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AASLD PRACTICE GUIDELINE

Evaluation for Liver Transplantation in Adults: 2013 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation

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This practice guideline has been approved by the American Association for the Study of Liver Diseases and the American Society of Transplantation and represents the position of both Associations.

Preamble

Guidelines on Evaluation for Liver Transplantation (LT) were published in 2005 by the American Association for the Study of Liver Diseases (AASLD).[1] In the interim there have been major advances in the management of chronic liver disease, most notably in antiviral therapy for chronic viral hepatitis. Nonalcoholic fatty liver disease (NAFLD) has assumed increasing prominence as a cause of cirrhosis and hepatocellular carcinoma (HCC) requiring liver transplant.[2] Furthermore, individual disease indications for LT such as HCC have been refined[3] and specific guidelines have appeared for chronic viral hepatitis.[4] Reflecting the need for a multidisciplinary approach to the evaluation of this complex group of patients who have the comorbidities typical of middle age, recommendations have been developed to assist in their cardiac management.[5] With an increasing number of long-term survivors of LT there has been a greater focus on quality of life and attention to comorbid conditions impacting recipient longevity.[6] The purpose of the current Guidelines is to provide an evidence-based set of recommendations for the evaluation of adult patients who are potentially candidates for LT.

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic; (2) guideline policies covered by the AASLD-Policy on Development and Use of Practice Guidelines; and (3) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

To more fully characterize the available evidence supporting the recommendations, the AASLD Practice Guidelines Committee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup with minor modifications (Table 1). The classifications and recommendations are based on three categories: the source of evidence in levels I through III; the quality of evidence designated by high (A), moderate (B), or low quality (C); and the strength of recommendations classified as strong or weak.*

Literature Review and Analysis

The literature databases and the search strategies are outlined below. The resulting literature database was

Abbreviations: GRADE, Grading of Recommendation Assessment, Development, and Evaluation; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, Model for Endstage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt; UNOS, United Network for Organ Sharing.

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*Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alono-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-926.

Table 1. Grading of Evidence

Strength of Recommendation	Criteria
1. Strong	Factors influencing the strength of the recommendations include the quality of the evidence, the presumed patient important outcomes, and the cost
2. Weak	There is variability in the preferences and values or more uncertainty. The recommendation is made with less certainty, or the cost or resource consumption is higher
Quality of Evidence	**Criteria**
A. High	Further research is unlikely to change confidence in the estimate of the clinical effect
B. Moderate	Further research may change confidence in the estimate of the clinical effect
C. Low	Further research is very likely to affect confidence in the estimate of the clinical effect

available to all members of the writing group. They selected references within their field of expertise and experience and graded the references according to the GRADE system. The selection of references for the guideline was based on a validation of the appropriateness of the study design for the stated purpose, a relevant number of patients under study, and confidence in the participating centers and authors. References on original data were preferred and those that were found unsatisfactory in any of these respects were excluded from further evaluation. There may be limitations in this approach when recommendations are needed on rare problems or problems on which scant original data are available. In such cases it may be necessary to rely on less qualified references with a low grading. Due to the important changes in the treatment of complications of cirrhosis (renal failure, infections, variceal bleeding), studies performed more than 30 years ago have generally not been considered for these guidelines.

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Introduction

Liver disease is the twelfth commonest cause of mortality in adults in the United States, resulting in 34,000 deaths annually from cirrhosis.[7] In addition, the rising incidence of HCC in the United States is reflected in an increasing number of deaths from HCC. Access to LT, however, has profoundly altered the management of advanced liver disease. Management of decompensated cirrhosis and acute liver failure before the advent of LT was limited to attempts to ameliorate complications. In contrast, successful LT extends life expectancy and enhances quality of life.[6] The term *orthotopic liver transplantation* (OLT) refers to placement of the new organ in the same location as the explanted liver. Although most LT recipients receive a whole organ from a deceased donor, an organ can be "split," with a pediatric recipient receiving a left lateral segment and an adult recipient the larger right lobe. Live donor transplant using the left hepatic lobe initially introduced for pediatric recipients has been extended into adult recipients using the donor's right lobe. Although live donor transplant is widely employed, it remains controversial, with continuing concern about potential risks to the donor, especially when right lobe resection is required for an adult recipient.[8-10] Recipients of live donor transplant have reduced waiting list mortality compared to potential recipients of deceased donor organs.[11] Live donor transplant should only be contemplated when LT with a deceased donor is unlikely to occur within a reasonable time frame given the severity of the potential candidate's liver disease. Irrespective of the source of the graft, deceased or live, LT is a surgically challenging procedure with dissection and removal of a diseased liver from an abdominal cavity with extensive venous collaterals due to portal hypertension with subsequent implantation of the graft and creation of vascular and biliary anastomoses. Reflecting the complexity of surgery in recipients who are often debilitated because of their advanced liver disease, a number of technical complications can occur as well as a variety of adverse effects from therapeutic immunosuppression. Despite these concerns, however, LT has revolutionized the management of severe liver disease. The United Network for Organ Sharing (UNOS) facilitates organ allocation in the United States and also records graft and recipient outcomes. The UNOS database allows critical evaluation of center- and disease-specific recipient outcomes with LT as well as guiding organ allocation policies. Analogous organizations are involved in organ allocation and data collection in other regions of the world. The greatest challenge in LT remains the inadequate supply of donor organs, limiting access to LT for many potential recipients.

Indications for Liver Transplant

LT is indicated for severe acute or advanced chronic liver disease when the limits of medical therapy have been reached (see Table 2). Recognition of cirrhosis *per se* does not imply a need for LT. Many patients with cirrhosis in the absence of an index complication such as ascites or variceal hemorrhage will not develop hepatic decompensation, although patients with cirrhosis have diminished survival compared to the population as a whole.[12,13] Occurrence of a major complication is an important predictor of decreased survival and should

Table 2. Indications for Liver Transplant

Acute Liver Failure
Complications of cirrhosis:
Ascites
Chronic gastrointestinal blood loss due to portal hypertensive gastropathy
Encephalopathy
Liver cancer
Refractory variceal hemorrhage
Synthetic dysfunction
Liver-based metabolic conditions with systemic manifestations:
α_1-Antitrypsin deficiency
Familial amyloidosis
Glycogen storage disease
Hemochromatosis
Primary oxaluria
Wilson disease
Systemic complications of chronic liver disease:
Hepatopulmonary syndrome
Portopulmonary hypertension

prompt discussion about a possible role for LT.[14] However, in many types of liver disease there is the potential for improvement even when major complications have already occurred. A patient with cirrhosis who has suffered a variceal hemorrhage may develop additional complications such as ascites following vigorous fluid resuscitation but with control of bleeding and diuretic therapy the patient's condition may dramatically improve. Similarly, an alcoholic patient with florid hepatic decompensation may have resolution of jaundice and other signs of advanced liver disease with protracted alcohol abstinence. Thus, even in a patient with marked hepatic decompensation LT may be deferred or even avoided if medical therapy is effective. Examples of specific therapies, which may markedly improve hepatocellular function, include oral antiviral agents for hepatitis B infection or corticosteroids for autoimmune hepatitis. However, even if there is a potentially reversible component to hepatic decompensation, LT evaluation should not be deferred if otherwise indicated, as improvement is not invariable even with specific therapy.

For certain diseases, notably primary biliary cirrhosis and primary sclerosing cholangitis, prognostic models are available which incorporate readily available clinical and biochemical parameters. For cirrhosis of other etiologies, the Child-Pugh Score had been used to assess prognosis but has been increasingly superseded by the Model for Endstage Liver Disease (MELD).[15] The MELD score was initially devised to evaluate 3-month prognosis in patients with cirrhosis undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure.[16,17] It is a mathematical model that incorporates serum creatinine and bilirubin levels with the international normalized ratio (INR) of prothrombin time. The MELD score is on a continuous scale from 6 to 40 that corresponded to a 3-month survival of 90% to 7%, respectively. The MELD score is now used to assess prognosis in cirrhosis in a variety of settings, including organ allocation for LT, and can be calculated for individual patients at online sites, including www.UNOS.org. As discussed in the AASLD Pediatric Guidelines, an analogous formula has been validated for children with liver disease omitting serum creatinine but additionally incorporating age, serum albumin, and growth failure. Application of the MELD score has determined that the risk of deceased donor LT in patients with a MELD <15 outweighs its benefits in most circumstances.[18] Development of hyponatremia in cirrhosis is a marker of increased waiting list mortality,[19] as well as neurological dysfunction post-LT.[20] Incorporation of serum sodium into the MELD score has been proposed to increase priority for organ allocation to candidates with hyponatremia to reduce waiting list deaths (www.UNOS.org).

