AASLD Practice Guidelines: Evaluation of the Patient for Liver Transplantation

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Preamble

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 [Medline search]; (2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines[1]; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines[2]; (4) 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. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a category to be assigned and reported with each recommendation (Table 1).[3] These recommendations are fully endorsed by the AASLD and the American Society of Transplantation.

Introduction

Liver transplantation has had a profound impact on the care of patients with end-stage liver disease and is the most effective treatment for many patients with acute or chronic liver failure resulting from a variety of causes. Before transplantation, patients with advanced liver disease usually died within months to years. These patients now have the opportunity for extended survival with excellent quality of life after liver transplantation.[4] Furthermore, the costs of liver transplants have steadily declined in recent years.[5]

Most liver transplants are performed using a whole liver from a deceased donor. During transplantation, the donor liver is placed in the orthotopic position, hence the term *orthotopic liver transplantation*. However, because of the unique anatomical organization of the liver, donor organs can be divided and the separate parts transplanted into two recipients (split liver transplantation).[6] Using this technique, a portion of the left lobe of an adult donor organ can be transplanted into a child and the remaining portion used to transplant the liver into an adult.[7-10] Under ideal circumstances, a deceased donor organ also can be split and transplanted into two adult recipients.[10] The same surgical techniques can be used to facilitate transplantation using living donors, where only a portion of the donor liver is removed for transplantation. Living donor transplantation for children, using a portion of the left lobe, is a well-established procedure.[7,8] Living donor transplantation for adults, in which the donor right lobe typically is transplanted, also is performed at many transplant centers, although donor safety remains an ongoing concern.[11,12] Perioperative complications typically are higher with these various techniques; however, long-term patient survival seems comparable with that of deceased whole liver transplantation.[10,13]

Liver transplantation is a complex, time-consuming operation that requires vascular reconstruction of the hepatic artery, the portal vein, and the hepatic venous drainage to the inferior vena cava. Biliary reconstruction usually is accomplished using an end-to-end anastomosis of the proximal donor bile duct to the distal recipient duct; however, in recipients with diseased ducts, the donor duct is usually anastomosed to the jejunum using a Roux-en-Y loop. A number of complications can be anticipated after liver transplantation, including perioperative and surgical complications, immunologic and infectious disorders, and a variety of medical complications.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; MELD, model for end-stage liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; CTP, Child-Turcotte-Pugh; PELD, pediatric end-stage liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; HPS, hepatopulmonary syndrome; NASH, nonalcoholic steatohepatitis.

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The outcome of all patients who receive liver transplants in the United States and Europe is continuously tracked in comprehensive databases: the United Network for Organ Sharing (UNOS) and the European Transplant Registry (ELTR), respectively. Using outcomes from these databases, computer models are available to address specific issues of organ allocation and to track the efficacy of cadaveric and living-related transplants both nationally and at individual centers.[14] The dramatic increase in transplants over the past two decades seems to have had a favorable impact on chronic liver disease mortality in the United States.[15] Nevertheless, many issues remain, including specific indications and contraindications to liver transplantation, the optimum timing of the operation, and the most appropriate use of scarce donor organs.

Indications for Liver Transplantation

Liver transplantation is indicated for acute or chronic liver failure from any cause. The major conditions that lead to the need for transplantation in adults and children are summarized in Table 2.

Table 2. Indications for Liver Transplantation

Chronic noncholestatic liver disorders
Chronic hepatitis C
Chronic hepatitis B
Autoimmune hepatitis
Alcoholic liver disease
Cholestatic liver disorders
Primary biliary cirrhosis
Primary sclerosing cholangitis
Biliary atresia
Alagille syndrome
Nonsyndromic paucity of the intrahepatic bile ducts
Cystic fibrosis
Progressive familial intrahepatic cholestasis
Metabolic disorders causing cirrhosis
Alpha-1-antitrypsin deficiency
Wilson disease
Nonalcoholic steatohepatitis and cryptogenic cirrhosis
Hereditary hemochromatosis
Tyrosinemia
Glycogen storage disease type IV
Neonatal hemochromatosis
Metabolic disorders causing severe extrahepatic morbidity
Amyloidosis
Hyperoxaluria
Urea cycle defects
Disorders of branch chain amino acids
Primary malignancies of the liver
Hepatocellular carcinoma
Hepatoblastoma
Fibrolamellar hepatocellular carcinoma
Hemangioendothelioma
Fulminant hepatic failure
Miscellaneous conditions
Budd-Chiari syndrome
Metastatic neuroendocrine tumors
Polycystic disease
Retransplantation

When Should Evaluation for Transplantation Be Considered?

The first step in considering a patient for potential liver transplantation is determining the need for the operation. The second step is to confirm that all other effective treatments have been attempted. Finally, the patient's likelihood of being an appropriate candidate for transplantation should be carefully assessed by a transplantation center.

Determining the Need for Liver Transplantation

The natural history of the patient's disease must be carefully compared with the anticipated survival after liver transplantation. The clinical tools most widely used to determine prognosis in patients with chronic liver diseases include disease-specific indices for primary biliary cirrhosis and sclerosing cholangitis, the Child-Turcotte-Pugh (CTP) classification, the prognostic model for end-stage liver disease (MELD), as well as the impact of specific complications of cirrhosis on patient survival.

Table 1. Quality of Evidence on Which a Recommendation Is Based[3]

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

The Mayo Clinic prognostic model for primary biliary cirrhosis (PBC) is the best-validated tool for determining prognosis in groups of patients with chronic liver disease.[16,17] However, this model is useful only for patients with PBC. A number of disease-specific models also have been developed for determining the prognosis of patients with primary sclerosing cholangitis (PSC).[18] However, in addition to being useful only for patients with this disease, it is not clear whether any of the PSC models add to simple means of assessing prognosis, such as the CTP classification.[19]

The CTP classification, which was designed to stratify the risk of portacaval shunt surgery in patients with cirrhosis and variceal bleeding, has gained favor over the past decade as a simple method for determining the prognosis of patients with chronic liver disease (Table 3).[20,21]

Although never formally validated as a prognostic tool, the CTP score is useful as a rapid means of assessing the relative risk of mortality among groups of patients with cirrhosis. The CTP score is as effective as quantitative

Table 3. Child-Turcotte-Pugh (CTP) Scoring System to Assess Severity of Liver Disease

Points	1	2	3
Encephalopathy (grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1-2	2-3	>3
Albumin (g/dL)	3.5	2.8-3.5	<2.8
Prothrombin time (seconds prolonged)	1-4	4-6	>6
Or (INR)	<1.7	1.7-2.3	>2.3
For primary biliary cirrhosis: bilirubin (mg/dL)	1-4	4-10	>10

*According to grading of Trey, Burns, and Saunders.[21]

liver function tests in determining short-term prognosis among groups of patients awaiting liver transplantation.[22] Although its limitations have been well described, the CTP score has been widely adopted for risk-stratifying patients before transplantation because of its simplicity and ease of use.[23] More than one third of patients with CTP scores of 10 or more (class C) who are waiting for transplantation can be expected to die within 1 year.[19,22] In contrast, patients with CTP scores of 7 to 9 (class B) have an 80% chance of surviving 5 years, and those with CTP scores of 5 to 6 (class A) have a 90% chance of surviving more than 5 years without transplantation.[19,24,25]

The MELD was originally developed to assess short-term prognosis in patients undergoing transjugular intrahepatic portosystemic shunts (TIPS). Among patients who had undergone this procedure, serum bilirubin, international normalized ratio of prothrombin time (INR), serum creatinine, and diagnosis seemed to be the best predictors of 3-month postoperative survival.[26] Using the MELD model, patients are assigned a score in a continuous scale from 6 to 40, which equates to estimated 3-month survival rates from 90% to 7%, respectively.[26] Subsequent studies of this model demonstrated its usefulness as an effective tool for determining the prognosis of groups of patients with chronic liver disease.[27] A modification of this model is now used to prioritize patients for donor allocation in the United States. The modified MELD score has been shown useful both in predicting short-term survival in groups of patients on the waiting list for liver transplantation as well as the risk of postoperative mortality.[28,29]

A similar model has been developed for pediatric end-stage liver disease (PELD). The variables included in this model are: age younger than 1 year, serum albumin level, serum bilirubin, INR and growth failure (<2 SD below the age-based mean).[30,31] The higher the PELD score, the lower the likelihood of 3-month survival without transplantation. This model has been useful in predicting deaths of pediatric patients waiting for transplantation.[32] Calculation of individual MELD or PELD scores for patients can be determined at http://www.unos.org/resources/meldpeldcalculator.asp.

