

AASLD Practice Guidelines: Evaluation of the Patient for Liver Transplantation

Karen F. Murray and Robert L. Carithers, Jr.

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 Guidelines¹; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines²; (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.

From the Division of Gastroenterology, University of Washington School of Medicine, Seattle, WA.

Received March 4, 2005; accepted March 4, 2005.

Address reprint requests to: Robert L. Carithers, Jr., M.D., Division of Gastroenterology, University of Washington School of Medicine, 1959 NE Pacific Street, Box 356174, Seattle, WA 98195-6174. E-mail: doctorc@u.washington.edu; fax: 206-548-6706.

Copyright © 2005 by the American Association for the Study of Liver Diseases.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20704

Potential conflict of interest: Nothing to report.

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.

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 Based³

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

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

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 \geq 7 and MELD \geq 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 pO₂ 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 PaO₂ 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 PaO₂ 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 successfully 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/m²).⁶¹ Obesity was more common in women and in patients with cryptogenic cirrhosis. Morbid obesity (BMI > 40 kg/m²) 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/m²).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 pre-existing 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/netforum/aasld/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- α 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 conservative-

ly.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 non-syndromic 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-antitrypsin 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 is 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/hemochromatosis.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 hyperox-

aluria 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 co-

agulopathy 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 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).

Acknowledgment: This guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. This committee, in concert with Michael R. Lucey, M.D., as the lead reviewer, provided extensive peer review of this manuscript. The members of the Practice Guidelines Committee include K. Rajender Reddy, M.D., Chair; Bruce R. Bacon, M.D.; Henry C. Bodenheimer, M.D.; Robert L. Carithers, Jr., M.D.; Stanley M. Cohen, M.D.; James E. Everhart, M.D.; Thomas W. Faust, M.D.; Steven L. Flamm, M.D.; Gregory J. Gores, M.D.; Elizabeth Hespeneheide, MSN, ACNP; Maureen M. Jonas, M.D.; Michael R. Lucey, M.D.; Timothy M. McCashland, M.D.; David R. Nelson, M.D.; F. Fred Poordad, M.D.; Margaret C. Shuhart, M.D., M.S.; Brent A. Tetri, M.D.; Zobair M. Younossi, M.D., M.P.H.; and Nizar N. Zein, M.D.