Once hepatic decompensation develops, the course of a patient with cirrhosis can be rapidly downhill, as additional complications including Hepatorenal Syndrome Type 1 or sepsis supervene.[17] If a determination has been made that LT is indicated, evaluation should be prompt, as most potential recipients face at least several months on the waiting list before receiving a donor organ.

An important indication for LT is liver graft failure. In the immediate postoperative period primary nonfunction and hepatic artery thrombosis are the most frequent causes of graft failure, whereas more remotely from LT, other important causes are recurrent disease (especially hepatitis C virus [HCV]) and chronic rejection. Results of retransplantation are generally inferior to initial transplant. A candidate for retransplantation for late graft failure needs to complete a similar formal evaluation process as for initial transplant, with weight given to the likelihood of a successful outcome, for instance, if the first graft has failed due to recurrent disease.[21]

Recommendations:

1. Evaluation for LT should be considered once a patient with cirrhosis has experienced an index complication such as ascites, hepatic encephalopathy, or variceal hemorrhage or hepatocellular dysfunction results in a MELD Score $\geq$15 (1-A).

2. In a liver transplant candidate potentially treatable etiologies and components of hepatic decompensation such as ascites, hepatic encephalopathy, or variceal hemorrhage should be treated (1-B).

3. Potential liver transplant candidates with worsening renal dysfunction or other evidence of rapid hepatic decompensation should have prompt evaluation for liver transplant (2-B).

Table 3. Transplantation Evaluation Process

Financial screening	Secure approval for evaluation
Hepatology evaluation	Assess disease severity and prognosis, confirm diagnosis and optimize management
Surgical evaluation	Confirm need for transplant, identify technical challenges (e.g. prior abdominal surgery, portal vein thrombosis etc.), discuss donor options (deceased, living, extended)
Laboratory testing	Assess hepatic synthetic function, serum electrolytes, renal function, viral serologies, markers of other causes of liver disease, tumor markers, ABO-Rh blood typing, creatinine clearance, urinalysis and urine drug screen
Cardiac evaluation	Initial non-invasive evaluation with echocardiography. Noninvasive stress testing and cardiology evaluation if cardiac risk factors are present (hyperlipidemia, hypertension, diabetes, cigarette consumption, age $>$ 60 years)
Hepatic imaging	Ultrasonography with Doppler to document portal vein patency, triple-phase computed tomography or gadolinium magnetic resonance imaging for tumor diagnosis and staging
General health assessment	Chest film, Pap smear and mammogram (women), colonoscopy if patient is age 50 years or older or has primary sclerosing cholangitis
Dental assessment	Identify dental caries, buried roots and dental abscesses. Coordinate dental extractions if necessary with hepatology
Anesthesia evaluation	Required if unusually high operative risk, i.e., patient has portopulmonary hypertension, hypertrophic obstructive cardiomyopathy, previous anesthesia complications
Psychiatry, psychology or mental health professional consultation	Determine if history of substance abuse, psychiatric illness, or adjustment difficulties (e.g. behavioral or adherence problems)
Social work evaluation	Address potential psychosocial issues, adequacy of support, and possible effect of transplantation on patient's personal and social system
Financial and insurance counseling	Itemize costs of transplantation and post-transplantation care, review insurance coverage, help develop financial management plans
Nutritional evaluation	Assess nutritional status and patient education
Infectious disease	Identify infectious processes that require intervention prior to transplant (e.g. latent TB or post-transplant e.g. CMV naïve recipient)

Adapted from O'Leary JG, Lepe R, Davis GL. Indications for liver transplantation. Gastroenterology 2008;134:1764-1776.

The Evaluation Process

Although liver disease severity is the initial concern in initiating LT evaluation, there are a number of other important considerations:

A. Does the patient have major comorbid conditions, which are likely to preclude successful LT? Examples include severe cardiac or pulmonary disease with an unacceptable perioperative risk.
B. Are there issues with alcohol or substance abuse that need to be addressed before LT can be contemplated? Does the patient have psychosocial issues that will interfere with their ability to undergo a major surgical procedure and adhere to a complicated and lifelong medical regimen? These could include lack of adequate social support to comply with the posttransplant regimen.
C. Can any medical comorbidities or psychosocial problems be treated pretransplant to improve posttransplant outcome? Are there contraindications such as sepsis, which can be successfully treated to permit transplant?

Table 4. Contraindications to Liver Transplant

MELD Score $<$ 15
Severe cardiac or pulmonary disease
AIDS
Ongoing alcohol or illicit substance abuse
Hepatocellular carcinoma with metastatic spread
Uncontrolled sepsis
Anatomic abnormality that precludes liver transplantation
Intrahepatic Cholangiocarcinoma
Extrahepatic malignancy
Fulminant hepatic failure with sustained ICP $>$50 mm Hg or CPP $<$40 mm Hg*
Hemangiosarcoma
Persistent noncompliance
Lack of adequate social support system

ICP, intracranial pressure; CPP, cerebral perfusion pressure.

The formal evaluation process includes a series of tests and consultations, to confirm the irreversible nature of the patient's liver disease and lack of effective medical therapy. In addition, the evaluation addresses any potential psychosocial issues as well as medical comorbidities. Although the specifics vary by center, the key components and considerations include (see Tables 3-5):

A. A comprehensive medical history and physical examination, including risk-appropriate cardiopulmonary evaluation.
B. A battery of laboratory tests to assess hepatic and renal function as well as viral serologies including hepatitis A, B, and C, in addition to establishing cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus (HIV) status.
C. Detailed abdominal imaging to assess patency of the portal vessels and to exclude a complicating HCC. If HCC is present, assessment of the size and number of HCC lesions will direct appropriateness of transplantation (i.e., inside or outside Milan criteria).
D. Psychosocial evaluation.

The transplant candidate is seen and examined by a hepatologist and transplant surgeon. Key aspects of the

Table 5. Infectious Disease Workup Pre-LT

Serological: HAV, HBV, HCV, HIV, EBV, CMV, RPR
Interferon γ Assay for TB: QuantiFERON Test or T. Spot TB
In selected candidates screening for coccidiomycosis, strongyloides
Dental evaluation

patient's history are reviewed including duration, severity, and complications as well as establishing that options for medical management have been exhausted. Attention is paid to comorbidities with the potential to diminish the likelihood of a good outcome. Issues related to drug and alcohol use are also discussed. In addition, the impact of liver disease on the patient's functional level as well as degree of available social support are reviewed. Insurance coverage for LT and immunosuppressive medications is confirmed. Physical examination in addition to confirming signs of advanced liver disease is also an opportunity to record other clinical signs that may impact LT, including loss of muscle mass and debility. The hepatology consult is an opportunity to identify interventions such as prophylaxis of variceal hemorrhage or vaccination against hepatitis A and B that are appropriate in any patient with advanced liver disease, as well as discussions regarding recurrent disease after transplantation, and possible HCV antiviral therapies pre- or posttransplantation. The surgical evaluation, in addition to addressing the patient's history and manifestations of liver disease, also identifies additional factors that may complicate the transplant operation including prior abdominal surgery, obesity, as well as the candidate's general robustness and ability to undergo a major surgical procedure. The surgical consultation facilitates education of the patient and family about the spectrum of donor and graft types, the complexity of the proposed surgery, potential complications, rejection rates, and other aspects of LT including long-term immunosuppression and its side effects.

Medical Comorbidities Including Obesity, Older Age, and Cardiac Disease

Evaluation for LT frequently uncovers unsuspected medical conditions such as cardiac disease or highlights other disorders such as obesity. In addition, increasingly older patients who frequently harbor associated comorbidities are now under consideration for LT.

Obesity. Obesity is on the rise in the general population[22] and this translates to an increase in the number of LT candidates with obesity. Concerns for LT in this group of patients include the impact of the other associated components of the metabolic syndrome and increased risk of complications and poorer outcomes following LT.[23,24] The World Health Organization defines a body mass index (BMI) from 25-29.9 as overweight, class 1 obesity 30-34.9, class 2 35-39.9, and class 3 $\geq$40. Consequences of obesity in LT recipients have included an increased risk of perioperative complications and reduced long-term survival,[25] although when corrected for ascites the obesity category was reduced in up to 20% of candidates.[14] However, in this study for each liter of ascites removed the mortality risk increased 7%, suggesting that the severity of the underlying liver disease increased risk rather than obesity *per se*. Unequivocally, severe obesity (BMI $\geq$40) is implicated in a variety of adverse outcomes post-LT.[15] Weight reduction in obese LT candidates can be attempted under the supervision of a dietician. Decompensated cirrhosis is a contraindication to bariatric surgery. However, there may be a role for innovative approaches such as a gastric sleeve operation for morbid obesity simultaneous with LT,[26] although evidence of reduction in risk with successful weight loss is lacking.

