

Management of the Cirrhotic Patient Before Liver Transplantation: The Role of the Referring Gastroenterologist

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Abstract: The referral of a patient with cirrhosis to a liver transplant center for evaluation is usually made by a local gastroenterologist. The role of the referring gastroenterologist begins with early identification and modification of high-risk behaviors, which may delay listing a patient for liver transplantation. The local gastroenterologist must also fully appreciate what constitutes a timely referral of a patient to a liver transplant center and the consequences of late referral. Although patients experience the inevitable deterioration of their liver function, which in turn advances their priority on the liver transplant waiting list, the referring gastroenterologist must also anticipate medical complications of cirrhosis, and should initiate appropriate surveillance and prophylaxis programs to detect and prevent these complications. Finally, the referring gastroenterologist constitutes a vital link of information between the patient and the transplant center. Adherence to these guidelines will increase the probability that a patient with chronic liver failure will undergo successful liver transplantation and will decrease post-transplant morbidity.

The medical management of patients with cirrhosis prior to liver transplantation usually falls to a referring gastroenterologist, who assumes the role of primary care physician in addition to liver specialist. Indeed, many primary care physicians are loathe to prescribe routine medications for fear of precipitating further liver injury or untoward side effects. The following review provides practical guidelines for referring gastroenterologists managing the primary care of the pre-liver transplant patient. Suggestions will be made to improve the management of these patients in order to increase their acceptability as liver transplant recipients. These considerations will not include a comprehensive review of the management of complications of cirrhosis, for which the reader is referred to other recent sources.¹⁻³

Keywords

Cirrhosis, liver failure, liver transplantation, portal hypertension

Table 1. Indications for Referral of a Patient With Cirrhosis to a Liver Transplant Center for Evaluation

1. First complication of cirrhosis <ul style="list-style-type: none"> • Ascites/hydrothorax • Hepatic encephalopathy • Azotemia • Variceal bleed
2. Child-Turcotte-Pugh (CTP) score ≥ 7
3. Model for End-stage Liver Disease (MELD) score ≥ 10
4. Suspicion of hepatocellular carcinoma <ul style="list-style-type: none"> • Mass on abdominal imaging • Rising alpha-fetoprotein level
5. Consideration of alternative therapies to liver transplantation with risk of decompensation

The CTP score is calculated as described in Table 2. The MELD score is calculated as $3.8 \times \log_e(\text{total bilirubin [mg/dL]}) \times 11.2 \log_e(\text{INR}) + 9.6 \log_e(\text{creatinine [mg/dL]})$, or online at www.mayo.edu/int-med/gi/model/mayomodl.htm.

Table 2. Modified Child-Turcotte-Pugh (CTP) Score for Assessing Severity of Liver Failure

Feature	1 Point	2 Points	3 Points
Encephalopathy	None	Mild	Mod/severe
Ascites	None	Mild	Mod/severe
Bilirubin (mg/dL)	<2.0	2–3	> 3.0
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged)	1–4	4–6	>6

A total score of 5–6 points correlates to CTP class A, 7–9 points to class B, and 10–15 points to class C.

When to Refer a Patient to a Liver Transplant Center

Perhaps the single most important question for a gastroenterologist managing a patient with liver disease is when to refer the patient to a liver transplant center for evaluation. Three criteria should be fulfilled before a patient is placed on a waiting list for liver transplantation. First, the patient must need a liver transplant. Second, alternative therapies for the underlying liver disease, which could delay or prevent the need for transplantation, should have been exhausted. Finally, contraindications to liver transplantation should have been excluded.³