References

- Eddy DM. Manual for Assessing Health Practices and Designing Practice Guidelines. Philadelphia, PA: American College of Physicians, 1996.
- Position and policy statement: American Gastroenterological Association policy statement on the use of medical practice guidelines by managed care organizations and insurance carriers. *Gastroenterology* 1995;108:925-926.
- Woolf SH, Sox HC Jr. The Expert Panel on Preventive Services: continuing the work of the U.S. Preventive Services Task Force. *Am J Prev Med* 1991;7:326-330.
- Belle SH, Porayko MK, Hoofnagle JH, Lake JR, Zetterman RK. Changes in quality of life after liver transplantation among adults. National Institute of Diabetes and Digestive and Kidney Diseases (NIIDK) Liver Transplantation Database (LTD). *Liver Transpl Surg* 1997;3:93-104.
- Best JH, Veenstra DL, Geppert J. Trends in expenditures for Medicare liver transplant recipients. *Liver Transpl* 2001;7:858-862.
- Keeffe EB. Liver transplantation: current status and novel approaches to liver replacement. *Gastroenterology* 2001;120:749-762.
- Otte JB, Ville-de-Goyet J, Reding R, Van-Obbergh L, Veyckemans F, Carlier MA, et al. Pediatric liver transplantation: from the full-size liver graft to reduced, split, and living related liver transplantation. *Pediatr Surg Int* 1998;13:308-318.
- Malago M, Hertl M, Testa G, Rogiers X, Broelsch CE. Split-liver transplantation: future use of scarce donor organs. *World J Surg* 2002;26:275-282.
- Gridelli B, Spada M, Petz W, Bertani A, Lucianetti A, Colledan M, et al. Split-liver transplantation eliminates the need for living-donor liver transplantation in children with end-stage cholestatic liver disease. *Transplantation* 2003;75:1197-1203.
- Renz JF, Emond JC, Yersiz H, Ascher NL, Busuttill RW. Split-liver transplantation in the United States: outcomes of a national survey. *Ann Surg* 2004;239:172-181.
- Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *New Engl J Med* 2002;346:1074-1082.
- Surman OS. The ethics of partial-liver donation. *New Engl J Med* 2002;346:1038.
- Settmacher U, Theruvath T, Pascher A, Neuhaus P. Living-donor liver transplantation—European experiences. *Nephrol Dial Transplant* 2004;19(Suppl 4):iv16-iv21.
- Sagmeister M, Mullhaupt B, Kadry Z, Kullak-Ublick GA, Clavien PA, Renner EL. Cost-effectiveness of cadaveric and living-donor liver transplantation. *Transplantation* 2002;73:616-622.
- Evans RW. Liver transplants and the decline in deaths from liver disease. *Am J Public Health* 1997;87:868-869.
- Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. *HEPATOLOGY* 1989;10:1-7.
- Murtaugh PA, Dickson ER, Van Dam GM, Malinchoc M, Grambsch PM, Langworthy AL, et al. Primary biliary cirrhosis: prediction of short-term survival based on repeated patients visits. *HEPATOLOGY* 1994;20:126-134.
- Dickson ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, et al. Primary sclerosing cholangitis: refinement and validation of survival models. *Gastroenterology* 1992;103:1893-1901.
- Shetty K, Rybicki L, Carey WD. The Child-Pugh classification as a prognostic indicator for survival in primary sclerosing cholangitis. *HEPATOLOGY* 1997;25:1049-1053.
- Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-648.
- Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. *New Engl J Med* 1966;274:473-481.
- Oellerich M, Burdelski M, Lautz H-U, Binder L, Pichlmayr R. Predictors of one-year pretransplant survival in patients with cirrhosis. *HEPATOLOGY* 1991;14:1029-1034.
- Conn HO. A peek at the Child-Turcotte classification. *HEPATOLOGY* 1981;1:673-676.
- Propst A, Propst T, Sangeri G, Ofner D, Judmaier G, Vogel W. Prognosis and life expectancy in chronic liver disease. *Dig Dis Sci* 1995;40:1805-1815.
- Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg* 1997;3:628-637.
- Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *HEPATOLOGY* 2000;31:864-871.
- Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *HEPATOLOGY* 2001;33:464-470.
- Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003;124:91-96.
- Freeman RB, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R. Results of the first year of the new liver allocation plan. *Liver Transpl* 2004;10:7-15.
- Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transpl* 2001;7:567-580.
- McDiarmid SV, Anand R, Lindblad AS. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation* 2002;74:173-181.
- Freeman RB, Rohrer RJ, Katz E, Lewis WD, Jenkins R, Cosimi AB, et al. Preliminary results of a liver allocation plan using a continuous medical severity score that de-emphasizes waiting time. *Liver Transpl* 2001;7:173-178.
- Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-472.

34. Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A, et al. Compensated cirrhosis: natural history and prognosis factors. *HEPATOLOGY* 1987;7:122-128.
35. Andreu M, Sola R, Sitges SA, Alia C, Gallen M, Vila MC, et al. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Gastroenterology* 1993;104:1133-1138.
36. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology* 1993;105:229-236.
37. Starzl TE, Todo S, Gordon RD, Makowka L, Tzakis A, Iwatsuki S, et al. Liver transplantation in older patients. *New Engl J Med* 1987;316:484-485.
38. Zetterman RK, Belle SH, Hoofnagle JH, Lawlor S, Wei Y, Everhart J, et al. Age and liver transplantation: a report of the Liver Transplantation Database. *Transplantation* 1998;66:500-506.
39. Collins BH, Pirsch JD, Becker YT, Hanaway MJ, Van der Werf WJ, D'Alessandro AM, et al. Long-term results of liver transplantation in older patients 60 years of age and older. *Transplantation* 2000;70:780-783.
40. Herrero JI, Lucena JF, Quiroga J, Sangro B, Pardo F, Rotellar F, et al. Liver transplant recipients older than 60 years have lower survival and higher incidence of malignancy. *Am J Transplant* 2003;3:1407-1412.
41. Plotkin JS, Scott VL, Pinna A, Dobsch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1996;2:426-430.
42. Plotkin JS, Benitez RM, Kuo PC, Njoku MJ, Ridge LA, Lim JW, et al. Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1998;4:253-257.
43. Donovan CL, Marcovitz PA, Punch JD, Bach DS, Brown KA, Lucey MR, et al. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. *Transplantation* 1996;61:1180-1188.
44. Williams K, Lewis JF, Davis G, Geiser EA. Dobutamine stress echocardiography in patients undergoing liver transplantation evaluation. *Transplantation* 2000;69:2354-2356.
45. Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *HEPATOLOGY* 2003;37:192-197.
46. Collisson EA, Nourmand H, Fraiman MH, Cooper CB, Bellamy PE, Farmer DG, et al. Retrospective analysis of the results of liver transplantation for adults with severe hepatopulmonary syndrome. *Liver Transpl* 2002;8:925-931.
47. Schenk P, Schoniger-Hekele M, Fuhrmann V, Madl C, Silberhumer G, Muller C. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* 2003;125:1042-1052.
48. Krowka MJ, Porayko MK, Plevak DJ, Pappas SC, Steers JL, Krom RA, et al. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. *Mayo Clin Proc* 1997;72:44-53.
49. Santamaria F, Sarnelli P, Celentano L, Farina V, Vegnente A, Mansi A, et al. Noninvasive investigation of hepatopulmonary syndrome in children and adolescents with chronic cholestasis. *Pediatr Pulmonol* 2002;33:374-379.
50. Hadengue A, Benahyoun M, Lebrec D, Benhamou JP. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology* 1991;100:520-528.
51. Colle IO, Moreau R, Godinho E, Belghiti J, Ertori F, Cohen-Solal A, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *HEPATOLOGY* 2003;37:401-409.
52. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl Surg* 1997;3:494-500.
53. Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl* 2000;6:443-450.
54. Starkel P, Vera A, Gunson B, Mutimer D. Outcome of liver transplantation for patients with pulmonary hypertension. *Liver Transpl* 2002;8:382-388.
55. Plotkin JS, Kuo PC, Rubin LJ, Gaine S, Howell CD, Laurin J, et al. Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. *Transplantation* 1998;65:457-459.
56. Ramsay MA, Spikes C, East CA, Lynch K, Hein HA, Ramsay KJ, et al. The perioperative management of portopulmonary hypertension with nitric oxide and epoprostenol. *Anesthesiology* 1999;90:299-301.
57. Mair P, Kaehler CH, Pomaroli A, Schwarz B, Vogel W, Margreiter R. Orthotopic liver transplantation in a patient with severe portopulmonary hypertension. *Acta Anaesthesiol Scand* 2001;45:513-518.
58. Kim WR, Krowka MJ, Plevak DJ, Lee J, Rettke SR, Frantz RP, et al. Accuracy of Doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. *Liver Transpl* 2000;6:453-458.
59. Torregrosa M, Genesca J, Gonzalez A, Evangelista A, Mora A, Margarit C, et al. Role of Doppler echocardiography in the assessment of portopulmonary hypertension in liver transplantation candidates. *Transplantation* 2001;71:572-574.
60. Cotton CL, Gandhi S, Vaitkus PT, Massad MG, Benedetti E, Mrtek RG, et al. Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates. *Liver Transpl* 2002;8:1051-1054.
61. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *HEPATOLOGY* 2002;35:105-109.
62. Ehlers SL, Rodriguez JR, Widows MR, Reed AI, Nelson DR. Tobacco use before and after liver transplantation: a single center survey and implications for clinical practice and research. *Liver Transpl* 2004;10:412-417.
63. Pungpapong S, Manzarbeitia C, Ortiz J, Reich DJ, Araya V, Rothstein KD, et al. Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. *Liver Transpl* 2002;8:582-587.
64. Lafayette RA, Pare G, Schmid CH, King AJ, Rohrer RJ, Nasraway SA. Pretransplant renal dysfunction predicts poorer outcome in liver transplantation. *Clin Nephrol* 1997;48:159-164.
65. Bilbao I, Charco R, Balsells J, Lazaro JL, Hidalgo E, Llopart L, et al. Risk factors for acute renal failure requiring dialysis after liver transplantation. *Clin Transplant* 1998;12:123-129.
66. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *HEPATOLOGY* 2002;35:1179-1185.
67. Seu P, Wilkinson AH, Shaked A, Busuttil RW. The hepatorenal syndrome in liver transplant recipients. *Am Surg* 1991;57:806-809.
68. Gonwa TA, Morris CA, Goldstein RM, Husberg BS, Klintmalm GB. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome: experience in 300 patients. *Transplantation* 1991;51:428-430.
69. Davis CL, Gonwa TA, Wilkinson AH. Pathophysiology of renal disease associated with liver disorders: implications for liver transplantation. Part I. *Liver Transpl* 2002;8:91-109.
70. Grewal HP, Brady L, Cronin DC, Loss GE, Siegel CT, Oswald K, et al. Combined liver and kidney transplantation in children. *Transplantation* 2000;70:100-105.
71. Rogers J, Bueno J, Shapiro R, Scantlebury V, Mazariegos G, Fung J, et al. Results of simultaneous and sequential pediatric liver and kidney transplantation. *Transplantation* 2001;72:1666-1670.
72. Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver-kidney transplantation: part II. *Liver Transpl* 2002;8:193-211.
73. Sokhi RP, Anantharaju A, Kondaveeti R, Creech SD, Islam KK, Van Thiel DH. Bone mineral density among cirrhotic patients awaiting liver transplantation. *Liver Transpl* 2004;10:648-653.