Recommendations:

4. Obese patients (WHO class 1 and greater) require dietary counseling prior to LT (1-C).

5. Class 3 obesity (BMI $\geq$40) is a relative contraindication to LT (2-B).

Coronary Artery Disease. The purpose of cardiac evaluation pre-LT is to assess perioperative risk and to exclude concomitant cardiopulmonary disorders that would preclude a good long-term outcome.[27] Although the hemodynamic state typical of advanced liver disease results in a low prevalence of systemic hypertension and impaired hepatic production of lipids may reduce serum cholesterol levels, coronary artery disease (CAD) is at least as frequent in LT candidates as in the general population and is influenced by typical cardiovascular risk factors.[28] Therefore, noninvasive testing with echocardiography is indicated for all adult LT candidates.[21] Patients with advanced liver disease may be unable to achieve the target heart rate during a standard exercise test. These patients should undergo pharmacological stress with adenosine, dipyridamole, or dobutamine, used to screen for cardiac disease with subsequent cardiac catheterization if CAD cannot be confidently excluded. Dobutamine stress echocardiography is frequently used as the initial screening test. Cardiac catheterization in a patient with cirrhosis is more likely to result in vascular complications such as bleeding compared to controls without liver disease.[29] In addition, many decompensated patients with cirrhosis have tenuous renal function, increasing the risk of contrast-induced nephropathy.

If significant coronary artery stenosis (>70% stenosis) is detected, revascularization may be attempted prior to LT, although rigorous proof of benefit in asymptomatic recipients is lacking. Cardiac surgery carries an increased risk in patients with cirrhosis, especially with more decompensated disease.[16] Coronary artery stenting is

increasingly performed prior to LT. Bare metal stents are favored to avoid the need for dual antiplatelet therapy (clopidogrel plus aspirin rather than the latter alone), although the requirement for antiplatelet agents to prevent stent occlusion may delay LT.[30] Of note, recent data demonstrates superior outcomes in patients who have undergone cardiac stenting with single vessel disease compared to outcomes for patients with prior CABG for multivessel disease.[30]

The cardiac evaluation may also need to address other entities including valvular heart disease and ventricular dysfunction, which may be of such severity to preclude LT. Anecdotally, aortic valve replacement has been performed simultaneously with LT; however, current medical therapies may sufficiently improve ventricular function to permit safe LT.[31] Unsuspected pulmonary hypertension as discussed subsequently may be initially detected by echocardiography during the LT evaluation.

Recommendations:

6. Cardiac evaluation needs to include assessment of cardiac risk factors with stress echocardiography as an initial screening test with cardiac catheterization as clinically indicated (1-B).

7. Cardiac revascularization should be considered in LT candidates with significant coronary artery stenosis prior to transplant (2-C).

Age. Physiological, not chronological, age determines whether an older patient can be accepted for LT, with careful attention to comorbidities and functional status.[32] Overall outcomes are acceptable in recipients >70 years of age, although they are inferior to those in younger age groups.[33]

Recommendation:

8. In the absence of significant comorbidities, older recipient age (>70 years) is not a contraindication to LT (2-B).

Pulmonary Hypertension

Pulmonary hypertension, an elevation of the mean pulmonary artery pressure (MPAP) ≥25 mmHg, occurring in the presence of portal hypertension, is referred to as portopulmonary hypertension (POPH).[34,35] It is not correlated with the severity of or etiology of portal hypertension. POPH is detected in 4-8% of LT candidates.[36] Mild POPH, MPAP <35 mmHg, is not of major concern but moderate (MPAP ≥35 mmHg) and severe POPH (MPAP ≥45 mmHg) are predictors of increased mortality following LT. In a report from the Mayo Clinic mortality was 50% with MPAP >35 mmHg and 100% with MPAP >50 mmHg.[37] Other causes of pulmonary hypertension need to be excluded, including left heart failure, recurrent pulmonary emboli, and sleep apnea. Contrast enhanced echocardiography is the initial screening test to estimate right ventricular systolic pressure (RVSP), with right heart catheterization as the gold standard confirmatory definitive test. In addition to demonstrating an elevated MPAP >35 mmHg, it should also confirm an elevated pulmonary vascular resistance (PVR) ≥240-dynes.s.cm^{-5} and a pulmonary wedge pressure ≤15 mmHg. Milder degrees of POPH do not adversely affect outcome of LT, but mortality rate climbs with more pronounced degrees.[37] However, if MPAP can be reduced by vasodilator therapy to less than 35 mmHg and PVR <400 dynes.s.cm^{-5} LT is possible, with acceptable short-term outcomes.[38-40] POPH can potentially improve with LT and vasodilator therapy can ultimately be discontinued in a subset of recipients.

Recommendations:

9. POPH should be excluded in LT candidates by routine echocardiography. For RVSP ≥45 mm Hg right heart cardiac catheterization is indicated. (1-B).

10. Potential recipients with POPH should be evaluated by a pulmonary or cardiac specialist for vasodilator therapy (1-A).

11. LT can be offered to potential recipients with POPH, which responds to medical therapy with an MPAP ≤35 mmHg (1-B).

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) resulting from intrapulmonary microvascular dilation in the setting of chronic liver disease and/or portal hypertension leads to arterial deoxygenation.[41] Intrapulmonary shunting can be demonstrated by contrast echocardiography or by ^{99m}TC macro aggregated albumin (MAA) lung-brain perfusion scanning. HPS is found in 5-32% of adult liver transplant candidates. LT offers a survival benefit in HPS, with 76% of LT recipients at the Mayo Clinic surviving 5 years compared to 26% of matched patients with equivalent severity of hypoxemia and liver disease who were not transplanted.[42] LT reverses HPS in almost all patients who survive more than 6 months,[35] although perioperative mortality appears to be high in those with severe HPS,[35] with a preoperative PaO_2 <50 mmHg alone or in combination with an MAA shunt scan of greater than 20% predictors of increased mortality after LT. More recent experience indicates that more severe hypoxemia predicts the need for longer-term supplemental oxygen and a longer recovery rather than increased mortality

post-LT.[43-46] Current Organ Procurement Transplant Network/UNOS policy assigns a MELD exception score of 22 for patients with evidence of portal hypertension, intrapulmonary shunting, and a room air PaO_2 <60 mmHg, with a 10% mortality equivalent increase in points every 3 months if the PaO_2 remains <60 mmHg. Screening of LT candidates by pulse oximetry is indicated to detect HPS patients with a PaO_2 <70 mmHg, using a threshold value of SPO_2 <96% at sea level to trigger complete evaluation.[47] Preoperative evaluation of patients suspected of having HPS should include a room air arterial blood gas, transthoracic contrast echocardiography, and an evaluation to exclude alternate causes for arterial deoxygenation including chest x-ray (CXR), pulmonary function tests (PFTs), and chest computed tomography (CT) scanning. Arterial response to administration of 100% oxygen (performed with a nose clip and mouth piece) may be used to gauge the ability to provide adequate oxygenation in the perioperative period but does not appear to influence outcome.[35,48]

Recommendations:

12. HPS is relatively common in patients evaluated for LT and should be screened for by pulse oximetry (1-A).

13. The presence of severe HPS is associated with increased mortality and affected individuals should undergo expedited LT evaluation (1-B)