The decision of whether a patient needs a liver transplant usually first falls to the referring gastroenterologist (Table 1). In general, a patient should be referred to a

liver transplant center after the first complication of cirrhosis, such as the appearance of ascites, variceal bleeding, progressive azotemia, or hepatic encephalopathy, or when the patient has developed liver failure as estimated by a Child-Turcotte-Pugh (CTP) score of 7 or greater (Table 2). More recently, transplant centers have placed patients on the liver transplant waiting list only after a patient has progressed to a certain Model for End-stage Liver Disease (MELD) score. Originally developed to estimate 3-month mortality after transjugular intrahepatic porto-systemic shunt placement,⁴ MELD constitutes a continuous score of 6 to 40 points, determined by serum creatinine, total bilirubin, and international normalized ratio. A modification of the original MELD score has been adopted by all US liver transplant centers to prioritize patients on the waiting list, and has been shown in prospective studies to predict waiting list mortality more accurately than the CTP score.⁵ Because a MELD score of less than 9 is associated with a 3-month mortality of less than 2% (Figure 1), a MELD score of 10 or greater has been proposed as a criterion for referral of a patient to a liver transplant center for evaluation (Table 1).³ Although most liver transplant programs place patients on waiting lists after more severe decompensation of their disease (eg, a MELD score of ≥ 15), the referring gastroenterologist cannot be criticized for early referral even if the center defers listing because the patient is not yet “sick enough.” Indeed, late referral increases the likelihood of disqualification due to disease severity or the appearance of comorbid medical conditions.

There are other less well-defined indications for referring a patient to a liver transplant center for evaluation (Table 1). The referring gastroenterologist should seriously consider referring any potential liver transplant candidate who develops a mass on abdominal imaging, because liver transplantation has become the most effective therapy for hepatocellular carcinoma (HCC) in patients with cirrhosis.⁶ Furthermore, differentiation of HCC from other liver masses requires expertise rarely available at a community hospital, and many benign lesions in a cirrhotic liver (eg, dysplastic nodules) will eventually progress to HCC.⁷ Another relative indication for referral pertains to the second criterion noted above, namely, whether alternative therapies for a patient’s underlying liver disease have been exhausted. Often, such alternatives to transplantation carry some risk of further decompensation, such as the use of antiviral therapy in the patient with cirrhosis due to chronic hepatitis C.⁸ In such cases, patients with fairly well-compensated cirrhosis should be evaluated prior to antiviral therapy in anticipation of the possible need for urgent transplantation. Furthermore, the alternative therapies and the expertise to administer them may only be available at a liver transplant center.

The third criterion for liver transplant evaluation, whether there are contraindications to the procedure, should be the purview of the transplant center. Contraindications may be medical, financial, or psychosocial, but often are center-specific. Therefore, except in the most obvious cases (eg, a patient with end-stage malignancy), the referring gastroenterologist should allow the center to determine if a patient is unsuitable for liver transplantation. One exception to this recommendation is ongoing alcohol or substance abuse, which most centers regard as contraindications to liver transplant evaluation.

General Care of the Liver Transplant Candidate

After referring a patient for liver transplant evaluation, the local gastroenterologist becomes a critical link of communication between patient and transplant center. Optimally, information pertaining to the patient's medical status should be exchanged so that important events occurring either locally or at the transplant center are appreciated by physicians in both locations. Ideally, the frequency of communication should increase as a patient becomes increasingly ill, since the United Network for Organ Sharing requires more frequent laboratory data as patients ascend the transplant list, in order to calculate their MELD score and reassign priority. Patients with MELD scores of 11–18 require updating every 3 months; scores of 19–24, monthly; and scores of 25 or greater, weekly. In addition, immediate contraindications to transplantation, such as an active infection, occur more frequently as liver failure worsens, and must be reported promptly so that a patient can be inactivated from the waiting list until the problem has been corrected.