74. Menon KV, Angulo P, Weston S, Dickson ER, Lindor KD. Bone disease in primary biliary cirrhosis: independent indicators and rate of progression. *J Hepatol* 2001;35:316-323.
75. Floreani A, Mega A, Tizian L, Burra P, Boccagni P, Baldo V, et al. Bone metabolism and gonad function in male patients undergoing liver transplantation: a two-year longitudinal study. *Osteoporos Int* 2001;12:749-754.
76. Carey EJ, Balan V, Kremers WK, Hay JE. Osteopenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. *Liver Transpl* 2003;9:1166-1173.
77. Trautwein C, Possienke M, Schlitt HJ, Boker KH, Horn R, Raab R, et al. Bone density and metabolism in patients with viral hepatitis and cholestatic liver diseases before and after liver transplantation. *Am J Gastroenterol* 2000;95:2343-2351.
78. Ragni MV, Bontempo FA, Lewis JH. Organ transplantation in HIV-positive patients with hemophilia. *New Engl J Med* 1990;322:1886-1887.
79. Bouscarat F, Samuel D, Simon F, Debat P, Bismuth H, Saimot AG. An observational study of 11 French liver transplant recipients infected with human immunodeficiency virus type 1. *Clin Infect Dis* 1994;19:854-859.
80. Gordon FH, Mistry PK, Sabin CA, Lee CA. Outcome of orthotopic liver transplantation in patients with haemophilia. *Gut* 1998;42:744-749.
81. Neff GW, Bonham A, Tzakis AG, Ragni M, Jayaweera D, Schiff ER, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transpl* 2003;9:239-247.
82. Stock PG, Roland ME, Carlson L, Freise CE, Roberts JP, Hirose R, et al. Kidney and liver transplantation in human immunodeficiency virus-infected patients: a pilot safety and efficacy study. *Transplantation* 2003;76:370-375.
83. Schvarcz R, Rudbeck G, Soderdahl G, Stahle L. Interaction between nelfinavir and tacrolimus after orthotopic liver transplantation in a patient coinfecting with HIV and hepatitis C virus (HCV). *Transplantation* 2000;69:2194-2195.
84. Sheikh AM, Wolf DC, Lebovics E, Goldberg R, Horowitz HW. Concomitant human immunodeficiency virus protease inhibitor therapy markedly reduces tacrolimus metabolism and increases blood levels. *Transplantation* 1999;68:307-309.
85. Tolan DJ, Davies MH, Millson CE. Fibrosing cholestatic hepatitis after liver transplantation in a patient with hepatitis C and HIV infection. *New Engl J Med* 2001;345:1781.
86. Prachalias AA, Pozniak A, Taylor C, Srinivasan P, Muiesan P, Wendon J, et al. Liver transplantation in adults coinfecting with HIV. *Transplantation* 2001;72:1684-1688.
87. Roland ME, Stock PG. Review of solid-organ transplantation in HIV-infected patients. *Transplantation* 2003;75:425-429.
88. Yerdel MA, Gunson B, Mirza D, Karayalcin K, Olliff S, Buckels J, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation* 2000;69:1873-1881.
89. Manzanet G, Sanjuan F, Orbis P, Lopez R, Moya A, Juan M, et al. Liver transplantation in patients with portal vein thrombosis. *Liver Transpl* 2001;7:125-131.
90. Sobhonslidsuk A, Reddy KR. Portal vein thrombosis: a concise review. *Am J Gastroenterol* 2002;97:535-541.
91. Mitchell A, John PR, Mayer DA, Mirza DF, Buckels JA, de Ville dG. Improved technique of portal vein reconstruction in pediatric liver transplant recipients with portal vein hypoplasia. *Transplantation* 2002;73:1244-1247.
92. Smith PA, Klein AS, Heath DG, Chavin K, Fishman EK. Dual-phase spiral CT angiography with volumetric 3D rendering for preoperative liver transplant evaluation: preliminary observations. *J Comput Assist Tomogr* 1998;22:868-874.