Renal Dysfunction

The recognition of renal dysfunction in a patient with cirrhosis has a dramatic effect on prognosis, with a substantial increase in the risk of mortality. In a recent meta-analysis the risk of death increased 7-fold in patients with renal dysfunction, with 50% of patients with cirrhosis dying within a month of the onset of renal dysfunction.[17] The differential diagnosis of renal failure in patients with cirrhosis is broad and includes intercurrent sepsis, hypovolemia, parenchymal renal disease, and, most commonly, hepatorenal syndrome (HRS).[49] A recent working group has proposed the following definitions of renal dysfunction complicating liver disease: acute kidney injury that includes all causes of acute deterioration of renal function with an increase in serum creatinine of >50% from baseline, or a rise in serum creatinine of ≥26.4 μmol/L (≥0.3 mg/dL) in <48 hours. Chronic renal disease is defined as an estimated glomerular filtration rate (GFR) of <60 mL/min calculated using the Modification of Diet in Renal Disease 6 (MDRD6) formula.[49] Evaluation of renal dysfunction in patients with decompensated cirrhosis should include an accurate calculation of the true glomerular filtration rate (GFR) and determination of the precise etiology as it impacts prognosis both with and without LT. In a recent study of 463 patients with cirrhosis and renal dysfunction, survival was significantly worse in patients with HRS versus those without HRS.[50] Since the introduction of MELD for organ allocation the number of simultaneous liver kidney (SLK) transplants has increased from <3% to nearly 5% in 2009[51] and continues to rise. Because of concerns surrounding the increased use of renal grafts in LT recipients, a panel of experts convened to evaluate and recommend the most appropriate indications for SLK.[52] SLK was sanctioned for (1) end-stage renal disease (acute HRS etiology excluded) with cirrhosis; (2) liver failure with chronic kidney disease (CKD) and GFR <30 mL/min, (3) acute kidney injury or HRS with creatinine ≥2.0 mg/dL and dialysis for ≥8 weeks; or (4) liver failure with CKD and renal biopsy demonstrating >30% glomerulosclerosis or >30% fibrosis. These recommendations may evolve with increased experience of SLK.[53]

Recommendations:

14. Renal dysfunction requires vigorous evaluation prior to LT to determine etiology and prognosis (1-A).

15. Simultaneous liver-kidney transplantation is indicated for LT candidates in whom renal failure reflects CKD with GFR <30 mL/min or acute kidney injury with dialysis >8 weeks or if extensive glomerulosclerosis is present (1-B).

Tobacco Consumption

Cigarette smoking is implicated in a number of adverse outcomes in LT recipients including cardiovascular mortality[54] and an increased incidence of hepatic artery thrombosis,[55] although the risk of the latter diminishes with smoking cessation, by over two-thirds within 2 years of cessation in one report.[44] Oropharyngeal and other neoplasms following LT are also linked to cigarette smoking and can result in significant potentially avoidable long-term mortality.[56-58] While tobacco use is common in patients with a history of liver disease, the use of chewing tobacco, which is associated with oropharyngeal malignancies, is not well studied.[56] There are compelling reasons to prohibit all tobacco use in LT candidates, and indeed some programs make cigarette cessation a condition for listing for LT and require negative serial nicotine screens for documenting tobacco cessation.

Recommendation:

16. Tobacco consumption should be prohibited in LT candidates (1-A).

Extrahepatic Malignancy

LT recipients are at increased risk of a variety of cancers.[59] In an LT recipient with a preexisting malignancy, treatment should have been curative and sufficient time should have elapsed to exclude recurrence. The Israel Penn International Transplant Tumor Registry (www.ipittr.com) has accumulated a large database of outcomes after LT in recipients with a variety of tumors and can guide an appropriate strategy for LT candidates with a history of extrahepatic malignancy. The interval from cancer diagnosis to treatment and subsequent presumed cure, to transplant listing candidacy, varies depending on the type of malignancy and the proposed evidence-based efficacy of treatment. All LT candidates should undergo age-appropriate screening for malignancies including colonoscopy, mammography, and Papanicolaou smear. In candidates with particular risk factors for malignancy, additional screening should be considered such as ENT evaluation and chest imaging in current or prior smokers.

Recommendations:

17. LT candidates with a prior extrahepatic malignancy should have received definitive treatment with adequate tumor-free survival prior to listing for LT (1-B).

18. Candidates should undergo age and risk factor-appropriate cancer screening, e.g., colonoscopy, mammography, Papanicolaou smear (1-A).

Infectious Diseases

Due to hepatocellular dysfunction, LT candidates are at increased risk of a variety of infections, including spontaneous bacterial peritonitis, aspiration pneumonia, urinary tract, and catheter-associated bloodstream infections.[60] Active infection needs to be adequately treated before LT can be attempted. As part of the transplant evaluation, a candidate should be screened serologically for viral infections including HBV, HCV, and HIV, as discussed separately below.[61] Hepatitis A and B immunity should be confirmed and vaccination performed if necessary. Serological testing for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) is also indicated. Latent syphilis and tuberculosis (TB) infections should be tested for. Screening for TB can be done by tuberculin skin testing (TST) or interferon-γ release assays such as QuantiFERON (QFT,Cellestis) or T-SPOT.TB (Oxford Immunotec).[62] If latent TB is detected, antimicrobial therapy is indicated pre-LT, typically with isoniazid 300 mg daily plus pyridoxine 50 mg daily for 6-9 months, a 3-month regimen of weekly isoniazide and rifapentine, or rifampin 600 mg daily for 4 months. There had been concerns previously about hepatotoxicity with anti-TB regimens but more recent experience with isoniazid has been reassuring in LT candidates with cirrhosis.[63,64] Syphilis, if detected, needs to be treated pre-LT. In areas such as the American Southwest where *Coccidiomycosis* is endemic, pretransplant screening is indicated; if seropositive for *Coccidiomycosis,* active infection should be excluded and lifelong prophylaxis with fluconazole posttransplant considered. By contrast, routine screening for histoplasmosis or blastomycosis is not recommended and treatment for a positive result should be discussed with the ID team. Serological screening for *Stronglyloides* is indicated in candidates with a history of residence in endemic areas; patients who are seropositive should be treated with ivermectin prior to transplant.

As part of transplant evaluation, vaccination for a variety of preventable diseases, in addition to hepatitis A and B, should be undertaken, especially as live vaccines including measles, mumps, rubella (MMR), and varicella (Varivax and Zostavax) are contraindicated post-LT.[65] Prior to transplant the following vaccinations should be administered: Pneumococcal vaccine, influenza, diphtheria, pertussis, and tetanus. If live vaccines are indicated (mumps, measles, rubella, varicella, or herpes zoster) they should be administered as soon as possible to avoid their use within several weeks of transplant and the associated introduction of therapeutic immunosuppression. Current indications for vaccination against Human Papilloma virus (HPV) are administration in males and females 9-26 years of age with a quadrivalent and bivalent vaccine, respectively. The quadrivalent vaccine can be used in women up to the age of 45 years. HPV vaccination should be administered prior to LT.

A potential source of infection post-LT is extensive dental decay, and formal evaluation by a dentist is necessary and critical for all liver transplant candidates. Dental extractions, if deemed necessary, should be performed with close attention to hemostasis.[66]

Recommendations:

19. LT candidates should be screened for bacterial, viral, and fungal infections prior to LT (1-A).

20. Treatment for latent TB should be initiated pre-LT (1-B).

21. Vaccination should be encouraged against pneumococcus, influenza, diphtheria, pertussis, and tetanus (1-A).

22. Live vaccines (mumps, measles, rubella, and varicella), if indicated, should be administered early in the evaluation process (1-B).

Nutrition

LT candidates experience a variety of nutritional challenges including the effects of a catabolic chronic illness often accompanied by reduced appetite. The specific etiology of liver disease can also lead to additional nutritional deficiencies such as fat-soluble vitamin malabsorption in cholestatic liver disease. Malnutrition leads to poorer outcomes following LT[67] with a BMI <18.5 identified by UNOS data as a key predictor.[23] Importantly, the severity of muscle wasting can be masked by ascites and obesity. A recent report demonstrated that over 70% of LT candidates were cachectic.[68] Assessment and counseling by a dietician is an integral part of the evaluation process, including correcting misconceptions about restriction of protein[69] and addressing the possible need for enteral or even parental feeding prior to LT.[70] However, a recent Cochrane Review was unable to identify benefit from nutritional support in LT candidates.[71] With the increasing prominence of NAFLD as an indication for LT,[72] many candidates have features of the metabolic syndrome resulting in the development of posttransplant diabetes mellitus.[73] Pre-LT diabetes is managed with insulin and oral hypoglycemics, although the latter should be used with caution because of the risk of hypoglycemia. Hyperlipidemia, if present, should be managed as in the general population.[74]

Recommendation:

23. Nutritional assessment should be performed in every LT candidate (1A).

Bone Disease

Osteoporosis is frequent in patients with cirrhosis, up to 55% in some studies.[75] This reflects risk factors common in patients with cirrhosis including inactivity, inadequate nutritional status, hypogonadism, chronic cholestasis, and alcohol excess. An additional risk factor in patients with autoimmune hepatitis is the use of corticosteroids. Osteoporosis is particularly frequent in cholestatic liver disease.[76,77] Bone densitometry is indicated pre-LT, given the frequency of osteoporosis in cirrhosis as well as determining vitamin D and calcium levels. Bone mass diminishes in the initial 3 months following transplant due to high-dose steroids, which in turn increases fracture risk. This risk returns to pretransplant levels within 2 years of transplant. The benefits of vitamin D and calcium supplementation in this population likely outweigh concerns about increased cardiovascular events[78] and should be prescribed in osteopenic LT candidates. Bisphosphonates have been safely used in patients in patients with cirrhosis,[79] although concerns remain about esophageal bleeding with oral preparations and more recently ischemic necrosis of the jaw.[80]

Recommendation:

24. Bone densitometry should be obtained as part of transplant evaluation and treatment of osteoporosis initiated prior to LT (1-A).