The development of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome also have a significant impact on the prognosis of patients with cirrhosis. The 5-year survival rate of individuals in whom any of these complications develop is only 20% to 50% of patients with compensated cirrhosis.[33,34] The most ominous complications are spontaneous bacterial peritonitis and rapid-onset (type I) hepatorenal syndrome. Less than half of those in whom spontaneous bacterial peritonitis develops can be expected to survive 1 year, whereas the median survival among patients with type I hepatorenal syndrome is less than 2 weeks.[35,36]

The natural history of disease should be compared with the expected survival after liver transplantation. Current survival rates 1, 3, and 5 years after liver transplantation in the United States are 88%, 80%, and 75%, respectively (http://www.optn.org/latestdata/step2.asp). As a result, patients with a MELD score of 15 or more and a CTP score of 7 or more can be expected to achieve improved survival with liver transplantation.[25,28,29] Because complete evaluation for transplantation can take weeks to months and patients must wait for variable periods of time before receiving a deceased donor organ, referral before the patient's anticipated mortality exceeds that of the estimated postoperative survival is important.

Recommendations

1. Patients with cirrhosis should be referred for transplantation when they develop evidence of hepatic dysfunction (CTP ≥ 7 and MELD ≥ 10) or when they experience their first major complication (ascites, variceal bleeding, or hepatic encephalopathy) (II-3).

2. Children with chronic liver disease should be referred when they deviate from normal growth curves or develop evidence of hepatic dysfunction or portal hypertension (II-3).

3. Patients with type I hepatorenal syndrome should have an expedited referral for liver transplantation (II-3).

Exploring Alternative Forms of Treatment

Because of the need for long-term immunosuppressive therapy, liver transplantation can be associated with higher mortality and long-term morbidity than many alternative treatments for patients with various chronic liver diseases. As a result, every therapeutic option should be carefully considered before committing a patient to this operation. Examples of alternative treatments are detailed

in Specific Indications for Liver Transplantation.. However, in patients with severe liver disease in whom the outcome of another treatment is uncertain, it is reasonable to begin evaluation for transplantation while assessing the outcome of the alternative form of therapy. Examples include immunosuppressive therapy for patients with severe autoimmune hepatitis, chelation therapy for patients with severe chronic Wilson disease, and antiviral therapy for patients with decompensated cirrhosis secondary to chronic hepatitis B.

Recommendations

4. Every option for disease-specific treatment should be considered in patients with chronic liver disease.

a. Only when there is no effective alternative therapy or when treatment has been shown to be ineffective should liver transplantation be considered (II-3).

b. However, in critically ill patients in whom the outcome of medical therapy is uncertain, it is appropriate to simultaneously begin specific treatment for the disease and to initiate evaluation for potential liver transplantation (III).

Determining the Potential for Successful Liver Transplantation

As soon as it has been determined that a patient is sick enough to require consideration for transplantation and that no other alternative treatments are available, a careful evaluation should be performed to address the following fundamental questions:

A. Can the patient survive the operation and the immediate postoperative period?

B. Can the patient be expected to comply with the complex medical regimen required after liver transplantation?

C. Does the patient have other comorbid conditions that could so severely compromise graft or patient survival that transplantation would be futile and an inappropriate use of a scarce donor organ?

Recipient Evaluation at the Transplant Center

The typical evaluation of potential transplant recipients performed at most transplant centers includes:

A. A careful history and physical examination;

B. Cardiopulmonary assessment, including cardiac echocardiography, pulmonary function tests, dobutamine stress testing, and cardiac catheterization in selected patients;

C. Laboratory studies to confirm the etiology and severity of liver disease;

D. Creatinine clearance;

E. Laboratory studies to determine the status of current or previous hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus (HIV) infections; and

F. Abdominal imaging to determine hepatic artery and portal vein anatomy and the presence of hepatocellular carcinoma (HCC).

Specific Medical, Surgical, and Psychosocial Issues

Specific medical, surgical, and psychosocial issues that are important in the evaluation of potential liver transplant recipients include the following.

Age. There is no specific age limitation to successful liver transplantation.[37,38] However, older patients have diminished long-term survival after transplantation compared with younger individuals, primarily because of an increased risk of death from malignancies.[39,40]

Coronary Artery Disease. Perioperative mortality after liver transplantation is high in patients with coronary artery disease.[41] Dobutamine stress echocardiography, in most but not all studies, seems to be an effective screening test for occult coronary disease in this setting.[42-44] However, cardiac catheterization should be performed in patients with positive stress tests to confirm and to delineate further the extent of the coronary disease.[41,42]

Recommendations

5. Chronic smokers, patients over the age of 50, and those with a clinical or family history of heart disease or diabetes should undergo evaluation for coronary artery disease (III).

6. Dobutamine stress echocardiography appears to be an effective screening test in this setting; however, positive test results should be confirmed with cardiac catheterization (II-2).

The Hepatopulmonary Syndrome

The hepatopulmonary syndrome (HPS) consists of the clinical triad of chronic liver disease, arterial deoxygenation, and widespread intrapulmonary vasodilation. Preoperative evaluation of patients suspected of having HPS should include arterial blood pO_2 determination, transthoracic contrast echocardiography, arterial oxygen response to 100% oxygen administration, and quantification of intrapulmonary shunting using a macroaggregated albumin (MAA) scan.[45] With careful management, moderate abnormalities of gas exchange are not a deterrent to successful liver transplantation. However, patients with severe hypoxia have increased perioperative mortality.[45,46] Preoperative PaO_2 of 50 mmHg or less alone or in combination with a MAA shunt fraction of 20% or more are the strongest predictors of postoperative mortality.[45] The

median survival of patients with cirrhosis and severe HPS is less than 12 months.[47] Because the condition is reversible after liver transplantation, HPS has become an indication for urgent transplantation.[48,49] Patients with clinical evidence of HPS and PaO_2 of less than 60 mmHg on room air with no underlying lung disease can receive enhanced prioritization for organ allocation to allow them a reasonable possibility of receiving a deceased donor organ within 3 months. Given the ominous prognosis of severe HPS and the potential reversibility of the condition, transplantation seems to be a reasonable, albeit high-risk, option for these patients.

Recommendation

7. Because patients with cirrhosis and severe hepatopulmonary syndrome have an extremely poor prognosis without transplantation, they should have an expedited referral and evaluation for liver transplantation (II-2).

Portopulmonary Hypertension

Portopulmonary hypertension is seen in 2% to 4% of patients with cirrhosis.[50,51] In a retrospective analysis of 1205 consecutive patients who underwent liver transplantation, 81 (7%) had mild pulmonary hypertension (systolic pulmonary artery pressure, 30-44 mmHg), 14 (1%) had moderate pulmonary hypertension (systolic pulmonary artery pressure, 45-59 mmHg), and 7 had severe pulmonary hypertension (systolic pulmonary artery pressure, ≥60 mmHg) before surgery. The presence of mild and moderate pulmonary hypertension did not influence the outcome of the procedure. In contrast, among patients with severe pulmonary hypertension, the postoperative mortality was 42% at 9 months and 71% at 36 months. Only 2 of the 7 patients with severe pulmonary hypertension survived transplantation with good quality of life. The remaining 5 continued to deteriorate with progressive right heart failure, with no evidence that transplantation ameliorated the pulmonary hypertension.[52] A number of studies have found that mild pulmonary hypertension is not associated with an increased risk of liver transplantation.[52-54] However, severe pulmonary hypertension is associated with high perioperative mortality and, if not successfully treated, is a contraindication to liver transplantation.[52,53] Nevertheless, patients with severe pulmonary hypertension who have been sucessfully treated with medical therapy have undergone transplantation safely. In most of these patients, pulmonary hypertension gradually resolves within 4 to 6 months after transplantation and medical therapy can be discontinued.[55-57]

Doppler echocardiography is a sensitive method of detecting the presence of pulmonary hypertension.[51,58-60] However, the positive predictive value of the test is low. Therefore, positive results should be confirmed with right heart catheterization.

Recommendations

8. All patients undergoing evaluation for potential liver transplantation should undergo screening for pulmonary hypertension (II-3).

9. Doppler echocardiography is an excellent screening test in this setting; however, positive test results should be confirmed with right heart catheterization (II-2).

10. Patients with severe pulmonary hypertension should be considered for liver transplantation only if the condition can be effectively controlled with medical therapy (II-3).

Obesity

Obesity, which is a common problem in patients being considered for liver transplantation, has an adverse impact on both immediate and long-term survival. Most patients in the United States who underwent liver transplantations between 1988 and 1996 were overweight (body mass index [BMI] > 25 kg/m^2).[61] Obesity was more common in women and in patients with cryptogenic cirrhosis. Morbid obesity (BMI > 40 kg/m^2) was associated with decreased 30-day, 1-year, and 2-year postoperative survival. Five-year survival was reduced both in patients with morbid and severe obesity (BMI > 35 kg/m^2).[61]

Cigarette Smoking

In one survey of more than 200 liver transplant recipients, 60% reported a lifetime history of smoking.[62] A number of recent studies have demonstrated the deleterious effects of smoking on outcomes after transplantation. The risk of hepatic artery thrombosis appears to be significantly increased among chronic smokers.[63] This effect disappears in chronic smokers who discontinue nicotine use 2 years before transplantation.[63] Long-term postoperative survival of smokers also is decreased because of an increase in cardiac mortality and death from malignancies.[40]

Recommendations

11. Morbid obesity should be considered a contraindication to liver transplantation (II-3).

12. All patients considered for liver transplantation should be encouraged to undergo efforts to abstain from smoking (III).

