it unpalatable and inconvenient to take several times a day. Colestipol hydrochloride is another bile acid binding resin that may be more palatable. The typical starting dose is 2 mg twice a day. The dose can be increased 2 to 4 mg a day after a month to a suggested maximum of 16 mg/day. Other therapies include antihistamines such as hydroxyzine and diphenhydramine. The antihistamine dose should be titrated to clinical improvement and sedation. Because of their sedative properties antihistamines are especially useful for nocturnal pruritus and as an adjunct to specific treatments. Patients should be advised of the sedative effects of antihistamines.

The large number of other therapies illustrates the difficulty of treating the 10% of patients who do not respond to cholestyramine. In short-term double-blind randomized crossover trials, patients treated with rifampicin had a significant reduction of pruritus. Long-term use of rifampicin has been found to be effective. The starting dose of rifampicin is 150 mg taken orally twice daily; the dose can be increased to 10 mg/kg. Almost 50% of patients with pruritus respond to rifampicin. Relief can be found as early as 5 to 7 days, but most patients who respond do so by 30 days. Because of the potential for bone marrow and liver toxicity, treated patients should have regular complete blood counts and liver tests performed. The efficacy of rifampicin
may differ among the various causes of liver disease.\textsuperscript{[134]} The advent of ursodeoxycholic acid has been an important adjunct for pruritus relief.\textsuperscript{[82]} Although its major indication is the treatment of primary biliary cirrhosis, it can alleviate pruritus in other forms of liver disease. The starting dose of ursodeoxycholic acid is 13 to 15 mg/kg per day. Opiate antagonists have been increasingly used in the treatment of refractory pruritus. Naloxone is an opiate antagonist that has been shown in several studies to be efficacious in treating pruritus.\textsuperscript{[10]}\textsuperscript{[17]} High costs and the need for continuous parenteral infusion have limited its use. Nalmefene is an orally administered opiate antagonist with efficacy against pruritus.\textsuperscript{[16]} Early studies, however, reported patients experiencing symptoms of opiate withdrawal with its use. Another oral opiate antagonist is naltrexone. A significant decrease in daytime and nocturnal pruritus was found in a double blinded randomized clinical trial using naltrexone.\textsuperscript{[133]} Further studies are awaited.

Malabsorption of fat soluble vitamins often accompanies pruritus as a manifestation of cholestasis. As a result, prothrombin time, and serum vitamin A and D levels should be monitored. Vitamin K should be used to correct a prolonged prothrombin time, and oral replacement of vitamins A and D provided. The typical dose of vitamin A is 10,000 to 20,000 units daily and of vitamin D is 0.5 to 2 \textmu g daily. Excessive doses should be avoided.

**SUMMARY**

Although only the expansion of the donor pool will have a major impact on the survival of patients with decompensated cirrhosis awaiting OLT, anticipation of complications such as SBP may improve the likelihood of a patient surviving until OLT, and may ameliorate some of the major causes of morbidity of cirrhosis, such as osteoporosis. Close communication between the treating physicians and the transplant center is crucial to ensure that the patients’ UNOS status can be appropriately adjusted if additional complications of cirrhosis, such as intractable ascites, have occurred.

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