93. Cheng YF, Chen CL, Jawan B, Huang TL, Chen TY, Chen YS, et al. Multislice computed tomography angiography in pediatric liver transplantation. *Transplantation* 2003;76:353-357.
94. Eubank WB, Wherry KL, Maki JH, Sahin H, Funkhouser CP, Schmiel UP. Preoperative evaluation of patients awaiting liver transplantation: comparison of multiphasic contrast-enhanced 3D magnetic resonance to helical computed tomography examinations. *J Magn Reson Imaging* 2002;16:565-575.
95. Erbay N, Raptopoulos V, Pomfret EA, Kamel IR, Kruskal JB. Living donor liver transplantation in adults: vascular variants important in surgical planning for donors and recipients. *AJR Am J Roentgenol* 2003;181:109-114.
96. Kanchana TP, Kaul V, Manzarbeitia C, Reich DJ, Hails KC, Munoz SJ, et al. Liver transplantation for patients on methadone maintenance. *Liver Transpl* 2002;8:778-782.
97. Liu LU, Schiano TD, Lau N, O'Rourke M, Min AD, Sigal SH, et al. Survival and risk of recidivism in methadone-dependent patients undergoing liver transplantation. *Am J Transplant* 2003;3:1273-1277.
98. Weinrieb RM, Barnett R, Lynch KG, DePiano M, Atanda A, Olthoff KM. A matched comparison study of medical and psychiatric complications and anesthesia and analgesia requirements in methadone-maintained liver transplant recipients. *Liver Transpl* 2004;10:97-106.
99. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl* 2004;10:886-897.
100. Seeff LB. Natural history of chronic hepatitis C. *HEPATOLOGY* 2002;36:S35-S46.
101. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000;20:17-35.
102. Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology* 2002;122:1609-1619.
103. Kim WR. The burden of hepatitis C in the United States. *HEPATOLOGY* 2002;36:S30-S34.
104. Gane EJ, Portman BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, et al. Long-term outcome of hepatitis C infection after liver transplantation. *New Engl J Med* 1996;334:815-820.
105. Shuhart MC, Bronner MP, Gretch DR, Thomassen LV, Wartelle CF, Tateyama H, et al. Histological and clinical outcome after liver transplantation for hepatitis C. *HEPATOLOGY* 1997;26:1646-1652.
106. Boker KHW, Dalley G, Bahr M, Maschek H, Tillmann HL, Trautwein C, et al. Long-term outcome of hepatitis C virus infection after liver transplantation. *HEPATOLOGY* 1997;25:203-210.
107. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, Rayon M, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. *J Hepatol* 2000;32:673-684.
108. Charlton M. Patient and graft survival following liver transplantation for hepatitis C: much ado about something. *Gastroenterology* 2002;122:1162-1165.
109. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889-896.
110. Berenguer M. Natural history of recurrent hepatitis C. *Liver Transpl* 2002;8:S14-S18.
111. Testa G, Crippin JS, Netto GJ, Goldstein RM, Jennings LW, Brkic BS, et al. Liver transplantation for hepatitis C: recurrence and disease progression in 300 patients. *Liver Transpl* 2000;6:553-561.
112. Samuel D, Bizollon T, Feray C, Roche B, Ahmed SN, Lemonnier C, et al. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. *Gastroenterology* 2003;124:642-650.
113. Shiffman ML, Vargas HE, Everson GT. Controversies in the management of hepatitis C virus infection after liver transplantation. *Liver Transpl* 2003;9:1129-1144.
114. Everson GT. Treatment of patients with hepatitis C virus on the waiting list. *Liver Transpl* 2003;9:S90-S94.
115. Lok AS, McMahon BJ. Chronic hepatitis B. *HEPATOLOGY* 2001;34:1225-1241.
116. Perrillo RP, Wright T, Rakela J, Levy G, Schiff E, Gish R, et al. A multicenter United States-Canadian trial to assess lamivudine mono-