Renal Failure

A number of studies have identified elevated serum creatinine as an independent risk factor for the development of renal failure and decreased survival after liver transplantation.[64-66] Acute renal failure from the hepatorenal syndrome usually improves dramatically after liver transplantation and does not appear to have an impact on posttransplant survival.[67,68] In contrast, patients with preexisting chronic renal disease have diminished survival and an increased risk of requiring dialysis after transplantation.[64] However, it can be quite difficult to distinguish these two conditions in patients with severe liver disease.[69] Combined liver and renal transplantation is an attractive option for selected patients with preexisting renal disease who develop liver failure.[70,71] However, given the large number of patients on renal transplant waiting lists, the benefit of performing combined liver and renal transplantation must be weighed against the risk of depriving renal transplant recipients of donor organs.[72]

The serum creatinine level is one of the major variables in the MELD model used to allocate donor organs for liver transplantation.[28] As a result, an increasing number of patients with renal insufficiency are being selected for liver transplantation. There is concern that this may decrease overall survival rates and also may increase the need for combined liver and kidney transplants.[66,72] This area needs continued research and reevaluation.

Additional details on the medical management of hepatorenal syndrome are included in the Practice Guidelines on Management of Patients with Ascites Due to Cirrhosis, which can be found at http://www.aasld.org/netforumaasld/eweb/docs/ascites.pdf.

Recommendations

13. The presence of renal insufficiency is an important predictor of postoperative renal failure and mortality after liver transplantation, and hence a thorough pretransplantation evaluation of renal function is important (II-2).

14. Because rapidly progressive hepatorenal syndrome (type 1) has an ominous prognosis and usually is reversed by transplantation, patients with this condition should have an expedited referral for evaluation (II-3).

15. Selected patients with chronic renal and liver disease should be considered for combined liver–kidney transplantation (III).

Extrahepatic Malignancies

Patients with a history of extrahepatic malignancy are at high risk for recurrent disease because of the immunosuppression required after liver transplantation. Thus, it is prudent to defer transplantation for a reasonable period after cure of any such malignancy. However, at present there is no consensus on the optimum window of time between presumed cure of various extrahepatic malignancies and liver transplantation. This is an area in need of continued evaluation.

Recommendation

16. Because the natural history and chance of recurrence varies with different tumors, close consultation between a patient's oncologist and transplantation physicians should occur before evaluation for liver transplantation in patients with extrahepatic malignancies (III).

Osteoporosis

Osteoporosis is a common complication among patients with cirrhosis.[73] This is particularly true for postmenopausal women, patients with cholestatic disorders such as PBC and PSC, and patients who have received prolonged corticosteroid therapy.[74] However, osteoporosis also is common in patients with chronic hepatitis C and alcoholic cirrhosis.[75,76] Osteoporosis is of particular concern in patients being considered for liver transplantation because of the loss of bone density and the risk for pathological fractures that can occur in the perioperative period.[77]

Recommendations

17. All patients with chronic liver disease should be screened for osteoporosis during evaluation for liver transplantation (II-3).

18. In those with significant bone loss, efforts to improve bone density and to prevent pathological fractures should be pursued both before and after transplantation (III).

Patients With HIV Infection

The early experience with liver transplantation for patients with HIV infection was discouraging. Most patients died within a few years after transplantation from overwhelming infections.[78-80] However, even in these early series, there were a few long-term survivors. With the widespread use of highly active antiretroviral therapy (HAART), both the natural history of HIV infection and the outcome after transplantation have improved dramatically. In addition, cirrhosis secondary to chronic hepatitis C has emerged as a leading cause of death among individuals with well-controlled HIV infection.

As a result, an increasing number of patients with HIV infection are being referred for liver transplantation. Recent results suggest that short-term survival after trans-

plantation in patients with HIV infection that is well controlled with HAART is comparable with that seen in HIV-negative recipients.[81,82] Most patients have undetectable HIV RNA after the operation; however, a number of serious interactions have been reported between antiretroviral drugs and the immunosuppressive agents used after liver transplantation.[83,84] In addition, severe recurrent hepatitis C has been observed in a number of patients.[82,85,86] Because of these various issues, the care of transplantation recipients with HIV infection requires a well-coordinated, multidisciplinary team with expertise both in transplantation and HIV management.[87]

Recommendation

19. Liver transplantation in patients with HIV infection requires a well-coordinated, multidisciplinary team with expertise both in transplantation and HIV management (III).

Surgical Issues

The most commonly encountered surgical contraindication to liver transplantation is absence of a viable splanchnic venous inflow system, either from portal vein thrombosis or cavernous transformation of the portal vein in children. Thrombosis of the main portal vein can be successfully bypassed; however, if the entire portal venous system is occluded or atrophied, attempts at transplantation are associated with a high risk of graft loss and perioperative mortality.[88-91] Computed tomographic and magnetic resonance angiography can provide accurate preoperative assessment of both hepatic arterial anomalies and the integrity of portal inflow to the liver.[92-94] Such studies also are valuable in assessing both the donor and recipient vasculature before living-related transplantation.[95]

Recommendation

20. Patients with occlusion or hypoplasia of the splanchnic blood supply require careful anatomical evaluation before transplantation because of the increased risk of perioperative mortality and graft loss (II-3).

Psychosocial Issues

Psychosocial issues often are the greatest deterrent to successful liver transplantation. Significant psychiatric disorders must be under excellent medical control with assurance that the patient can be compliant after transplantation. In addition, patients must have adequate support from family or friends during the perioperative period. Prisoners and children with mental retardation pose significant logistical and ethical challenges. The most frequently encountered contraindication to transplantation is continued destructive behavior resulting from drug and alcohol addiction.

Medical compliance must be effectively addressed before patients are considered for transplantation. Any form of addictive behavior also should be addressed and be well controlled before patients are accepted for transplantation. This may require extensive counseling and inpatient or outpatient treatment programs. Three small studies have indicated that posttransplantation outcome and compliance among patients on methadone maintenance is comparable with that of other transplant recipients, although more pain medications and higher doses of methadone may be required during the perioperative period.[96-98]

Recommendations

21. Individuals should meet reasonable expectations of compliance before placement on a donor waiting list (II-3).

22. However, before a candidate is refused liver transplantation, every effort should be made to provide expert counseling and treatment of disorders that may adversely affect postoperative compliance (III).

23. Patients receiving methadone maintenance who are otherwise good candidates for transplantation should not be denied consideration for the operation (II-2).

Specific Indications for Liver Transplantation

Chronic Noncholestatic Liver Disorders

Cirrhosis secondary to chronic noncholestatic disorders is the most common indication for liver transplantation in adults, accounting for more than 60% of all transplants performed annually. Included among this group are patients with end-stage liver disease secondary to chronic viral hepatitis, autoimmune hepatitis, and alcoholic cirrhosis. Postoperative survival for this group of patients is slightly less than for transplantation recipients with cholestatic liver disorders (1 year, 86%; 3 years, 77%).[99]

Chronic Hepatitis C

It is estimated that 15% to 20% of patients with chronic HCV infection develop cirrhosis within 20 years of disease onset.[100] Chronic alcohol abuse appears to accelerate this process.[101] Although the 10-year survival rate of patients with well-compensated cirrhosis is more than 80%, 5-year survival is less than 50% after complications develop.[33] Patients with cirrhosis secondary to chronic hepatitis C also have a 2% to 8% annual risk of developing HCC.[102]

End-stage liver disease secondary to chronic hepatitis C virus infection accounts for an estimated 4,500 in-hospital deaths annually in the United States.[103] As a result, this condition has become the leading reason for liver transplantation among adults. Persistent viremia with HCV is virtually universal after liver transplantation, and the majority of patients develop recurrent liver injury.[104,105] Postoperative survival in early studies appeared to approximate that of patients transplanted for other conditions.[104-106] However, recent series suggest decreased survival of patients with hepatitis C compared with other liver transplantation recipients.[107-109] Although many patients do well with minimal liver damage despite persistently high levels of circulating virus, a minority of patients develop rapidly progressive fibrosis and cirrhosis within the first few years after transplantation.[110,111]

Antiviral treatment after transplantation often is poorly tolerated. Although virological responses to treatment have been well documented, the overall impact of antiviral therapy on histological progression or patient and graft survival is not clear.[112,113] In contrast, emerging data suggest that preoperative treatment with interferon and ribavirin can be quite effective in some patients with relatively well-compensated cirrhosis, particularly those with genotype 2 and 3 infection. Furthermore, successful treatment before transplantation usually prevents postoperative HCV infection.[114]

Additional details on the treatment of hepatitis C are contained in the 2003 guidelines on hepatitis C, which can be found at: https://www.aasld.org/eweb/docs/hepatitisc.pdf.