General Counseling of the Cirrhotic Patient

The referring gastroenterologist may increase the likelihood of a patient becoming an acceptable liver transplant candidate by anticipating the need for transplant and proactively counseling the patient with regard to several health maintenance issues. First, the possibility of the need for liver transplant should be discussed early. Substance abuse problems, including alcohol, drugs (including prescriptions), and marijuana, should be openly discussed and referral to a substance abuse professional should be considered. In order to decrease post-transplant recidivism, most liver transplant centers arbitrarily require 6 months of abstinence from such substances, although the effectiveness of this requirement remains unproven. The referring gastroenterologist should also counsel the patient about smoking cessation, since smoking increases the risk of cardiopulmonary complications after transplantation, and also may increase the risk of hepatic

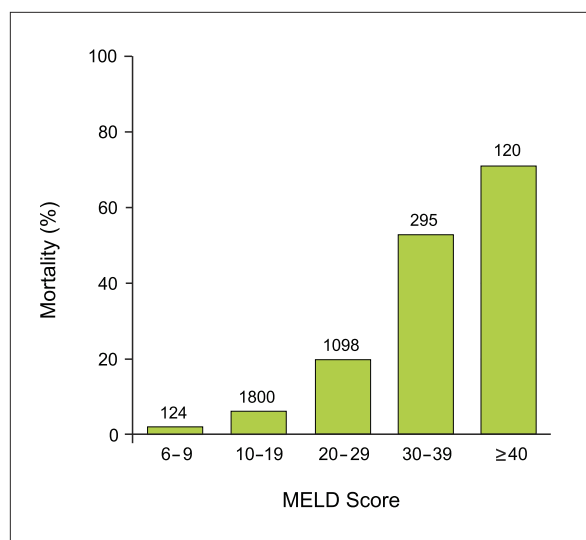


Figure 1. Three-month mortality in patients with cirrhosis according to Model for End-stage Liver Disease (MELD) score. Values above bars represent patient numbers in each MELD category. Data from Wiesner et al.⁵

artery thrombosis in the graft.^{9,10} Nutritional problems on both ends of the spectrum should be addressed,¹¹ as both morbid obesity (body mass index >40 kg/m²)¹² and malnutrition¹³ may increase morbidity and mortality after liver transplantation. Routine surveillance for malignancy (breast, cervical, prostate, and colon) should also be encouraged, particularly because the incidence of the latter is increased 2.5-fold after liver transplantation.¹⁴ Patients with a history of alcohol abuse and smoking should be referred for oropharyngeal cancer screening. The use of sunscreens should also be encouraged, since the incidence of skin cancer increases after liver transplantation.¹⁵

Management of Liver-specific Complications Prior to Liver Transplantation

The referring gastroenterologist also naturally assumes a primary role in managing complications of liver failure. In such a role, it is helpful to observe an important dictum: overtreatment of a complication of liver failure is often more harmful than undertreatment, and may hinder a patient's transplant candidacy.

Ascites: Mild ascites usually constitutes a cosmetic problem, but can further degenerate into hepatic hydrothorax, spontaneous bacterial peritonitis, and abdominal-wall herniation. The development of ascites also serves as an important marker, identifying patients with vulnerable renal function due to renal vasoconstriction, the most severe manifestation of which is the hepatorenal syn-

drome.¹⁶ When massive, ascites can also contribute to malnutrition by restricting gastric distension, thereby causing early satiety. Therefore, tense ascites requires treatment.¹⁷

Diagnostic paracentesis should be performed on all patients with new-onset ascites in order to determine the protein characteristics of the fluid, and thereby infer its etiology. Ascites from cirrhosis and portal hypertension typically has a low total protein concentration (<1–2 g/dL), and a high serum-to-ascites albumin gradient (SAAG), reflecting the fibrosis (capillarization) of the sinusoidal subepithelial space, which excludes large molecules from gaining access to lymph (ascites). A high total protein concentration or SAAG less than 1.1 g/dL suggests that a disease process other than cirrhosis and portal hypertension is responsible for the ascites, and should prompt a redirected search for other causes (eg, malignancy, heart failure, nephrogenic ascites).¹⁷