HIV

With the advent of effective antiretroviral regimens to control HIV infection, LT became feasible in HIV infected patients.[81] Patients with HIV infection need to have a CD4 count >100/μL with a viral load anticipated to be completely suppressed at time of LT. Collaboration with an infectious disease specialist is helpful. Overall survival rates are similar to non-HIV-infected recipients, with the exception of HCV coinfected patients, in whom recurrent HCV leads to inferior outcomes.[82] Factors implicated in the latter include BMI <21, combined liver/kidney transplant, and older donor age.[83]

Recommendation:

25. Patients with HIV infection are candidates for LT if immune function is adequate and the virus is expected to be undetectable by the time of LT (1-A).

Psychosocial Evaluation

Social workers and/or mental health professionals typically provide psychosocial evaluation with input from psychiatrists or other specialty physicians (e.g., addiction medicine). Components of the psychosocial evaluation that are especially relevant to transplant outcomes include evidence of compliance with medical directives, adequate support from able caregivers especially in the perioperative period, and an absence of active psychiatric disorders with the potential to impact compliance or include behaviors harmful to health (e.g., alcohol, tobacco, or illicit drug use). While the effect of nonsubstance abuse-related psychiatric disorders on transplant outcomes have not been fully determined, experience to date suggests that depressive symptoms particularly in the early postoperative period are associated with poorer outcomes after LT.[84,85] However, there is no psychiatric disorder that is an absolute contraindication to transplantation and even the most psychiatrically complex patient, for example, with a psychotic disorder or mental retardation, with proper evaluation and preparation, as well as adequate social support, can have successful long-term outcomes. Patients on methadone as opioid replacement therapy should continue on their current dose to prevent relapse and should not be

tapered off as a requirement for transplant listing. While some programs exclude patients with active marijuana use from LT, this remains controversial,[86] despite well-founded fears of its adverse effect on the course of liver disease.[87,88]

In addition to addressing psychiatric and substance abuse issues, the evaluation process should also include an assessment of the patient's social support network. As the care of a transplant patient involves frequent office visits and tests, a caregiver needs to be identified to undertake transport and other logistical tasks, especially in patients with a history of encephalopathy who should not be left alone to drive or care for themselves. Given today's complexities of insurance for medical care, it is also necessary to ensure that a potential recipient will have adequate posttransplant medication coverage.

Recommendations:

26. Patients should be evaluated for and meet reasonable expectations for adherence to medical directives and mental health stability as determined by the psychosocial evaluation (1-A).

27. Methadone-maintained patients should not be denied transplantation based on methadone use alone, and expectations of methadone reduction or discontinuation should not be a requirement for transplant listing (1-B).

28. Patients should have adequate social/caregiver support to provide the necessary assistance both while waitlisted and until independently functioning in the postoperative period (1-B).

Disease-Specific Indications for LT

Hepatitis C. Cirrhosis due to chronic HCV infection remains the commonest indication for LT in the United States. In the era of lack of curative antiviral therapy prior to LT, nearly all grafts became reinfected immediately after transplant. After LT the tempo of HCV infection is accelerated, with high rates of graft dysfunction and progression to cirrhosis in 20-30% of patients with graft failure due to recurrent HCV in 10% of HCV-infected recipients within 5-10 years of LT, which is reflected in decreased survival compared to other LT indications.[89] Despite this, the outcomes for LT for HCV are acceptable. Indications for LT for HCV do not differ from that of other causes of liver disease and include decompensated cirrhosis and HCC. The optimal approach to prevent graft reinfection is clearance of HCV pre-LT. However, many transplant candidates have contraindications to interferon and ribavirin therapy. However, consideration should be given to treating those with compensated disease who are awaiting transplant with modified interferon and ribavirin dosing, especially if the genotype is favorable (genotype II, III), the patient has a potential living donor, or MELD exception points for HCC.[90] This strategy may be helpful to prevent graft infection; however, interferon-based therapy in this setting may be poorly tolerated. A recent preliminary report of an interferon-free regimen using sofosbuvir plus ribavirin prior to LT indicates that HCV RNA clearance substantially reduces the risk of recurrent HCV post-LT.[91] This new approach is particularly important, as recurrent HCV is one of the major causes of long-term graft failure. Retransplantation in patients with severe recurrent HCV is controversial and is associated with worse outcome than primary transplants if the recipient remains viremic for HCV RNA and if severe recurrence (decompensated cirrhosis or fibrosing cholestatic HCV) occurs in <5 years after the initial LT.

Recommendations:

29. LT transplant candidates with HCV have the same indications for LT as for other etiologies of cirrhosis (1-A).

30. Antiviral therapy pre-LT should be contemplated to reduce the risk of recurrent HCV post-LT (1-B).

Hepatitis B. Prior to the use of HBV immune globulin (HBIG) as immunoprophylaxis after transplantation for chronic HBV, recurrence of HBV in the liver allograft occurred in up to 80%, and was usually complicated by graft dysfunction and death. The advent of oral antiviral agents has markedly reduced the number of LT candidates with a diagnosis of HBV.[92] Control of the virus prior to transplantation is critical in preventing graft reinfection. With the availability of antiviral medications with a high genetic barrier to resistance, suppression of the virus before transplant is feasible. The combination of HBIG with oral antivirals has allowed for HBV-infected patients to evolve from having the poorest posttransplant outcomes to having survival rates among the best of all recipients. With the use of HBIG and oral nucleos(-t)ide therapy, the 5-year graft survival for those transplanted for HBV is 85% and retransplantation for recurrent HBV cirrhosis is rare. The ability to control HBV pre-OLT has resulted in a decrease in need for LT for decompensated HBV. However, LT for HCC as a complication of HBV has increased and there are still patients, albeit rare, with acute or chronic decompensated disease who do not improve with oral antiviral therapy and still require LT.

Recommendation:

31. Patients with HBV liver disease should receive antiviral therapy to suppress HBV replication pre-transplant and continued surveillance for HCC (1-A).

Autoimmune Hepatitis

Autoimmune hepatitis may result in the development of cirrhosis and hepatocellular failure despite the efficacy of corticosteroid-based immunosuppressive regimens that result in remission in 80% of patients and in favorable long-term survival rates (80-90%) over 10 years. LT is an effective therapy for patients with decompensated chronic autoimmune hepatitis and in patients with autoimmune hepatitis who present with acute liver failure. Long-term outcomes after LT for autoimmune hepatitis are excellent, with 5 to 10-year survival rates of ~75%.[93] Factors associated with poor outcome and need for LT in type I autoimmune hepatitis include delayed aminotransferase response to therapy, younger age, greater acuity at presentation, MELD score >12, and multiple relapses.[94]

The clinical and histological features of acute liver failure due to autoimmune hepatitis are not fully defined but central zone perivenular inflammation on biopsy appears to be a common feature in this presentation of autoimmune hepatitis not typically seen in chronic autoimmune hepatitis.[95,96] Corticosteroid administration in acute liver failure due to autoimmune hepatitis is controversial and is best reserved for less severe disease (MELD <28)[97] to minimize the risk of sepsis which could preclude transplantation.[97,98]

Additional information on this disease is contained within the Practice Guidelines on Autoimmune Hepatitis.

Recommendations:

32. LT should be considered in patients with decompensated autoimmune hepatitis who do not respond to or are not appropriate candidates for medical therapies (I-A).