Recommendations

24. Patients with clinically decompensated cirrhosis from chronic hepatitis C infection should be referred for consideration of liver transplantation (II-3).

25. Antiviral therapy should be considered in patients who have been accepted as candidates for liver transplantation, as long as treatment is administered by experienced clinicians, with vigilant monitoring for adverse events (II-3).

26. Treatment of HCV-related disease following liver transplantation should be undertaken with caution because of the increased risk of adverse events and should be performed under the supervision of a physician experienced in transplantation (II-2).

Chronic Hepatitis B

An estimated 350 million persons worldwide and 1.25 million in the United States are infected with HBV. HBV carriers, particularly those who acquire the disease at birth or in early childhood, are at risk for the development of cirrhosis and HCC. HBV carriers with compensated cirrhosis have an 84% 5-year survival rate and a 68% 10-year survival rate; however, patients with decompensated cirrhosis have a 5-year survival rate of only 14%.[115]

Dramatic improvements have occurred in the treatment of hepatitis B over the last decade. Particularly important is the development of agents that are safe and effective both before and after liver transplantation. Lamivudine therapy is well tolerated and results in clinical improvement in many patients with decompensated cirrhosis; however, the development of resistance is common.[116-119] Adefovir also is effective, either as primary therapy or in patients who develop resistance to lamivudine.[120-123] Furthermore, the likelihood of drug resistance is much lower than with lamivudine.[120] However, nephrotoxicity can occur in patients with decompensated cirrhosis. As a result, periodic monitoring of renal function is recommended in patients who receive adefovir.[115] Although treatment with interferon alfa (IFN-α) may be effective in some patients with decompensated cirrhosis, significant side effects resulting from bacterial infection and exacerbation of liver disease can occur, even with low doses of the drug.[124,125]

The early results of liver transplantation for hepatitis B were discouraging, because many patients developed rapidly progressive recurrent disease (fibrosing cholestatic hepatitis) that resulted in death within 12 to 18 months after the operation.[126,127] However, perioperative treatment with lamivudine or adefovir combined with prolonged administration of hepatitis B immune globulin has dramatically reduced both the reinfection rate and the severity of recurrent hepatitis B after liver transplantation.[128,129] With routine use of these approaches, survival of patients transplanted for chronic hepatitis B now exceeds that of patients transplanted for many other conditions.[99,130,131] The optimal regimen for prevention of recurrent HBV infection after liver transplantation remains controversial. However, it is clear that some form of antiviral therapy is needed, probably for the lifetime of the patient.[132]

Additional details on the treatment of hepatitis B are contained in the 2001 practice guidelines on chronic hepatitis B, which can be found at: https://www.aasld.org/eweb/docs/chronichep_B.pdf, and the recently updated recommendations at: https://www.aasld.org/eweb/docs/updatechronichep_B.pdf.

Recommendations

27. Patients with decompensated cirrhosis secondary to chronic hepatitis B should be considered for treatment with antiviral therapy in coordination with the transplant center (II-3).

28. Interferon-alfa should not be used in patients with decompensated cirrhosis because of the risk of exacerbation of liver disease (II-3).

29. The posttransplantation care of patients with HBV should include antiviral therapy (II-3).

Autoimmune Hepatitis

Autoimmune hepatitis can result in progressive inflammation and fibrosis of the liver with subsequent cirrhosis and hepatic failure. Corticosteroid therapy is associated with clinical remission of disease in 80% of patients, prolongs immediate survival, and results in 10-year survival rates of 90% in adults.[133] Nevertheless, some patients who achieve biochemical and histological remission of disease develop intractable portal hypertension and slowly progressive liver failure, despite medical therapy.

Liver transplantation is the only effective treatment for patients with severe autoimmune hepatitis who fail to respond to immunosuppressive therapy or who develop advanced decompensated disease despite treatment. Outcome after liver transplantation is excellent, with reported 5- and 10-year survival rates of more than 75% in adults.[99,134,135] Recurrent disease can occur but is usually mild and easily managed.[136-138] However, the risk of both acute and chronic rejection seems to be greater in patients with autoimmune hepatitis.[134,135,137] Occasionally, recurrent autoimmune hepatitis results in graft loss; however, these few cases have not had an appreciable impact on overall patient survival after transplantation.[136,139-141]

Autoimmune hepatitis in children is a mixture of type I (anti–smooth muscle antibody positive, most common in older children) and type II (anti–liver kidney microsomal antibody positive, more common in younger children). Children with type II disease tend to have a more aggressive course that is less responsive to therapy, with a higher percentage requiring liver transplantation.[142,143] Furthermore, posttransplantation survival is lower in children with type II disease, most likely reflecting their pretransplant morbidity entering the transplant.[142] As with autoimmune hepatitis in adults, recurrence after transplantation occurs frequently in children. However, more severe disease recurrence has been observed, and as a result, the outcome in children seems to be less favorable than that in adults.[144]

Additional details on the treatment of autoimmune hepatitis are contained in the 2002 practice guideline on the diagnosis and treatment of autoimmune hepatitis, which can be found at: https://www.aasld.org/eweb/docs/autoimmune_hepatitis.pdf.

Recommendations

30. Liver transplantation should be considered in decompensated patients with autoimmune hepatitis who are unable to undergo or be salvaged by medical therapy (II-3).

31. Due to the risk of recurrent disease and enhanced risk of rejection, patients with autoimmune hepatitis may require more immunosuppression than patients transplanted for other indications (II-3).

Alcoholic Cirrhosis

Alcoholic liver disease is the most common cause of cirrhosis and accounts for 40% of deaths from cirrhosis in the United States.[145] Abstinence is the only effective treatment for most patients, but even among patients with decompensated cirrhosis, it can be associated with a dramatic improvement in survival.[146,147] As a result, many patients with apparently far-advanced alcoholic liver disease who completely abstain can recover to the degree that transplantation is not required.[148] Unfortunately, there is no effective means of predicting which patients will have such a dramatic response. Nevertheless, because the results can be so dramatic, a period of abstinence before providing transplantation for patients with alcoholic liver disease seems to be appropriate. More than 85% of transplantation programs in the United States require 6 months of abstinence and careful evaluation by professional counselors to directly address the addiction to alcohol before transplantation.[149] Patients who have CTP scores of 11 or more (Child C disease), despite at least 6 months of abstinence, have improved survival with transplantation compared with the natural history of disease predicted from prognostic models.[150] However, there may be a benefit of delaying transplantation further in patients with milder disease. A recent clinical trial carefully evaluated 120 patients with Child's B cirrhosis who were randomized to receive immediate transplantation (60 patients) or to be observed expectantly (60 patients). Only 41 patients randomized to surgery received a transplantation because 6 improved, 6 died before surgery could be performed, and 7 developed a contraindication to the operation. An additional 15 patients in the control arm ultimately underwent transplantation for decompensated disease. Two-year survival was higher in the observational group (80% vs. 73%), primarily because of a high risk of postoperative malignancy in those who were randomized to receive immediate transplantation.[151]

The outcome after liver transplantation for alcoholic liver disease is comparable to that of patients transplanted for most other conditions, with 7-year survival rates of 60%.[99,152-154] Rejection, graft failure, and the need for retransplantation all are less common in patients with

alcoholic liver disease compared with patients transplanted for other conditions.[155,156] Although alcohol relapse rates vary considerably from center to center, graft loss as a consequence of destructive drinking after transplantation is uncommon.[157-159]

Patients with alcoholic cirrhosis are more likely to develop profound confusion in the early postoperative period than other transplant recipients.[160] This can result in prolonged hospitalization and can increase the costs of transplantation.[160-162] In addition, patients with alcoholic liver disease have an increased risk of pharyngeal, esophageal, and gastric malignancies after transplantation.[158,159,163,164]

Recommendations

32. To be considered for transplantation, potential candidates with alcoholic liver disease should have careful assessment by a health care professional experienced in the management of patients with addictive behavior (III).

33. It is prudent to delay transplantation for a minimum of 3 to 6 months of abstinence from alcohol to avoid exposing patients who may not need transplantation to the risk of unnecessary surgery (II-2).