- therapy before and after liver transplantation for chronic hepatitis B. *HEPATOLOGY* 2001;33:424-432.
117. Villeneuve JP, Condrey LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, et al. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *HEPATOLOGY* 2000;31:207-210.
 118. Yao FY, Terrault NA, Freise C, Maslow L, Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. *HEPATOLOGY* 2001;34:411-416.
 119. Fontana RJ, Hann HW, Perrillo RP, Vierling JM, Wright T, Rakela J, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. *Gastroenterology* 2002;123:719-727.
 120. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *New Engl J Med* 2003;348:808-816.
 121. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *New Engl J Med* 2003;348:800-807.
 122. Perrillo R, Hann HW, Mutimer D, Willems B, Leung N, Lee WM, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004;126:81-90.
 123. Peters MG, Hann HH, Martin P, Heathcote EJ, Buggisch P, Rubin R, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2004;126:91-101.
 124. Perrillo R, Tamburro C, Regensteiner F, Balart L, Bodenheimer J, Silva M, et al. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B. *Gastroenterology* 1995;109:908-916.
 125. Hoofnagle JH, Di Bisceglie AM, Waggoner JG, Park Y. Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B. *Gastroenterology* 1993;104:1116-1121.
 126. Todo S, Demetris AJ, Van Thiel DH, Teperman L, Fung JJ, Starzl TE. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *HEPATOLOGY* 1991;13:619-626.
 127. O'Grady JG, Smith JM, Davies SE, Daniels HM, Donaldson PT, Tan KC, et al. Hepatitis B virus reinfection after liver transplantation: serological and clinical implications. *J Hepatol* 1992;14:104-111.
 128. Shouval D, Samuel D. Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: a concise review. *HEPATOLOGY* 2000;32:1189-1195.
 129. Lok AS. Prevention of recurrent hepatitis B post-liver transplantation. *Liver Transpl* 2002;8:S67-S73.
 130. Anselmo DM, Ghobrial RM, Jung LC, Weaver M, Cao C, Saab S, et al. New era of liver transplantation for hepatitis B: a 17-year single-center experience. *Ann Surg* 2002;235:611-619.
 131. Steinhilber T, Seehofer D, Rayes N, Muller AR, Settmacher U, Jonas S, et al. Increasing applicability of liver transplantation for patients with hepatitis B-related liver disease. *HEPATOLOGY* 2002;35:1528-1535.
 132. Samuel D. Management of hepatitis B in liver transplantation patients. *Semin Liver Dis* 2004;24(Suppl 1):55-62.
 133. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. *HEPATOLOGY* 2002;36:479-497.
 134. Neuberger J. Transplantation for autoimmune hepatitis. *Semin Liver Dis* 2002;22:379-386.
 135. Vogel A, Heinrich E, Bahr MJ, Rifai K, Flemming P, Melter M, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. *Clin Transplant* 2004;18:62-69.
 136. Gonzalez-Koch A, Czaja AJ, Carpenter HA, Roberts SK, Charlton MR, Porayko MK, et al. Recurrent autoimmune hepatitis after orthotopic liver transplantation. *Liver Transpl* 2001;7:302-310.
 137. Molmenti EP, Netto GJ, Murray NG, Smith DM, Molmenti H, Crippin JS, et al. Incidence and recurrence of autoimmune/alloimmune hepatitis in liver transplant recipients. *Liver Transpl* 2002;8:519-526.
 138. Duclos-Vallee JC, Sebah M, Rifai K, Johanet C, Ballot E, Guettier C, et al. A 10 year follow up study of patients transplanted for autoimmune hepatitis: histological recurrence precedes clinical and biochemical recurrence. *Gut* 2003;52:893-897.