33. LT is indicated in autoimmune hepatitis presenting as acute liver failure if recovery is unlikely (1-B).

Primary Biliary Cirrhosis (PBC)

Therapy with ursodeoxycholic acid has improved outcomes in PBC, reflected in a decrease in the number of patients with PBC requiring LT.[99] Indications for LT in PBC mirror those for other causes of cirrhosis and may also include severe portal hypertension refractory to medical/surgical interventions and occasionally pruritus refractory to medical therapy. Transplant outcomes in PBC are excellent, with 5-year patient survival rates of 80-85% after either living or deceased donor transplantation.[100,101]

Additional information is contained within the Practice Guidelines on Primary Biliary Cirrhosis.

Recommendations:

34. LT is indicated for decompensated PBC (I-A).

35. Severe pruritus, refractory to medical therapy, may also be an indication for LT (I-B).

Primary Sclerosing Cholangitis (PSC)

No effective medical therapy is available for PSC,[74-77] which is associated with an increased risk of cholangiocarcinoma and gallbladder carcinoma as well as colon cancer in patients with associated inflammatory bowel disease (IBD).[75] LT is an effective intervention in patients with PSC who develop decompensated disease. Recurrent bacterial cholangitis and, in very highly selected patients, cholangiocarcinoma are additional indications for which patients may be eligible for MELD exception points.[102,103] Continued surveillance for cholangiocarcinoma is necessary while awaiting transplant, although the optimal screening strategy has not been defined. Transplant outcomes for PSC are excellent, with 5-year patient survival rates of ~90% after either living or deceased donor transplantation.[104] Roux-en-Y choledochojejunostomy with resection of the recipient distal common bile duct to prevent recurrent PSC or *de novo* cholangiocarcinoma is the standard approach, although duct-to-duct biliary reconstruction has also been advocated by some when the native distal bile duct is free of overt disease.[105] The presence of active IBD prior to LT appears to worsen posttransplant outcomes.[106] Endoscopic surveillance at 1 to 2-year intervals to detect colorectal neoplasia is appropriate for PSC patients with IBD both prior to and following LT due to an increased risk of colon malignancies.[107] Poorly controlled IBD prior to LT has been implicated in diminished graft survival and thrombotic episodes and management of IBD should be optimized prior to LT.[108]

LT for cholangiocarcinoma in PSC is an evolving area (see below). Additional information on PSC is contained within the Practice Guidelines on Primary Sclerosing Cholangitis.

Recommendations:

36. LT is an effective therapy for decompensated liver disease due to PSC, including bouts of recurrent cholangitis and sepsis (I-A).

37. Colonoscopy should be performed annually in patients with PSC and IBD both before and after transplantation due to the high incidence of colorectal cancer (II-3).

Alcoholic Liver Disease

Alcoholic liver disease (ALD) remains the second most common indication for LT. However, an estimated 95% of patients with endstage ALD are not referred for evaluation, even when AASLD Guidelines for referral are met.[109]

In a report 20 years ago on outcomes of patients transplanted for ALD, Starzl et al.[110] reported comparable outcomes for ALD recipients versus those with other liver diseases, although controversy still surrounds LT for this indication. Recent studies continue to demonstrate acceptable outcomes for ALD with graft loss due to resumption of alcohol post-LT comparable to PBC, being 2% by 10 years.[111] Most patients with ALD have the comorbid psychiatric diagnosis of alcohol dependence with a relapsing, remitting course.[112] Patients with ALD require evaluation by clinicians skilled in mental health, optimally with addiction experience, in order to establish the correct psychiatric diagnoses and adequate treatment plan.[113-116] Even patients not referred for ALD, especially those with HCV, may have significant alcohol use disorders that are missed on referral but should be identified by structured psychiatric and substance abuse counselor interviews.[80-83]

A 6-month minimum period of abstinence is commonly enforced on the basis that this period allows addiction issues to be addressed, and in patients with recent alcohol consumption or acute alcoholic hepatitis, may allow for spontaneous recovery and obviate the need for LT as well as reduce the risk of alcohol relapse if LT remains necessary.[117] In acute alcoholic hepatitis there will be some patients who will not respond to or will continue to deteriorate despite medical therapy. For these patients early LT, before 6 months abstinence is achieved, has been demonstrated to improve survival but remains controversial.[118] It is critical that the requirement for addiction rehabilitation not be neglected during this time. To merely achieve 6 months sobriety without assessment or treatment does not therapeutically address a potential addictive disorder and abstinence alone may not meet the listing criteria for LT. Post-LT contracting for alcohol aftercare and counseling may be considered for those patients who are too sick to attend appropriate rehabilitation treatment.

Optimally, a patient with ALD should be referred in ample time to permit the transplant mental health clinicians to complete initial LT evaluation for the patient to begin/complete any addiction treatment requirements, and for any necessary reassessment to be performed. While some programs may not consider evaluating a patient with less than 6 months sobriety, waiting until they achieve 6 months before the referral or evaluation for LT is arranged may result in deterioration of the patient's medical condition so that psychosocial or addiction requirements determined from the initial evaluation may not be achievable. Ongoing monitoring by interview and toxicology screening may be considered for waitlisted candidates to document sobriety and continued participation in rehabilitation. Two studies have identified alcohol use by up to 25% of waitlisted ALD candidates,[119,120] and most recoveries are made through scheduled or random blood alcohol levels.[121] Discovery of alcohol use on the waitlist typically results in delisting and requirement for further psychiatric and alcohol counselor input.

Recommendations:

38. Early referral of ALD patients for initiation of LT evaluation facilitates psychosocial assessment and setting addiction treatment goals (1-A).

39. Given the chronic nature of alcohol dependence, ongoing monitoring is an important part of a comprehensive treatment plan (1-B).

Acute Liver Failure

Acute liver failure (ALF) is the rapid development of encephalopathy and coagulopathy (INR $\geq$1.5) in a patient without documented preexisting liver disease. Acetaminophen toxicity accounts for approximately half of all causes of ALF in the United States.[122] Patients with ALF of any etiology should be referred for urgent LT evaluation, as transplant centers have the expertise to anticipate the complications of ALF. Etiology is the most important predictor of spontaneous recovery in ALF with acetaminophen, acute hepatitis A, pregnancy-related liver disease, and shock liver having the highest likelihood of spontaneous survival. There are several tools designed to help predict which patients will recover and which will ultimately require LT. These tools include criteria such as the Kings College Criteria, Clichy Criteria, and, more recently, the MELD score, and have all been applied in this setting, although the frequent and unpredictable complications of ALF limit their utility and the decision to proceed to LT needs to be individualized.[123-126] Patients with ALF are eligible for UNOS Status 1a, which gives them preference in organ allocation over all forms of chronic liver disease as well as broader UNOS regional sharing. Criteria for Status 1 listing in addition to care in an ICU include one of the following: (1) ventilator dependence, (2) renal replacement therapy with hemodialysis or hemofiltration, or (3) INR $\geq$2 in a patient

with onset of hepatic encephalopathy within 8 weeks of initial symptoms of liver disease (www.UNOS.org).

Transplant outcomes for ALF are generally worse in the first postoperative year compared to recipients with chronic liver disease due to infectious and neurological complications, whereas beyond 1 year they surpass survivals for LT for chronic liver disease.[87,127] Intractable cerebral edema with cerebral perfusion pressure <40 mmHg for more than 2 hours, other evidence of irreversible neurological complications such as an intracerebral bleed, uncontrolled infection, high-dose pressor requirements, or other evidence of medical instability such as increasing FiO2 are contraindications to LT.[128]

Recommendations:

40. Patients with ALF require immediate referral to a liver transplant center (1-A).

41. Patients with acetaminophen overdose should be evaluated for and meet reasonable expectations for adherence to medical directives and mental health stability as determined by the psychosocial evaluation (1-A).