Cholestatic Liver Disorders

Liver transplantation is the only effective treatment for adults with end-stage liver disease secondary to PBC and PSC. Biliary atresia is the most common indication for liver transplantation in children, accounting for 60% to 70% of all procedures performed. Other cholestatic diseases in children for which transplantation is indicated include PSC, Alagille syndrome, nonsyndromic intrahepatic paucity, cystic fibrosis, and progressive familial intrahepatic cholestasis. Survival after transplantation for either adults or children with cholestatic disorders is excellent, with 1-year postoperative survival of more than 90% and 3-year survival approximating 85%.[99]

Primary Biliary Cirrhosis

PBC is a chronic destructive disorder of interlobular bile ducts that can progress to cirrhosis and liver failure. The disease most commonly affects women in the fourth to seventh decades of life. After liver transplantation, 70% of patients with PBC survive at least 10 years after the operation.[99,165,166] Numerous studies using disease-specific prognostic models have documented improved survival after transplantation compared with estimated survival without surgery.[165-167] The survival benefit of transplantation is evident as soon as 3 months after surgery, and 2-year survival of transplanted patients is more than twice that predicted for those treated conservatively.[165] Occasional patients with PBC and good liver function have such severe pruritus and associated sleep deprivation and emotional disturbance that liver transplantation may be required.[168] However, every possible medical treatment should be explored before transplantation is undertaken in these patients.[169] Although recurrent PBC after transplantation has been well documented, it has not had a major impact on long-term postoperative survival.[166]

Additional details on the management of PBC are contained in the 2000 practice guidelines on the management of PBC, which can be found at: https://www.aasld.org/eweb/docs/biliarycirrhosis.pdf.

Recommendations

34. Liver transplantation is the only effective treatment for liver failure secondary to primary biliary cirrhosis (II-2).

35. Liver transplantation also may occasionally be indicated in appropriately selected patients for uncontrolled pruritus (III).

Primary Sclerosing Cholangitis

PSC is a chronic cholestatic disorder of unknown cause characterized by progressive inflammation and stricture formation affecting both intrahepatic and extrahepatic bile ducts. The disease typically occurs in young men, 70% to 75% of whom have inflammatory bowel disease.[170] Although the natural history of patients with PSC is quite variable, most patients with symptomatic disease develop liver failure within 10 to 12 years.[171] No specific medical treatment has been shown to improve survival in patients with PSC.[171,172]

Most studies have reported transplantation outcomes for PSC patients that equal or surpass those reported for PBC, with 3-year survival rates of more than 90%.[99,173-177] However, one recent report demonstrated higher retransplantation rates and lower long-term survival among patients with PSC.[178] Nevertheless, survival of patients with PSC after liver transplantation has been shown to be far superior to that predicted for patients treated conservatively.[18,179,180] Although recurrent disease is common after transplantation, this has not had a significant impact on long-term postoperative survival.[176,181] However, the discovery of cholangiocarcinoma before or during surgery dramatically reduces survival.[176] Furthermore, development of colorectal cancer can adversely influence postoperative survival if regular screening is not performed in patients with ulcerative colitis.[174,182,183]

Recommendations

36. Liver transplantation is the only effective treatment for decompensated cirrhosis secondary to primary sclerosing cholangitis (II-2).

37. Patients with PSC and cholangiocarcinoma should be excluded from transplantation unless they are enrolled in a clinical trial of experimental therapy (II-3).

38. Because of the high incidence of colon cancer, regularly scheduled colonoscopies should be performed both before and after transplantation in all patients who have inflammatory bowel disease (II-3).

Childhood Cholestatic Diseases

Chronic cholestasis in children can result from a variety of conditions, including biliary atresia, α-1-antitrypsin deficiency, cystic fibrosis, various types of intrahepatic cholestasis, and PSC. Extrahepatic biliary atresia is the most common cause of chronic childhood cholestasis and is the leading pediatric indication for liver transplantation.

Biliary atresia is a destructive inflammatory process of unknown etiology that results in fibrosis and obliteration of the extrahepatic bile ducts and variable involvement of the intrahepatic ducts. If untreated, death usually results within the first 1 to 2 years of life.[184] There is no effective medical therapy for children with biliary atresia. However, if the diagnosis can be established within the first few months of life, a Kasai portoenterostomy can result in prolonged survival in as many as 70% of infants.[185,186] As a consequence, portoenterostomy, performed within the first 2 months of life by an experienced surgeon, is considered the treatment of choice for most children with biliary atresia. However, if the diagnosis is delayed beyond 3 months, successful results from the Kasai procedure are significantly reduced. Children who are not offered surgery because of a delay in diagnosis, as well as those with unsuccessful Kasai procedures, invariably die before their second birthday. Small children who need transplantation can be successfully transplanted using a reduced-size deceased donor organ or a portion of the liver from a living related donor.[7,187] In addition, children with successful Kasai procedures can develop cirrhosis and progressive portal hypertension over a period of years. These children may also require liver transplantation for long-term survival.[184,188]

There are no controlled studies directly comparing liver transplantation with portoenterostomy. However, the advantages of delaying transplantation from the first few months of life until 5 to 10 years of age are considerable, the most important of which are increased opportunities for an acceptable donor organ, diminished risk of primary nonfunction of the transplanted donor organ, and decreased rates of rejection.[189] Furthermore, if transplantation can be delayed until the child is at least 6 years of age, both graft and patient survival are greatly increased.[190] These benefits must be weighed against the potential for increased blood loss, longer operative time, and increased perioperative complications of transplantation in children with a previous portoenterostomy.[191] However, recent surgical series do not suggest increased perioperative mortality in such children.[191] Overall, children with biliary atresia have the best posttransplant outcome of any group of patients, with 1-year survival of 93% and 5-year survival of more than 85%.

Other less common causes of chronic cholestasis in children include syndromic (Alagille syndrome) and nonsyndromic forms of intrahepatic paucity of bile ducts, cystic fibrosis, PSC in adolescents, and the progressive familial intrahepatic cholestasis disorders. Approximately 20% of children with Alagille syndrome develop cirrhosis, and a greater number develop intractable drug-resistant pruritus. Although the number of transplants performed for this condition is limited, the results seem to approximate those seen for other chronic cholestatic conditions. Furthermore, in many children growth is accelerated and quality of life is substantially improved after successful transplantation.[192,193] Mortality of children with Alagille syndrome is caused not only by liver disease (25%) but also by intracranial bleeding (25%) and complex congenital heart disease (15%). Consequently, the risk of these extrahepatic features of the syndrome must be considered in the evaluation for transplantation.[194]

Cystic fibrosis, which can cause cholestatic liver disease resulting in extensive fibrosis, biliary cirrhosis, or sclerosing cholangitis, accounts for 3% to 5% of pediatric liver transplants. However, many of these children also have advanced restrictive lung disease, and most deaths after liver transplantation are the result of pulmonary or septic events within the first few years after the operation.[195]

The progressive familial intrahepatic cholestasis (PFIC) disorders are a collection of autosomal recessive defects of hepatocellular transport involved in bile salt formation. Infants with these disorders develop progressive cholestasis and fibrosis within the first year of life, which often progresses to cirrhosis with liver failure later in childhood.[196,197] If the diagnosis is established before the development of cirrhosis, partial external biliary diversion can result in clinical, biochemical, and histological improvement in the majority of patients.[198,199] On the other hand, if cirrhosis has already been established or if partial external biliary diversion is not successful, liver transplantation is usually required for long-term survival.[199] However, the extrahepatic manifestations of these

conditions, such as short stature and diarrhea, are not always improved by transplantation.[200]

Recommendations

39. Liver transplantation is indicated in appropriately selected children with biliary atresia if portoenterostomy is unsuccessful, or if intractable portal hypertension or liver failure develops despite successful portoenterostomy (III).

40. Liver transplantation should be considered for its ability to significantly prolong survival and improve quality of life by reducing pruritus in syndromic and nonsyndromic forms of intrahepatic cholestasis in children (III).

41. Children with Alagille syndrome should have preoperative assessment for congenital heart disease, which is common in this condition (III).

42. In evaluating patients with cystic fibrosis for liver transplantation, careful assessment of lung disease should be performed (III).

Metabolic Diseases

A variety of metabolic diseases can result in progressive liver injury and cirrhosis. The most common metabolic diseases in adults are α-1-antitrypsin deficiency, Wilson disease, hereditary hemochromatosis, and nonalcoholic steatohepatitis (NASH). Common metabolic disorders that can cause liver failure in children include α-1-antitrypsin deficiency, Wilson disease, tyrosinemia, glycogen storage diseases, and neonatal hemochromatosis. Although these conditions account for less than 5% of the liver transplants performed in the United States, the outcome after transplantation in adults is excellent (1-year survival, 88%; 3-year survival, 84%) and is even better in children (1-year survival, 94%; 5-year survival, 92%).[99,201]

α-1-Antitrypsin Disease

α-1-Antitrypsin disease is the most common inherited cause of liver disease for which liver transplantation is performed in children.[202] Although the prevalence of this genetic disorder is high, only 10% to 15% of individuals with the PiZZ phenotype develop liver disease.[203-205] Children with α-1-antitrypsin deficiency often present with neonatal cholestasis.[206] In most of these children, the jaundice gradually resolves, but 25% develop cirrhosis within the first decade of life. However, many children with cirrhosis remain stable for extended periods and do not require transplantation.[207] Cirrhosis secondary to α-1-antitrypsin disease also can have its first presentation in adults of any age.[205] Men with α-1-antitrypsin disease have an increased risk for HCC.[208] In the evaluation of patients with liver disease, care must be taken not to base the diagnosis of α-1-antitrypsin disease on the serum α-1-antitrypsin level. With significant liver insufficiency from any cause, the serum level of this protein can be low because of poor synthetic function and, because it is an acute-phase reactant, the level can be artificially elevated in the setting of inflammation. Paradoxically, lung disease is uncommon in either children or adults with liver disease secondary to α-1-antitrypsin deficiency.