Large-volume paracentesis (LVP), defined as the removal of more than 5 L of ascites, has become a mainstay of the treatment of large-volume ascites, and has been shown to be more effective than diuretics and sodium restriction alone.¹⁸ A cell count and differential on the fluid should be sent even in the absence of symptoms/signs of infection to screen for evidence of spontaneous bacterial peritonitis (>250 polymorphonuclear leukocytes/mm³).¹⁷ In addition to the very small risk of procedure-related complications (bleeding, infection, bowel perforation), post-paracentesis circulatory dysfunction occurs in proportion to the volume of ascites removed above 5 L.¹⁹ Accordingly, intravenous albumin should be administered in a dose of approximately 6–8 g/L of fluid removed; albumin may be omitted with volumes of less than 5 L. Such albumin infusion has been shown to decrease the risk of post-paracentesis circulatory function and to improve the effectiveness of diuretics.²⁰ In the absence of the medication-induced complications noted above, diuretics should be continued after LVP to decrease the rate of ascites recurrence.

The management of ascites should begin with patient education, emphasizing dietary sodium restriction of no more than 2 g daily.¹⁷ Oral diuretics, consisting of a loop diuretic in combination with the aldosterone antagonist spironolactone, should be added. This combination effects a diuresis by inducing renal sodium wasting at successive regions of the nephron (the loop of Henle and distal convoluted tubule), and counteracts the sodium-retaining hyperaldosteronemic state characteristic of cirrhosis.²¹ A useful ratio of the two diuretics, which generally maintains normal serum potassium concentrations, is 40 mg furosemide/100 mg spironolactone, doses of which can be increased in a step-wise fashion to a maximum of 160 mg furosemide/400 mg spironolactone.¹⁷ Amiloride (15–60 mg/day), a potassium-sparing diuretic without

the unpleasant side effect of gynecomastia seen frequently in males on spironolactone, can be substituted, but is less effective because it does not antagonize the hyperaldosteronemic state.²² Eplerenone, an aldosterone antagonist that was recently approved by the Food and Drug Administration (FDA), binds more selectively to mineralocorticoid receptors and less to progesterone receptors and thus does not cause gynecomastia; however, its use in cirrhotic patients has not yet been explored.²³

Complications of the overly zealous use of diuretics are among the most common iatrogenic misadventures of managing patients with cirrhosis (Table 3), and include electrolyte depletion (sodium, magnesium, calcium), abnormalities in serum potassium (hypo- and hyperkalemia), hepatic encephalopathy, and azotemia. Azotemia during diuretic therapy reflects an exacerbation of renal hypoperfusion, and requires dose reduction as serum creatinine approaches 2.0 mg/dL, or cessation if creatinine exceeds 2.0 mg/dL. Similarly, dose reduction or cessation of diuretics should be considered if serum sodium drops below 130 or 125 mEq/L, respectively. Restriction of free water should be instituted if serum sodium drops below 120 mEq/L. Hepatic encephalopathy during the use of diuretics may reflect hypokalemia, which decreases renal excretion of ammonium,²⁴ or dehydration. Suggestions for correcting these complications of diuretic therapy are outlined in Table 3.

Other iatrogenic complications in patients with ascites follow the administration of nonsteroidal anti-inflammatory drugs or aminoglycosides, which exacerbate renal hypoperfusion by inhibiting vasodilatory endogenous prostaglandins, and can precipitate the hepatorenal syndrome.²⁵ In any but life-threatening infections with resistant organisms, patients with ascites should not be given aminoglycosides.

Hepatic encephalopathy: The prevalence of hepatic encephalopathy in patients awaiting liver transplantation exceeds that of ascites when subclinical forms are included; indeed, the prevalence of “minimal hepatic encephalopathy” affected 2 of 3 compensated cirrhotic patients after detailed psychometric testing in one series.²⁶ Recently, patients with cirrhosis and minimal hepatic encephalopathy were shown to exhibit impaired driving skills compared to a control population without liver disease.²⁷ Therefore, the referring gastroenterologist may be uniquely qualified to identify and treat such patients with the earliest stages of hepatic encephalopathy, and advise them against driving.