Hepatocellular Carcinoma

HCC has become an increasingly important indication for LT. A landmark report by Mazzaferro et al.[129] from Milan indicated that the 4-year survival after transplant was 75% and the recurrence-free survival was 83% provided the tumor burden was either one lesion ≤5 cm, or three lesions each ≤3 cm without metastatic spread at the time of LT. Patients diagnosed with HCC who fall within the "Milan Criteria" are automatically assigned a MELD priority score of 22. The diagnosis is based on cross-sectional imaging with the following radiological characteristics diagnostic of HCC: contrast enhancement on the late arterial phase with one of the following features washout on portal venous phase: late capsule, pseudocapsule enhancement or growth on serial studies, or consistent biopsy confirming a tissue diagnosis of HCC. The tumor must not be amenable to resection and metastatic spread needs to have been excluded by a chest CT and bone scan. The tumor dimensions need to be confirmed by an magnetic resonance imaging (MRI) or CT scan interpreted by a radiologist at an OPTN-approved center (OPTN.transplant.hrsa.gov). The assigned MELD score currently increases every 3 months consistent with a 10% increase in candidate mortality until the patient is either transplanted or progresses beyond Milan criteria based on serial imaging. Frequently, these patients have low "biological" MELD scores due to preserved hepatocellular function and, thus, exception points afford them the opportunity to receive LT prior to tumor progression.[130] Extending the size limits beyond the Milan criteria may be possible without sacrificing survival outcome, the most common being the UCSF criteria.[131] However, these patients are not given additional MELD priority and it can be difficult to access a deceased donor graft. Tumors beyond the Milan criteria may be eligible for downstaging to Milan criteria, with the ultimate goal of transplantation.[132] Candidates successfully downstaged to within the Milan criteria can be the subject of a petition for MELD exception points to the Regional Review Board. The role of locoregional therapies to control tumor growth in waitlisted candidates within the Milan criteria is an area of active investigation and a decision to perform tumor ablation can reflect a number of factors, including the candidate's projected waiting time for transplant and ability to tolerate an intervention based on the biological MELD Score.[133]

Recommendations:

42. LT is an effective therapy for HCC within the Milan criteria (1-A).

43. LT may be an option for HCC in excess of the Milan criteria in combination with tumor downstaging to Milan (2-C).

Cholangiocarcinoma

Although surgery remains the only therapeutic option for intrahepatic and extrahepatic cholangiocarcinoma, LT has been attempted for perihilar tumors (i.e., involving the bile duct between the cystic duct junction and the secondary branches of the right/left hepatic ducts) deemed nonresectable due to involvement of hilar structures and/or underlying liver disease, typically PSC. Initially, results of LT were poor, with 2-year recurrence rates of 50% and 5-year survival rates of <30%.[134-136] Extension of the resection to include pancreaticoduodenectomy failed to improve outcomes.[137,138] However, two single-center reports of protocols incorporating neoadjuvant chemoradiation therapy, rigorous assessment for extrahepatic (nodal and/or metastatic) disease, avoidance of direct transperitoneal biopsy, and LT describe 5-year patient survival rates of nearly 80%.[139-142] In response, UNOS granted exception status in June 2009 to unresectable, early stage, peri-hilar cholangiocarcinoma treated under a preapproved protocol of neoadjuvant chemoradiation with an initial award of MELD exception score commensurate with a 10% 3-month mortality risk and escalation commensurate with a 10% increase in mortality risk every 3 months. Recently, a report

summarizing the combined experience of 12 transplant centers with 287 peri-hilar cholangiocarcinoma patients, of whom 214 underwent neoadjuvant chemoradiation prior to LT, has confirmed acceptable 5-year patient survival rates (53% [95% confidence interval 46-60%] intention to treat survival; 65% [95% confidence interval 57-73%] posttransplant survival).[143] Moreover, the dropout rate increased every 3 months by 11.5% (range, 7-17%), confirming the appropriateness and magnitude of incremental MELD awards every 3 months for qualified candidates who remain on the waitlist.

Recommendations:

44. Patients diagnosed with early-stage cholangiocarcinoma and deemed unresectable due to parenchymal liver disease or anatomic location may be considered for LT in combination with neoadjuvant chemoradiation (1B).

45. Patients with cholangiocarcinoma who are potential transplant candidates should be expeditiously referred to centers that have established protocols for oncologic assessment and treatment approved by UNOS (1B).

Metabolic Diseases

A number of metabolic diseases can lead to progressive liver injury and cirrhosis. The most common disorders in adults are nonalcoholic steatohepatitis (NASH), α-1-antitrypsin deficiency, hereditary hemochromatosis, and Wilson's disease. One- and 3-year survival after LT for these disorders is similar to LT for other indications.[144]

NASH

NAFLD includes a spectrum of disease from isolated steatosis to NASH with cirrhosis. The prevalence of NAFLD and NASH are increasing and are closely linked to the dramatic rise in obesity and components of the metabolic syndrome.[145] As many as 30% of adults in Western countries have NAFLD and up to 12% of whom have NASH.[146,147] In those with NASH, progression to advanced fibrosis and cirrhosis occurs in ∼30% and 10%, respectively, over a 5-year period.[148,149] In addition, NASH, with, and uncommonly without, cirrhosis is associated with an increased risk for the development of HCC.[150,151] Currently, no medical therapies for NASH have consistently resulted in a reduction in hepatic fibrosis.

There has been a significant increase in the proportion of patients undergoing LT in the U.S., with a primary diagnosis of NASH from 1.2% in 2001 to 9.7% in 2009.[152] NASH is now the third most common indication for LT and is on pace to become the most frequent. In addition, a significant number of patients transplanted with cryptogenic cirrhosis have clinical features similar to those seen in patients with NASH and similar rates of recurrent disease following transplant, suggesting that the frequency of LT for NASH may be underestimated.[152-154] The impact of coexistent NASH in those with other causes of liver disease leading to LT has also not been quantified.

Patient and graft survivals in patients with NASH undergoing LT are similar to that in patients with other major indications for LT over a 3 to 5-year follow-up period.[152,155] However, NAFLD and NASH also share risk factors for cardiovascular and chronic kidney disease.[156] Therefore, longer follow-up is needed to understand the influence of the metabolic syndrome on post-LT outcomes. NAFLD and NASH recur following LT, with steatosis reported on biopsy in more than 60% of recipients transplanted with these diagnoses early after LT, and NASH is observed in from 10-40% of the post-LT patients.[157] Although rapid disease recurrence resulting in graft loss within 3 years of LT has been described,[152] it appears that only ∼10% of NASH recipients develop advanced fibrosis or cirrhosis within 10 years of LT.[157] The impact of recurrent disease on outcomes in patients transplanted with NASH requires further evaluation.

Additional information on NASH is contained within the Practice Guidelines on NAFLD.

Recommendation:

46. LT is an effective therapy for decompensated liver disease due to NASH or cryptogenic cirrhosis (1-A).

α-1-Antritrypsin Deficiency

Adults with α-1-antritrypsin deficiency commonly have no prior history of liver disease and only a minority present with abnormal liver biochemistries levels regardless of the severity of liver disease.[158] The prevalence of liver disease in adults ranges from 2-43% and appears to increase with age.[159] An autopsy study of PiZZ individuals found that almost 50% had cirrhosis and 28% had HCC present at the time of death.[160]

Testing for α-1-antritrypsin deficiency is indicated in unexplained liver disease[161] and measurement of the serum or plasma α-1-antritrypsin level coupled with genotype testing if levels are below normal[158] should be done in these patients. LT is the only effective therapy for decompensated liver disease due to α-1-

antritrypsin deficiency and is the indication for transplant in ~1% of adult recipients.[162] Patient (83%) and graft (77%) survivals over 5 years in adults with α-1-antritrypsin deficiency are excellent.[162] The donor α-1-antritrypsin phenotype is expressed following LT and serum levels return to normal within weeks after surgery, so recurrence is not a concern. Concomitant lung disease should be excluded before LT by pulmonary function tests and chest imaging.[163]

Recommendations:

47. LT is indicated for decompensated cirrhosis due to α-1-antritrypsin deficiency (I-A).

48. Screening to exclude lung disease with pulmonary function tests and chest imaging should be undertaken in patients with α-1-antritrypsin deficiency being evaluated for LT (I-A).

Hereditary Hemochromatosis

Although the majority of C282Y homozygotes will accumulate hepatic iron, only 4-6% of whom appear to develop cirrhosis.[164] Therapeutic phlebotomy, if undertaken early, can prevent the development of cirrhosis and other complications.[165] HCC develops in ~6% of affected men and 1.5% of women, most often but not always in those with cirrhosis.[166,167] The risk of HCC in cirrhosis due to hereditary hemochromatosis appears to be greater than in other causes of cirrhosis.[168] Although elevated iron studies may be seen in patients with other causes of liver disease, particularly alcohol, NAFLD, and HCV, coexisting hereditary hemochromatosis is uncommon.[169]

Hereditary hemochromatosis is a relatively uncommon indication for LT, accounting for 0.5-1% of all transplants despite the frequency of the HFE gene.[170] LT is indicated for HCC or decompensated liver disease. Cardiovascular events, most notably arrhythmias and infectious complications, are increased after LT in hereditary hemochromatosis, resulting in outcomes inferior to other indications for LT.[170,171] However, the judicious use of iron reduction therapy pretransplant and careful selection and follow-up appear to have resulted in improved outcomes after LT, which are now similar to other indications for LT in more recent analyses.[170,172]

Additional information is contained within the Practice Guidelines on Hemochromatosis.