Liver transplantation is the only effective treatment for decompensated cirrhosis secondary to α-1-antitrypsin disease. After transplantation, the donor α-1-antitypsin phenotype is expressed and serum levels of α-1-antitrypsin return to the normal range within weeks after the operation. Although reported series are small, the long-term outcome of these patients after liver transplantation is excellent.[209-212]

Recommendations

43. Liver transplantation is the only effective treatment for decompensated cirrhosis secondary to α-1-antitrypsin deficiency (II-3).

44. Careful assessment for lung disease should be performed before transplantation in patients with cirrhosis secondary to α-1-antitrypsin deficiency, although coexistent disease in uncommon (III).

Wilson Disease

Wilson disease is an autosomal recessive disorder of copper excretion that can result in either acute or chronic hepatitis with liver failure.[213,214] Other complications of the disease include neurological dysfunction, hemolytic anemia, and renal involvement. Although most patients with chronic liver failure resulting from Wilson disease have low serum ceruloplasmin values, this level can be elevated with inflammation or acute liver disease or can be depressed by the presence of severe liver disease of any etiology. Most patients with chronic liver disease respond dramatically to treatment with penicillamine, trientine, or oral zinc and have long-term sustained remission of the disease with continued treatment.[215] Liver transplantation for chronic Wilson disease is necessary only for patients with decompensated cirrhosis who fail to respond to medical therapy. However, patients who present with fulminant hepatic failure usually die unless urgent liver transplantation can be performed.[216,217] Liver transplantation usually reverses all of the metabolic abnormalities associated with Wilson disease. However, long-standing neurological dysfunction may not improve in some patients.[218-220] Survival rates have ranged from 80% to 90% 1 year after transplantation. Although the reported series are small, long-term survival appears to be excellent.[217,220]

Copper chelation and zinc therapy are not necessary after transplantation.

Additional details on the management of Wilson disease are contained within the practice guideline on Wilson disease, which can be found at: https://www.aasld.org/eweb/docs/wilson_withcorrection.pdf.

Recommendations

45. Urgent liver transplantation is the only effective option for patients with fulminant hepatic failure resulting from Wilson disease (II-3).

46. Liver transplantation also is indicated for patients with decompensated chronic disease who fail to respond to medical therapy (II-2).

47. Liver transplantation is not recommended as primary treatment for neurological Wilson disease because the liver disease is stabilized by medical therapy in most of these individuals, and outcomes with liver transplantation are not always beneficial (III).

Nonalcoholic Steatohepatitis and Cryptogenic Cirrhosis

NASH is a syndrome in which patients with no history of alcohol abuse have histological features similar to those of alcoholic hepatitis.[221,222] Most patients with NASH are between 40 and 60 years of age, although the condition has been seen in children.[223] The etiology of NASH is unknown; however, it is often associated with insulin resistance and obesity, type II diabetes, and hyperlipidemia.[224-226] There also is an association with prior surgical techniques for morbid obesity, particularly jejunoileal bypass surgery, but not with more recent bariatric procedures. The prognosis of the condition has not been well defined; however, a number of patients with NASH have progressed to cirrhosis and required liver transplantation.[227] No medical therapy has yet been proven to be beneficial in patients with NASH.[228] NASH may be the underlying cause of many cases of cryptogenic cirrhosis, particularly among older diabetic women.[229] There also is evidence for an increased risk of HCC in patients with NASH.[230,231] A number of cases of severe recurrent disease with progression to cirrhosis have been reported after liver transplantation for NASH.[227,232,233] These findings, and the observation that recurrent disease has been stabilized by gastric bypass surgery, suggest that the underlying metabolic defect may not be cured by transplantation.[234]

End-stage liver disease from cryptogenic cirrhosis accounts for 7% to 14% of adults who undergo liver transplantation in the United States and Europe.[235] Five-year survival rates in adults with cryptogenic cirrhosis who have undergone liver transplantation range from 72% to 81%.[235,236] Careful clinical-pathological correlation of liver biopsies obtained before and after transplantation often reveals the underlying etiology, which is most commonly NASH, autoimmune hepatitis, or alcoholic cirrhosis.[237] After transplantation, a number of patients with presumed cryptogenic cirrhosis have developed aggressive NASH or autoimmune disease.[232,233] Cryptogenic cirrhosis in children often is an aggressive disease that progresses to liver failure, necessitating liver transplantation. Disease recurrence is not uncommon after transplantation.[143]

Additional information on NASH is contained in the 2002 AGA medical position statement on nonalcoholic fatty liver Disease, which can be found at: http://www2.gastrojournal.org/scripts/om.dll/serve?action=searchDB&searchDBfor=art&artType=fullfree&id=agast1231702.

Recommendations

48. Liver transplantation should be considered for selected patients with decompensated cirrhosis secondary to nonalcoholic steatohepatitis (NASH). The post-transplantation care of these patients should include metabolic monitoring (III).

49. Liver transplantation should be considered for selected patients with decompensated cryptogenic cirrhosis. These patients should be screened for metabolic dysregulation because of the possibility of underlying nonalcoholic steatohepatitis (III).

Hereditary Hemochromatosis

Despite the frequency of the genetic abnormality, liver failure requiring transplantation for hereditary hemochromatosis is quite uncommon.[238,239] However, in some affected individuals, chronic iron accumulation can result in decompensated cirrhosis, cardiomyopathy, diabetes mellitus, arthritis, hypogonadism, and HCC. If iron depletion can be accomplished before the development of cirrhosis or diabetes mellitus, long-term phlebotomy results in a normal life expectancy.[240] However, if cirrhosis is present at the time of diagnosis, survival is diminished and patients remain at high risk for HCC despite adequate iron depletion.[241] The prevalence of HCC seems to be particularly high in patients with decompensated cirrhosis.[242]

Patients with end-stage liver disease secondary to chronic hepatitis C, alcohol abuse, or both can have elevated ferritin and transferrin saturation levels similar to those seen in patients with hereditary hemochromatosis.[243-246] However, only a few of these patients have hepatic iron levels consistent with hemochromatosis and even fewer have both increased hepatic iron stores and genetic abnormalities consistent with hereditary hemochromatosis.[245,247]

Liver transplantation is the only effective treatment for patients with decompensated cirrhosis secondary to hereditary hemochromatosis. However, there is considerable controversy about the efficacy of the procedure. There are numerous reports of lower postoperative survival in patients with hemochromatosis compared with patients transplanted for other conditions.[242,247-250] Furthermore, most, but not all, studies suggest that significant hepatic iron overload from any cause is associated with decreased survival after transplantation.[247,249,251,252] Although not well characterized, these suboptimal results seem to result from a high rate of postoperative infections as well as occasional deaths from cardiac failure and recurrent HCC.[242,247,249,253-255] It is uncertain whether this risk can be reduced by aggressive phlebotomy before transplantation.

Additional information on the diagnosis and management of patients with hemochromatosis are contained in the practice guidelines on the diagnosis and management of hemochromatosis, which can be found at: https://www.aasld.org/eweb/docs/hemochratosis.pdf.

Recommendations

50. All patients with newly diagnosed cirrhosis should be screened for hemochromatosis using serologic tests, with genetic testing in equivocal cases (III).

51. Survival of transplanted patients with hereditary hemochromatosis is lower than in those transplanted for other causes of liver disease. Due to the increased risk of cardiac complications, a pretransplantation cardiac evaluation is essential (II-3).

52. Efforts should be made to phlebotomize these patients before transplantation (III).

Neonatal Hemochromatosis

Neonatal hemochromatosis is the leading cause of liver failure in neonates. Infants typically present with hepatic failure within the first few days of life and usually die within months unless liver transplantation can be performed. Marked elevation of iron levels in nonreticuloendothelial organs can be documented by magnetic resonance imaging or by detecting the presence of siderosis in salivary glands.[256] Although postoperative survival has been poor, liver transplantation seems to be the only effective treatment for this devastating condition.

Recommendation

53. Liver transplantation is the only effective treatment for infants with severe neonatal hemochromatosis. Urgent evaluation at a transplant center is recommended (II-3).