The pathogenesis of hepatic encephalopathy involves the accumulation of neurotoxins of gut bacterial origin.²⁸ The incriminated substances, which include ammonia, endogenously synthesized benzodiazepines, and others,

Table 3. Management of Complications of Diuretic Therapy in Cirrhotic Patients With Ascites

Complication		Responsible Drug(s)	Proposed Management
Hyponatremia	<130 mEq/L <125 mEq/L <120 mEq/L	F/S	Decrease dose by 1 step* Hold diuretics Hold diuretics and restrict free water
Hypokalemia		F	Replete; increase dose of S
Hyperkalemia		S	Decrease dose of S
Hypomagnesemia, hypocalcemia		F	Replete
Azotemia	Creatinine >2 mg/dL Creatinine >2.5 mg/dL	F/S	Decrease dose by 1 step* Hold diuretics
Encephalopathy	With hypokalemia With azotemia	F F/S	Replete potassium Decrease dose by 1 step*
Gynecomastia		S	Substitute amiloride

* 1 step refers to 40 mg/d of furosemide (F) and 100 mg/d of spironolactone (S). Adapted from Stravitz.⁷⁵

Table 4. Medical Therapy of Hepatic Encephalopathy

Drug	Mechanism of Action	Usual Dose in Hepatic Encephalopathy	Adverse Effects
Lactulose	Catharsis; acidification of gut lumen	30 mL qd–tid	Diarrhea, hypernatremia, hyperglycemia
Neomycin	Inhibition of bacterial ammonia production	Acutely: 3–6 g/d Chronically: 2–4 g/d	Ototoxicity, nephrotoxicity, malabsorption
Metronidazole	Inhibition of bacterial ammonia production	250 mg tid	Peripheral neuropathy, dysgeusia
Rifaximin	Inhibition of bacterial ammonia production	400 mg bid–tid	None reported

escape hepatic clearance as a result of hepatocellular insufficiency and portosystemic shunting.²⁸ The treatment of hepatic encephalopathy most importantly includes a search for precipitating factors, including iatrogenic dehydration and electrolyte abnormalities from diuretics, gastrointestinal bleeding, constipation, and infection.²⁹ Nonabsorbable disaccharides such as lactulose constitute the most useful medical therapy, and should be titrated to produce 2 to 3 bowel movements per day (Table 4). Patients who find lactulose unpalatably sweet, and the gastrointestinal side effects (bloating, flatulence, diarrhea) intolerable, may be candidates for oral antibiotic therapy. The use of neomycin, the first such antibiotic used for this purpose, has fallen from favor because of reports of oto- and nephrotoxicity caused by low level systemic absorption.³⁰ Similarly, metronidazole (250 mg orally, 3 times daily) may lower gut ammonia production by inhibiting

bowel anaerobes,³¹ but toxic metabolites accumulate in patients with cirrhosis and may increase side effects such as peripheral neuropathy.³² Recently, the FDA approved the use of rifaximin (Xifaxan, Salix Pharmaceuticals), a nonabsorbable rifampin derivative, to treat hepatic encephalopathy.³³ This agent inhibits a wide spectrum of enteric bacterial species and has been shown to be at least as, if not more, effective in treating acute hepatic encephalopathy than disaccharides.³⁴

Screening, Surveillance, and Prophylaxis in the Liver Transplant Candidate

One of the most important roles of the referring gastroenterologist in managing the pre-liver transplant candidate is to anticipate the development of several potentially lethal complications of cirrhosis (Table 5). In the following dis-

Table 5. Recommended Screening/Surveillance and Prophylaxis Programs for Patients With Cirrhosis