 139. Milkiewicz P, Hubscher SG, Skiba G, Hathaway M, Elias E. Recurrence of autoimmune hepatitis after liver transplantation. *Transplantation* 1999;68:253-256.
 140. Heneghan MA, Portmann BC, Norris SM, Williams R, Muiesan P, Rela M, et al. Graft dysfunction mimicking autoimmune hepatitis following liver transplantation in adults. *HEPATOLOGY* 2001;34:464-470.
 141. Salcedo M, Vaquero J, Banares R, Rodriguez-Mahou M, Alvarez E, Vicario JL, et al. Response to steroids in de novo autoimmune hepatitis after liver transplantation. *HEPATOLOGY* 2002;35:349-356.
 142. Cattani P, Berney T, Conti F, Calmus Y, Homberg JC, Houssin D, et al. Outcome of orthotopic liver transplantation in autoimmune hepatitis according to subtypes. *Transpl Int* 2002;15:34-38.
 143. Bahar RJ, Yanni GS, Martin MG, McDiarmid SV, Vargas JH, Gershman GB, et al. Orthotopic liver transplantation for autoimmune hepatitis and cryptogenic chronic hepatitis in children. *Transplantation* 2001;72:829-833.
 144. Birnbaum AH, Benkov KJ, Pittman NS, McFarlane FY, Rosh JR, Le-Leiko NS. Recurrence of autoimmune hepatitis in children after liver transplantation. *J Pediatr Gastroenterol Nutr* 1997;25:20-25.
 145. Kim WR, Brown RS Jr, Terrault NA, El Serag H. Burden of liver disease in the United States: summary of a workshop. *HEPATOLOGY* 2002;36:227-242.
 146. Powell WJ, Klatskin G. Duration and survival in patients with Laennec's cirrhosis. *Am J Med* 1968;44:406-420.
 147. Borowsky SA, Strome S, Lott E. Continued heavy drinking and survival in alcoholic cirrhotics. *Gastroenterology* 1981;80:1405-1409.
 148. Veldt BJ, Laine F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, Brissot P, Deugnier Y, Moirand R. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002;36:93-98.
 149. Everhart JE, Beresford TP. Liver transplantation for alcoholic liver disease: a survey of transplantation programs in the United States. *Liver Transpl Surg* 1997;3:220-226.
 150. Poyndt T, Naveau S, Doffoel M, Boudjema K, Vanlemmens C, Mantion G, et al. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis using matched and simulated controls: 5-year survival. Multi-centre group. *J Hepatol* 1999;30:1130-1137.
 151. Miguet JP, Vanlemmens C, Milan C, Messner M, Minello A, Bocage L, et al. Impact of liver transplantation on survival in Pugh B alcoholic cirrhotic patients: a multicenter randomized trial [Abstract]. *HEPATOLOGY* 2003;38(Suppl 1):90A.
 152. Wiesner RH, Lombardero M, Lake JR, Everhart J, Detre KM. Liver transplantation for end-stage alcoholic liver disease: an assessment of outcomes. *Liver Transpl Surg* 1997;3:231-239.
 153. Pereira SP, Williams R. Liver transplantation for alcoholic liver disease at King's College Hospital: survival and quality of life. *Liver Transpl Surg* 1997;3:245-250.
 154. Belle SH, Beringer KC, Detre KM. Liver transplantation for alcoholic liver disease in the United States: 1988 to 1995. *Liver Transpl Surg* 1997;3:212-219.
 155. Farges O, Saliba F, Farhamant H, Samuel D, Bismuth A, Reynes M, et al. Incidence of rejection and infection after liver transplantation as a function of the primary disease: possible influence of alcohol and polyclonal immunoglobulin. *HEPATOLOGY* 1996;23:240-248.
 156. Bathgate AJ, Hynd P, Sommerville D, Hayes PC. The prediction of acute cellular rejection in orthotopic liver transplantation. *Liver Transpl Surg* 1999;5:475-479.
 157. Osorio RW, Ascher NL, Avery M, Bacchetti P, Roberts JP, Lake JR. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. *HEPATOLOGY* 1994;20:105-110.