Tyrosinemia and Glycogen Storage Disease

Hereditary tyrosinemia type 1 is an inborn error of tyrosine metabolism. The most common presentation is a systemic illness associated with liver dysfunction in children a few months old. Cirrhosis and HCC are common at the time of diagnosis. The underlying metabolic condition can be partially treated with dietary restriction of tyrosine and phenylalanine, but the metabolism of protein results in continued formation of the toxic metabolites succinylacetone and succinyl acetoacetate. Formation of these metabolites can be reduced by providing nitro-trifluoromethyl benzoyl cyclohexanedione (NTBC).[257] Although NTBC has significantly improved longevity, with children achieving normal growth for up to 12 years in some cases, the long-term benefit of this approach has yet to be determined. Transplantation is still required in many children who have an incomplete response to dietary restrictions and in those who have HCC at presentation or develop HCC during treatment.[258]

Glycogen storage diseases are uncommon disorders of glycogen metabolism that result in the accumulation of abnormal glycogen in the liver. Children with these disorders can develop cirrhosis, ascites, portal hypertension, HCC, liver failure, and renal insufficiency. Although early diagnosis and initiation of effective dietary therapy has improved the outcome of children with some glycogen storage diseases, transplantation often is required for poor metabolic control, multiple hepatic adenomas, HCC, or progressive liver failure.[259]

Children with these conditions can have a variety of renal, cardiac, or neurological abnormalities that may compromise the likelihood of survival with good quality of life after liver transplantation, and must therefore be considered during the evaluation for the operation.[259]

Recommendations

54. Children with tyrosinemia who develop hepatocellular carcinoma (HCC) and meet the criteria for liver transplantation for HCC, should be high-priority candidates (II-3).

55. Children with tyrosinemia and glycogen storage diseases unresponsive to medical management should be considered for transplantation (II-3).

56. Consideration of extrahepatic complications of the underlying disease must be carefully considered in potential transplant candidates (III).

Metabolic Diseases with Severe Extrahepatic Manifestations

Selected patients with metabolic diseases may require liver transplantation, not for liver failure but to prevent severe extrahepatic manifestations of the disease. Hyper-

oxaluria and amyloidosis are the most common conditions in adults, whereas the most frequent conditions in children are the urea cycle defects and defects in branched-chain amino acid metabolism.

Amyloidosis and Hyperoxaluria

Patients with hereditary amyloidosis, in which the mutant amyloid precursor protein is produced by the liver, may benefit from liver transplantation.[260] The variants for which liver transplantation has been most successful include mutations of the transthyretin, apolipoprotein A-1, and fibrinogen Aa amyloid precursors. The ideal timing of transplantation seems to be within the first year of symptoms and before the development of severe cardiac, renal, gastrointestinal, or neurological involvement.[261]

Patients with type 1 primary hyperoxaluria also may benefit from liver or combined liver and renal transplantation. In this autosomal recessive disorder, there is inadequate conversion of glyoxylate to glycine because of deficiency of hepatic alanine glyoxylate aminotransferase. As a consequence, there is marked enhancement of the conversion of glyoxylate to oxalate. Clinical manifestations of hyperoxaluria can first become apparent at any age.[262,263] Infants typically present with chronic renal failure and massive parenchymal oxalosis, but do not develop renal calculi.[264] In contrast, older children and adults typically present with symptoms of urolithiasis, with subsequent progression to renal failure.

Primary hyperoxaluria accounts for approximately 1% of all cases of end-stage renal disease in children.[262] If detected before the onset of significant renal disease, medical management can be quite effective.[265] Renal transplantation has historically been the treatment of choice for patients with end-stage renal disease. However, the results have been disappointing: 3-year graft survival has averaged only 20% because of recurrent renal oxalosis. Improved patient survival has been documented in patients who have undergone combined liver–kidney transplantation compared with those who underwent kidney transplantation alone. If these results are confirmed, combined liver–kidney transplantation may prove to be the treatment of choice for patients with primary oxaluria and renal failure.[266]

Recommendations

57. Patients with amyloidosis should be considered for liver transplantation to correct the underlying metabolic defect before end organ damage has occurred (II-3).

58. Liver transplantation, with or without combined kidney transplantation, is curative for hyperoxaluria and should be considered for patients with this disease (II-3).

Urea Cycle and Branched-Chain Amino Acid Disorders

Other metabolic conditions that result in significant extrahepatic morbidity include urea cycle defects (ornithine transcarbamylase deficiency, citrullinemia, carbamyl phosphate synthetase deficiency, argininosuccinic aciduria, and arginase deficiency) and disorders of branched-chain amino acids (maple syrup urine disease, methylmalonic acidemia, propionic acidemia, and isovaleric acidemia). In most of these conditions, proteinaceous meals or catabolism caused by normal childhood illnesses result in profound hyperammonemia or metabolic acidosis, which can cause progressive and additive central nervous system insult with intellectual decline. In patients recognized to have aggressive disease that is not satisfactorily treated with standard dietary and pharmacological interventions, liver transplantation has been effective.[267,268] However, a high rate of neurological complications after transplantation has been observed in children with some of these conditions, particularly the branched-chain amino acid disorders.[269,270]

In considering these patients for liver transplantation, one must evaluate the reversibility of the enzyme deficiency with whole or partial organ liver transplantation. This must be scrutinized even more carefully if parent-to-child living-donor transplantation is being considered, because these are usually autosomal recessive disorders in which parents frequently have reduction of enzyme activity, although to a lesser degree than their affected offspring. Additionally, because the major reason for liver transplantation is to prevent the progression of neurological injury, the potential for functional health after transplantation must be estimated, based on the child's health at the time of evaluation and the rapidity of decline.

Children and adults with inborn errors in metabolism for which liver transplantation is performed to correct the enzyme deficiency and halt progression of extra-hepatic organ damage have normally functioning livers in other respects. Based on the PELD and MELD scoring systems, these patients would never have a score that would avail them of a deceased donor organ. It is clearly recognized, however, that their need is urgent. Consequently, these patients can be given priority for deceased donor organs.

Recommendations

59. Liver transplantation is indicated in children with metabolic diseases that cause progressive extra-hepatic injury resulting in significant morbidity and mortality that are not responsive to disease-specific

medications or dietary modification and for which liver transplantation would result in the reversal of the enzyme deficiency and metabolic derangement (II-3).

60. Living related transplantation should be considered only if the enzyme activity of the donor would satisfactorily reverse the deficiency of the recipient (III).

61. The degree of neurological injury before transplantation should be considered when selecting patients for liver transplantation (III).

Hepatic Malignancies

Timely liver transplantation often is the most effective treatment for many patients with primary hepatic malignancies. The exception is cholangiocarcinoma, which usually recurs rapidly after transplantation.

Hepatocellular Carcinoma (HCC)

HCC causes approximately 1 million deaths worldwide each year. Patients with chronic hepatitis B, chronic hepatitis C, and hemochromatosis are at particularly high risk for HCC. In addition, almost all untreated children with tyrosinemia surviving to early childhood develop HCC. The prognosis of patients with HCC is dependent both on the stage of the tumor and the degree of liver function impairment.[271] Although primary hepatic resection has long been considered the treatment of choice for HCC, 5-year tumor-free survival rates are less than 50%.[272] Furthermore, most patients referred for resection are rejected because the tumor is unresectable or because hepatic reserve is considered inadequate.[273] Even in patients with well-compensated cirrhosis, perioperative mortality after surgical resection is extremely high if patients have evidence of portal hypertension or elevated serum bilirubin values.[274] Radiofrequency ablation and percutaneous alcohol injection are effective in tumors smaller than 3 cm but are far less successful for larger tumors.[275,276] In selected patients with otherwise untreatable tumors but relatively well-preserved liver function, chemoembolization has been shown to improve survival; however, these patients have much lower survival rates than those who are candidates for surgical or ablative therapy.[277-279]

The early experience in liver transplantations for patients with unresectable HCC was not encouraging. Although perioperative and short-term survival and quality of life were much better than for patients who received transplantation for decompensated cirrhosis, 90% of those transplanted for HCC developed recurrent disease within 2 years.[280,281] In contrast, patients with small tumors, especially those found incidentally at the time of transplantation, did well.[280] On the basis of these early results, HCC was considered a contraindication to transplantation for a number of years.

With continued analysis of outcomes, a consensus has gradually emerged that optimal results after transplantation can be achieved in patients with a single lesion 2 cm or larger and less than 5 cm, or no more than three lesions, the largest of which is less than 3 cm in size, and no radiographic evidence of extrahepatic disease.[282] The allocation policy for donor livers in the United States was recently modified to give such patients enhanced priority for deceased donor organs. Since implementation of this modification, the time on the donor waiting list for patients with HCC has decreased from a mean of 2.3 years to 0.7 months.[283]

The recent evolution in management of patients with HCC has been associated with a dramatic improvement in posttransplantation survival. For example, among patients in the United States who received transplantation for HCC during the periods 1987-1991, 1992-1996, and 1997-2001 (all before the enhanced prioritization of deceased donor organs for patients with HCC), 5-year survival increased from 25% to 46% to 61% ($P < .001$).[284]

Recommendations

62. Liver transplantation should be viewed as the treatment of choice for selected patients with hepatocellular carcinoma who are not candidates for surgical resection and in whom malignancy is confined to the liver (II-2).