Complication of Cirrhosis	Screening Test	Surveillance Interval	Prophylaxis
Esophageal varices, primary prophylaxis	EGD	3 years (no varices on initial screen)	None
		2 years (small varices on initial screen)	Beta-blockers
Esophageal varices, secondary prophylaxis	EGD	2-3 weeks until varices obliterated	Band ligation and beta-blockers
HCC	US AFP	6 months	None
Viral hepatitis	Anti-HAV Anti-HBc	None	HAV vaccine HBV vaccine
Decreased bone density	DEXA	2 years	Calcium, vitamin D, HRT, bisphosphonates
SBP	Paracentesis	Routinely on admission to the hospital (controversial) When clinically indicated	Antibiotics indicated in: 1. Low protein ascites, no previous SBP (controversial) 2. Previous SBP 3. UGI bleeding

AFP = alpha-fetoprotein; DEXA = dual energy x-ray absorptiometry; EGD = esophagogastroduodenoscopy; HAV = hepatitis A virus; HBV = hepatitis B virus; HBc = hepatitis B core; HCC = hepatocellular carcinoma; HRT = hormone replacement therapy; SBP = spontaneous bacterial peritonitis; UGI = upper gastrointestinal; US = ultrasound.

cussion, screening refers to the single application of a test to detect a complication of cirrhosis, while surveillance refers to the serial application of such a test. Based upon these tests, selected patients should receive appropriate prophylaxis against further complications, if available.

Screening for Esophageal Varices

Hemorrhage from esophageal varices occurs in approximately 30% of patients with cirrhosis, and carries a risk of mortality of 20–50% per bleeding episode.³⁵ Accordingly, patients with cirrhosis should undergo screening upper endoscopy for esophageal varices, especially those with decompensated disease, in whom the risk of hemorrhage increases proportionally.³⁶ In a landmark prospective trial, the Northern Italian Endoscopic Club established that larger esophageal varices (grades II and III) and varices with red wale markings are far more likely to bleed than small varices without such red signs.³⁶ Because the risk of hemorrhage from esophageal varices can be estimated by endoscopic findings, the screening esophagogastroduodenoscopy (EGD) provides a rationale for primary prophylaxis with nonselective beta-blockers (propranolol or nadolol), which meta-analyses have shown to reduce the risk of a first bleed by 50% at 2 years of follow-up.³⁷ The dose of beta-blocker should be titrated to a pulse of 50–60 beats per minute or a 25% reduction in pulse, although the reduction in pulse correlates poorly with reduction in portal pressure.³⁷ In patients who do not tolerate beta-

blockers because of side effects (bradycardia, hypotension, bronchospasm, poorly controlled diabetes), primary prophylaxis of high-risk varices with band ligation appears to be at least as effective as beta-blocker therapy in preventing a first bleed.^{38,39} However, primary prophylaxis with band ligation remains controversial because of high cost and the risk of bleeding complications.

Surveillance for Nonbleeding Esophageal Varices

In cirrhotic patients with low-risk (grade I) esophageal varices on initial screening, EGD surveillance for progression from small to large varices should be considered every 1 to 2 years based upon the natural history of small esophageal varices.⁴⁰ In cirrhotic patients without varices on initial screening EGD, the interval of surveillance may be lengthened to approximately every 3 years, because the incidence of developing medium or large varices in this population is only 9% from the index EGD.⁴¹

Surveillance and Prophylaxis After Variceal Bleeding

After first variceal hemorrhage, the gastroenterologist is obliged to enter the patient into a program of secondary prophylaxis to prevent rebleeding. Rebleeding from esophageal varices occurs in 30–40% of patients within 6 weeks of the index bleed, but the risk declines with time⁴²; therefore, secondary prophylaxis should be initiated early. The goal of repetitive endoscopic treatments is variceal eradication, and the sooner eradication can be