Recommendations:

49. LT is indicated for decompensated cirrhosis due to hemochromatosis (1-A).

50. Iron reduction therapy should be performed prior to LT in candidates with hemochromatosis (I-B).

Wilson's Disease

Hepatic manifestations of Wilson's disease include acute or chronic hepatitis, cirrhosis, and acute liver failure.[173] The disease may also present with neuropsychiatric dysfunction, hemolytic anemia, and renal impairment. Many, but not all, patients with chronic liver disease have low ceruloplasmin levels and the diagnosis is generally made on a composite of clinical findings and biochemical measurements.[174] In acute liver failure, a number of criteria have been evaluated that improve diagnostic accuracy. The ratio of alkaline phosphatase to bilirubin combined with aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio has a high sensitivity and specificity.[175] Copper chelation and removal are effective in chronic liver disease and result in sustained remission as long as compliance with therapy is maintained.[173] In those with decompensated disease not responsive to therapy or in those with fulminant hepatic failure, LT is appropriate.

The outcome of LT for hepatic Wilson's disease appears to be excellent and similar or better to outcomes in other etiologies of liver disease.[176,177] Living donor liver transplant (LDLT) from parents (obligate heterozygotes) to children has also been reported to be successful.[178,179] The majority of metabolic abnormalities, including renal dysfunction, improve after LT.[180] There is considerable uncertainty regarding the utility of LT in the setting of chronic and severe neurologic dysfunction not responsive to medical therapy.[177] Although case reports and series support that neurologic improvement may occur in a subset of patients who undergo LT, specific predictors of response and long-term outcomes are not well defined.[177,180]

Additional information is contained within the Practice Guidelines on Wilson's Disease.

Recommendations:

51. Urgent LT is indicated for Wilsonian acute liver failure (I-A).

52. LT is indicated in decompensated cirrhosis due to Wilson's disease unresponsive to medical therapy (I-A).

53. LT is not recommended as therapy for neuropsychological Wilson's disease, as LT does not reliably improve neurologic outcomes (I-B).

Hereditary Amyloidosis

Inherited forms of amyloidosis where mutated amyloid precursor proteins are predominately produced in the liver and affect other organs and tissues may benefit from LT.[180] The most common disorder where LT has been employed is familial amyloid polyneuropathy

(FAP) resulting from mutations in the transthyretin gene inherited in an autosomal dominant fashion.[181,182] Approximately 80% of all patients who have undergone LT have the Val30Met mutation in the transthyretin gene, but many mutations have been identified.[181] Common clinical findings include sensory-motor polyneuropathy, autonomic dysfunction, and frequent cardiac and ocular involvement. Renal dysfunction occurs in less than 50% of patients.[182] LT appears to improve survival in Val30Met FAP and 5-year survival is reported as >80%.[182-184] LT does not alter the course of cardiac or ocular involvement and may stabilize but does not reverse neuropathy.[182] Therefore, outcomes are best in patients who are <50 years old and have short duration and mild severity of disease.[180,182] Outcomes of LT for FAP related to non-Val30Met transthyretin mutations are inferior to those with the Val30Met mutation.[181] Domino LT using the functionally and structurally normal FAP liver is commonly employed and has low operative risk.[185] However, transmission of amyloidosis has been observed and symptomatic disease has been reported to develop within 5-10 years after LT using FAP livers.[186-188]

LT, typically with renal transplantation, has also been employed for autosomal dominant hereditary renal amyloidosis, most commonly associated with mutations in the fibrinogen α-chain gene.[189] Common clinical manifestations include proteinuria with rapid progression to End Stage Renal Disease (ESRD), cardiovascular dysfunction, autonomic dysfunction of the gastrointestinal tract, and retinal bleeding. Outcomes following transplantation for renal amyloidosis are less well characterized than for FAP. One recent small series found a 5-year survival rate of 67% in those undergoing combined liver and kidney transplantation but also found a high rate of coronary and systemic atherosclerosis that precluded transplant in a number of potential candidates.[189] Domino transplantation has been employed and has not resulted in symptomatic amyloidosis in the recipient of the amyloid-producing liver graft over a limited follow-up period.

Recommendation:

54. LT should be considered in FAP to eliminate hepatic amyloid production early in the course of disease and particularly prior to the development of cardiac and ocular complications, as these complications are not reliably improved by LT (I-B).

Primary Hyperoxaluria

Primary hyperoxaluria type I is a rare (3 cases per million population) autosomal recessive disorder caused by a defect in hepatic alanine glyoxylate aminotransferase which impairs glyoxylate metabolism to glycine and results in overproduction of oxalate and glycolate.[190,191] The clinical expression of disease in adults is heterogeneous, with recurrent urolithiasis and/or progressive nephrocalcinosis commonly leading to ESRD by 20-40 years of age.[191] The diagnosis is often delayed until ESRD has developed.[191,192] Medical therapy is effective in decreasing or normalizing oxalate excretion in ∼30% of patients and may prevent progression of disease if initiated early.[193] LT cures the defect in primary hyperoxaluria type I and may be effective as preemptive therapy in early disease with well-preserved renal function.[194] More commonly, combined liver and kidney transplantation is undertaken in those with ESRD with good reported 5-year survival rates of ∼80%.[195-197] Cardiomyopathy due to oxalate deposits has been reported to improve with combined liver kidney transplant.[198]

Recommendation:

55. Preemptive LT (prior to the development of advanced renal disease) or combined liver and kidney transplantation in the setting of ESRD are curative for primary hyperoxaluria and should be considered for patients who do not respond to medical therapy (I-A).

MELD Exceptions

Although the biological MELD score serves the majority of liver transplant candidates on the waitlist well, it fails a subset of patients with complications of cirrhosis, most notably HCC or with relatively rare etiologies of liver disease. At the time of implementing the MELD allocation policy, Regional Review Boards (RRBs) were established to provide peer review of individual patients poorly served by the standard allocation algorithm. As the number of "exception" cases grew, there was concern about potential inequity and inconsistency of access to the deceased donor liver pool. Moreover, underprioritization or overprioritization exerts an impact on not only the individual under consideration but also the remaining waitlist candidates.

To comprehensively review data and codify expert opinion, the MELD Exception Study Group (MESSAGE) Committee was convened by UNOS:[199]

1. To identify conditions for which a specific, objective, endpoint exists that defines the need for LT such that assignment of additional priority can be automatic (without RRB peer review) and recommend the amount of additional priority so assigned, and

2. To recommend specific, objective data elements to be collected for individual conditions for those conditions for which there was insufficient evidence for granting increased priority.

The MESSAGE committee deliberations were presented to an international panel of experts and the final recommendations for each individual condition considered were formulated and formalized.

Several important recommendations were made:

1. Budd-Chiari syndrome in its fulminant and chronic form was thought to be adequately served by the current allocation policy provisions for Status 1 designation and calculated MELD score prioritization, respectively.
2. Conditions such as polycystic liver disease and pruritus for which data failed to support an endpoint related to quantity but rather of quality of life were considered inappropriate for additional MELD points. RRBs were instructed to refrain from granting any exceptional consideration.
3. Three genetic disorders (primary hyperoxaluria, familial amyloidotic polyneuropathy, and cases of cystic fibrosis with ongoing pulmonary deterioration but listed for liver transplant alone) along with hepatopulmonary syndrome and small for size syndrome were recommended for automatic awarding of MELD exception points. For each disorder, parameters to confirm candidate appropriateness were specified. For the majority of conditions there was acknowledgment that the recommendation was for case-by-case consideration with specification of clinical data to be submitted to the RRB with prospective data collection.

A number of other rare disorders may also be considered for LT. Hereditary hemorrhagic telangiectasia can lead to severe portal hypertension and biliary necrosis in addition to cardiac failure, with LT reported as an effective intervention for each of these manifestations.[200] Encouraging results have also been reported for hepatic hemangioenthelioma.[201] LT for metastatic neuroendocrine tumors has also been reported to result in recipient survivals similar to those of HCC transplant within the Milan criteria.[202] For these infrequent indications, potential recipients do not typically have hepatocellular failure and need to have extra MELD points assigned to allow LT.

Recommendation:

56. For an LT candidate whose MELD score does not adequately reflect the severity of their liver disease, an appeal for MELD exception points should be made to the RRB (1-B).

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