63. Optimal results following transplantation are achieved in patients with a single lesion 2 cm or larger and less than 5 cm, or no more than three lesions, the largest of which is less than 3 cm, and no radiographic evidence of extrahepatic disease (II-2).

64. For ideal outcomes, patients who meet these criteria should receive a donor organ within 6 months of listing for transplantation (II-2).

Hepatoblastoma

Hepatoblastoma is the most common primary hepatic malignancy in children. This tumor usually is locally invasive with a better long-term prognosis than for HCC. As a result, successful results from transplantation can be achieved in children with much larger tumors. Results after transplantation are excellent if the tumor is confined to the liver. Even children with nonresectable hepatoblastoma have an excellent prognosis for long-term tumor-free survival if liver transplantation follows chemotherapy.[285] However, these children usually do not have underlying liver disease, and consequently the PELD scoring system does not adequately capture their need for transplantation. Accordingly, the transplantation center

may submit a request for enhanced prioritization for deceased donor organs, which is then reviewed through a regional peer review system.

Recommendation

65. Liver transplantation should be considered for children in whom hepatoblastoma is confined to the liver and is not resectable (II-3).

Fibrolamellar Hepatocellular Carcinoma and Hemangioendothelioma

Patients with the fibrolamellar variant of HCC and epithelioid hemangioendothelioma have far better prognoses than patients with HCC.[286,287] In contrast to HCC, most patients with these tumors do not have evidence of significant underlying liver disease. As a result, transplantation is uncommonly required. However, in contrast to HCC, large tumors are not contraindications to liver transplantation.[288] Although experience is limited, the prognosis for children with this tumor who have undergone transplantation remains guarded.[289]

Recommendations

66. When the tumor is not resectable, liver transplantation should be considered for patients with fibrolamellar HCC, if there is no evidence of extrahepatic disease (III).

67. When the tumor is not resectable, liver transplantation should be considered for patients with epithelioid hemangioendothelioma (III).

Cholangiocarcinoma

The outcome of liver transplantation for cholangiocarcinoma has been particularly frustrating. Even small tumors with no evidence of local invasion almost invariably recur within a few years after transplantation.[290] Highly selected patients may benefit from aggressive preoperative radiotherapy and chemotherapy followed by transplantation.[291] However, based on current outcomes, transplantation of patients for cholangiocarcinoma should be confined to careful experimental trials with approval by a local institutional review board and informed consent of potential recipients.

Recommendation

68. Transplantation in patients with cholangiocarcinoma should be confined to a few centers with well-designed clinical trials (III).

Fulminant Hepatic Failure

Fulminant hepatic failure (FHF) is defined as the development of hepatic encephalopathy and profound coagulopathy within 8 weeks of the onset of symptoms in patients without preexisting liver disease.[292] The various causes of this devastating condition include acetaminophen overdose, drug-induced liver injury from other medications, hepatitis A and B, ingestion of various hepatotoxins, fatty liver of pregnancy, and Wilson disease.[293] In many cases, the precise etiology is never discovered.[293]

There is no specific therapy for FHF.[294] However, if given appropriate critical care support, many patients spontaneously recover. In these instances, recovery typically is complete, with no evidence of residual liver injury. The prognosis for spontaneous recovery depends on the patient's age, the underlying etiology of disease, and the degree of encephalopathy.[293,295,296] Other important prognostic factors include acidosis, prolongation of prothrombin time values, and elevated APACHE II scores.[297]

Survival after liver transplantation for FHF has improved dramatically over the past few years.[298-300] However, patients with FHF can develop cerebral edema, multiorgan failure, or cardiovascular collapse within days to weeks after clinical presentation.[301,302] As a result, any delay in obtaining a donor organ can have fatal consequences. To address this urgency, a special category (status 1) was created to allow these patients to receive first preference for any deceased donor organ.

Recommendations

69. Patients with fulminant hepatic failure should be referred to a transplant center as quickly as possible for expectant critical care management (III).

70. Patients predicted to have little chance of spontaneous recovery should undergo transplantation as soon as possible (II-3).

Miscellaneous Conditions

Other less frequent indications for liver transplantation include liver failure secondary to hepatic vein occlusion (Budd-Chiari syndrome), selected metastatic neuroendocrine tumors, and polycystic disease.

Budd-Chiari Syndrome. Budd-Chiari syndrome results from occlusion of some or all of the hepatic veins. Patients with this condition can develop rapidly progressive liver failure or a more chronic form, with intractable ascites as the major symptom. Most cases of Budd-Chiari syndrome result from an underlying hypercoagulable state. The most common cause is a myeloproliferative disorder, such as polycythemia vera or essential thrombocytosis.[303] A number of inherited hypercoagulable states also have been associated with hepatic vein occlusion. Among these, the factor V Leiden mutation seems to be particularly important, accounting for 25% of cases in

recent series.[304] However, even in most cases of inherited hypercoagulable states, Budd-Chiari syndrome typically occurs in combination with a myeloproliferative disorder.[304,305] Another 10% of cases are caused by malignancies that cause compression or direct invasion of the hepatic veins or vena cava.

A number of approaches have been used for treatment of patients with Budd-Chiari syndrome. The three options that seem to be most effective in patients with severe disease include the use of transjugular intrahepatic portosystemic shunts, surgical shunts to decompress the swollen liver, and liver transplantation. Long-term survival has been documented with each approach; however, there also has been considerable morbidity associated with each procedure.[306-311] Survival after transplantation depends on the severity of disease at the time of transplantation, the extent of the thromboses, and the underlying cause of the condition. The best results have been achieved in patients who have thrombosis limited to the hepatic veins, in whom the underlying cause of the syndrome can be corrected by replacement of the liver.[312] In contrast, patients with an underlying malignancy and those with both hepatic and portal vein thrombosis have more perioperative complications and a lower long-term benefit.[313,314] As a result, choosing the optimal treatment for patients with this condition can be quite difficult.[315,316]

Recommendation

71. Because there are a variety of effective options available, the selection of patients for liver transplantation for Budd-Chiari syndrome must be individualized, considering alternative therapeutic options (III).

Metastatic Neuroendocrine Tumors. Metastases from neuroendocrine tumors often are slow growing and can be confined to the liver for long periods. A variety of options are available for managing these patients, including systemic somatostatin or radioactive metaiodobenzylguanidine therapy, surgical excision, radiofrequency ablation, chemoembolization, and liver transplantation.[317,318] The primary indications for liver transplantation include: (1) tumors not accessible to curative surgery or major tumor reduction; (2) tumors not responding to medical or interventional treatment; and (3) tumors causing life-threatening hormonal symptoms.[319] The outcome after transplantation for these tumors has been mixed. Most patients have died of recurrent disease within the first few years after the operation. However, there have been occasional long-term disease-free survivors.[319,320]

Recommendation

72. Liver transplantation for metastatic neuroendocrine tumors should be confined to highly selected patients who are not candidates for surgical resection in whom symptoms have persisted despite optimal medical therapy (III).

Polycystic Liver Disease. Liver failure is uncommon in patients with polycystic disease. However, occasional patients are so debilitated by abdominal pain, anorexia, or fatigue that consideration for liver transplantation is requested. The published experience with liver transplantation is quite limited. Dramatic improvement in symptoms and quality of life are typical after transplantation.[321-323] However, these patients seem to be unusually susceptible to infection after the procedure.[321]

Recommendation

73. Liver transplantation is occasionally indicated for patients with polycystic disease (III).

Retransplantation

Retransplant operations account for approximately 10% of all liver transplants. The most frequent indications for retransplantation are primary graft nonfunction, hepatic artery thrombosis, allograft rejection, and recurrent disease. The outcome of for retransplantation is significantly lower than for primary transplantation with 1-, 3-, and 5-year survival rates approximately 20% lower than for primary transplantation (http://www.optn.org/latestdata/rptstrat.asp). Patients who undergo retransplantation also have significantly longer hospital and intensive care unit stays and higher total hospital charges than those who receive only one transplant.[324,325] Retransplantation for liver failure from recurrent hepatitis C has been associated with particularly poor survival.[326]

A number of groups have attempted to develop prognostic models for patients undergoing retransplantation. The urgency of retransplantation, serum bilirubin and creatinine levels, CTP score of 10 or more, and MELD score of more than 25 all are associated with a poor prognosis after retransplantation.[324,325,327,328]

Recommendations

74. Liver retransplantation, which is the only means of prolonging life in patients whose initial graft has failed, makes an important contribution to overall survival and should be considered in selected patients with primary graft failure, hepatic artery thrombosis, severe rejection, or recurrent disease (II-3). However, retransplantation is associated with diminished survival and increased costs compared with primary transplantation.

75. Retransplantation should be considered before patients develop severe hepatic and renal failure (II-3).

76. Retransplantation should be used with discretion in the emergency setting and should be avoided in subgroups of patients with little chance of success (III).

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