accomplished, the lower the risk of rebleeding.⁴³ Many randomized studies have documented the superiority of band ligation over sclerotherapy for this purpose; in a meta-analysis, treatment failures after band ligation were approximately 50% fewer than after sclerotherapy.⁴³ The higher efficacy of band ligation over sclerotherapy in preventing variceal rebleeding is probably due to fewer sessions required and, therefore, a shortened time to achieve eradication.⁴³ In addition, the incidence of complications of endoscopic therapy, such as bleeding from esophageal ulcers, esophageal stricturing, and septic complications, is lower after band ligation than sclerotherapy.⁴³ Subsequent band ligations should be performed approximately every 2 weeks, because esophageal ulcers caused by previous procedures require this time to heal. Most studies also support the use of beta-blockers in decreasing the risk of variceal rebleeding, although the data are not as robust as those supporting their use in primary prophylaxis (~20% mean improvement in rebleeding rate).⁴⁴ Therefore, non-selective beta-blockers should be introduced during the early post-hemorrhage period, at least until band ligation has achieved variceal obliteration.

Surveillance for HCC

HCC has become an increasingly frequent complication of cirrhosis in recent times, and the risk of developing HCC depends upon the underlying liver disease.⁴⁵ In industrialized nations, patients with cirrhosis due to chronic active hepatitis B or C may be at highest risk (incidence of up to 7% and 5% per year, respectively),⁴⁶ although the absolute number of HCC cases in the setting of alcoholic cirrhosis may exceed those with underlying viral hepatitis.⁴⁷ The incidence of HCC in cirrhosis due to nonalcoholic steatohepatitis and other forms of nonviral hepatitis has not been well defined, but appears to be sufficiently increased to warrant a surveillance program.⁴⁶ In short, surveillance for HCC should be considered in any patient with cirrhosis who may be a liver transplant candidate.⁴⁸

Although the population at risk for developing HCC has been defined in general terms, the benefits of surveillance and its most effective application remain unproven and uncertain.⁴⁶ Notably, several studies have suggested that surveillance programs detect smaller tumors, which theoretically increases the likelihood of successful ablation and liver transplantation.^{49,50} However, randomized, controlled studies comparing the long-term survival of patients who received, or did not receive, surveillance for HCC have been deemed unethical, and therefore do not exist. The justification for a surveillance program therefore lies in the fact that cure is achieved only in patients with early-stage disease.⁴⁶

Ultrasound has become the HCC surveillance test of choice because of reasonably high sensitivity (60–80%), specificity (90%), and cost-effectiveness^{46,51}; however,

it is highly dependent on the expertise of the operator. The addition of alpha-fetoprotein may increase the sensitivity of ultrasound by 5% to 10% over ultrasound alone,^{52,53} but is inadequate as the sole surveillance tool.⁴⁶ Although no prospective studies exist, the interval of application of surveillance for HCC in a cirrhotic patient should be approximately 6 months based upon HCC tumor doubling time.⁵⁴ Several studies have suggested that 6- or 12-month surveillance intervals are equally effective, however.^{49,50}

Screening for Viral Hepatitis Exposure and Vaccinations

Patients with cirrhosis due to chronic hepatitis C and alcoholic cirrhosis may be at increased risk for severe liver injury after acute infection with hepatitis A or B viruses.^{55,56} Therefore, the referring gastroenterologist should screen patients with cirrhosis for exposure to these agents (total anti-hepatitis A virus and anti-hepatitis B core antibodies) and administer vaccines as appropriate. Documentation of seroconversion after vaccination should be considered, because patients with cirrhosis respond less reliably to both vaccines.⁵⁷⁻⁵⁹ In addition to vaccinations for hepatotropic viruses, patients awaiting liver transplantation should receive yearly influenza vaccine as well as pneumococcal vaccine at 5-year intervals.

Screening and Prophylaxis for Hepatic Osteodystrophy

Metabolic bone disease commonly complicates cirrhosis of all etiologies, especially the cholestatic liver diseases (primary biliary cirrhosis [PBC] and primary sclerosing cholangitis [PSC]).^{60,61} The decline in bone density accelerates after liver transplantation, and nontraumatic fractures represent a significant source of morbidity both before and after transplantation.^{61,62} The pathophysiologic processes responsible for osteoporosis pretransplant are multifactorial and differ according to the underlying liver disease. Patients with cirrhosis due to alcohol abuse tend to have milder degrees of bone density loss, primarily due to malnutrition, hypogonadism, and physical inactivity, but also as a direct toxicity of alcohol on bone precursors.^{60,63} In addition to these factors, patients with cirrhosis due to PBC and PSC occasionally exhibit osteomalacia due to malabsorption of vitamin D.^{64,65} Patients with PBC, the majority of whom are postmenopausal women at diagnosis, also naturally lose bone mass from low estrogen synthesis, and patients with autoimmune hepatitis may have steroid-induced bone density loss. Therefore, all patients with cirrhosis should be screened for osteopenia with dual-energy x-ray absorptiometry (DEXA), and those not meeting criteria for treatment should undergo surveillance every 2 to 3 years.⁶⁶

Few prospective studies have explored the optimal treatment of hepatic osteodystrophy.⁶¹ All patients with

cirrhosis, regardless of DEXA results, should receive calcium and vitamin D supplementation (1,000–1,500 mg/d and 400–800 IU/d, respectively) before liver transplantation, and should be counseled about smoking cessation and exercise.⁶⁶ Hormone replacement therapy, preferably delivered transdermally, should be considered in postmenopausal women with osteopenia; in older postmenopausal women or those with contraindications to estrogens, bisphosphonates should be administered.⁶⁷ Analogous to the situation with postmenopausal women, men with osteopenia should have their serum free testosterone level determined, and repleted, if low.⁶⁶ Bisphosphonates should be administered to cirrhotic patients with documented osteoporosis, a history of nontraumatic bone fractures, or a history of long-term corticosteroid use.⁶⁶ In a 2-year, randomized trial in severely osteopenic women with PBC, intermittent cyclical alendronate (Fosamax, Merck; 10 mg/day) was found to increase bone mineral density more than etidronate (Didronel, MGI Pharma; 400 mg/day), with no adverse gastrointestinal effects.⁶⁸ Osteopenic patients who do not tolerate, or have contraindications to, bisphosphonates should be referred to a bone disease specialist.

Indications for Antibiotic Prophylaxis in Patients With Cirrhosis

Patients with cirrhosis are uniquely susceptible to infection, which constitutes one of the most common causes of acute deterioration and the need to inactivate patients from the liver transplant waiting list. Several clearly defined indications for antibiotic prophylaxis have emerged from prospective, randomized trials (see Table 5). Patients who present with an acute upper gastrointestinal bleed should receive intravenous antibiotic prophylaxis empirically, because bleeding has been identified as an independent risk factor for sepsis⁶⁹ and, conversely, infection has been identified as a risk factor for the inability to control bleeding.⁷⁰ Patients with a history of spontaneous bacterial peritonitis or sepsis should receive indefinite oral antibiotic prophylaxis to prevent recurrence; suggested regimens include norfloxacin (400 mg/day),⁷¹ trimethoprim-sulfamethoxazole (1 double-strength tablet daily),⁷² or ciprofloxacin (750 mg once weekly).⁷³ Patients with low-protein ascites (≤ 1.0 g/dL), who are at the highest risk of spontaneous bacterial peritonitis, should be considered for primary prophylaxis with one of the above regimens, especially those with elevated serum bilirubin and thrombocytopenia.⁷⁴

Conclusions

The referring gastroenterologist can play an invaluable role as the primary physician for a cirrhotic patient await-

ing liver transplantation. The rationale for assuming such a role is based upon the long-term relationship between patient and gastroenterologist, the distance between patient and transplant center, and the hesitancy of other physicians to manage patients with decompensated cirrhosis for fear of worsening their condition. By anticipating the sources of liver-related and extrahepatic morbidity and applying the above remedies, the referring gastroenterologist will maximize a patient's chances of a favorable outcome after liver transplantation.

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