158. Lucey MR, Carr K, Beresford TP, Fisher LR, Shieck V, Brown KA, et al. Alcohol use after liver transplantation in alcoholics: a clinical cohort follow-up study. *HEPATOLOGY* 1997;25:1223-1227.
159. Campbell DA Jr., Punch JD. Monitoring for alcohol use relapse after liver transplantation for alcoholic liver disease. *Liver Transpl Surg* 1997;3:300-303.
160. Buis CI, Wiesner RH, Krom RA, Kremers WK, Wijdicks EF. Acute confusional state following liver transplantation for alcoholic liver disease. *Neurology* 2002;59:601-605.
161. Showstack J, Katz PP, Lake JR, Brown RS Jr., Dudley RA, Belle S, et al. Resource utilization in liver transplantation: effects of patient characteristics and clinical practice. NIDDK Liver Transplantation Database Group. *JAMA* 1999;281:1381-1386.
162. Lewis MB, Howdle PD. Neurologic complications of liver transplantation in adults. *Neurology* 2003;61:1174-1178.
163. Bellamy CO, DiMartini AM, Ruppert K, Jain A, Dodson F, Torbenson M, et al. Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence. *Transplantation* 2001;72:619-626.
164. Lee RG. Recurrence of alcoholic liver disease after liver transplantation. *Liver Transpl Surg* 1997;3:292-295.
165. Pasha TM, Dickson ER. Survival algorithms and outcome analysis in primary biliary cirrhosis. *Semin Liver Dis* 1997;17:147-158.
166. Liermann Garcia RF, Evangelista GC, McMaster P, Neuberger J. Transplantation for primary biliary cirrhosis: retrospective analysis of 400 patients in a single center. *HEPATOLOGY* 2001;33:22-27.
167. Tinmouth J, Tomlinson G, Heathcote EJ, Lilly L. Benefit of transplantation in primary biliary cirrhosis between 1985- 1997. *Transplantation* 2002;73:224-227.
168. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. *HEPATOLOGY* 2000;31:1005-1013.
169. Neuberger J, Jones EA. Liver transplantation for intractable pruritus is contraindicated before an adequate trial of opiate antagonist therapy. *Eur J Gastroenterol Hepatol* 2001;13:1393-1394.
170. Lee Y-M, Kaplan MM. Primary sclerosing cholangitis. *New Engl J Med* 1995;332:924-933.
171. Harnois DM, Lindor KD. Primary sclerosing cholangitis: evolving concepts in diagnosis and treatment. *Dig Dis Sci* 1997;15:23-41.
172. Lee YM, Kaplan MM. Management of primary sclerosing cholangitis. *Am J Gastroenterol* 2002;97:528-534.
173. Abu-Elmagd KM, Malinchoc M, Dickson ER, Fung JJ, Murtaugh PA, Langworthy AL, et al. Efficacy of hepatic transplantation in patients with primary sclerosing cholangitis. *Surg Gynecol Obstet* 1993;177:335-344.
174. Narumi S, Roberts JP, Emond JC, Lake J, Ascher NL. Liver transplantation for sclerosing cholangitis. *HEPATOLOGY* 1995;22:451-457.
175. Ricci P, Therneau TM, Malinchoc M, Benson JT, Petz JL, Klintmalm GB, et al. A prognostic model for the outcome of liver transplantation in patients with cholestatic liver disease. *HEPATOLOGY* 1997;25:672-677.
176. Goss JA, Shackleton CR, Farmer DG, Arnaout WS, Seu P, Markowitz JS, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. *Ann Surg* 1997;225:472-481.
177. Graziadei IW, Wiesner RH, Marotta PJ, Porayko MK, Hay JE, Charlton MR, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. *HEPATOLOGY* 1999;30:1121-1127.
178. Maheshwari A, Yoo HY, Thuluvath PJ. Long-term outcome of liver transplantation in patients with PSC: a comparative analysis with PBC. *Am J Gastroenterol* 2004;99:538-542.
179. Farrant JM, Hayllar KM, Wilkinson ML, Karani J, Portmann BC, Westaby D, et al. Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991;100:1710-1717.
180. Farges O, Malassagne B, Sebah M, Bismuth H. Primary sclerosing cholangitis: liver transplantation or biliary surgery. *Surgery* 1995;117:146-155.
181. Graziadei IW, Wiesner RH, Batts KP, Marotta PJ, LaRusso NF, Porayko MK, et al. Recurrence of primary sclerosing cholangitis following liver transplantation. *HEPATOLOGY* 1999;29:1050-1056.
182. Fabia R, Levy MF, Testa G, Obiekwe S, Goldstein RM, Husberg BS, et al. Colon carcinoma in patients undergoing liver transplantation. *Am J Surg* 1998;176:265-269.
183. Loftus EV Jr., Aguilar HI, Sandborn WJ, Tremaine WJ, Krom RA, Zinsmeister AR, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. *HEPATOLOGY* 1998;27:685-690.
184. Davenport M, Kerkar N, Mieli VG, Mowat AP, Howard ER. Biliary atresia: the King's College Hospital experience (1974-1995). *J Pediatr Surg* 1997;32:479-485.
185. Ohi R, Ibrahim M. Biliary atresia. *Semin Pediatr Surg* 1992;1:115-124.
186. Otte JB, de Ville dG, Reding R, Hausleithner V, Sokal E, Chardot C, et al. Sequential treatment of biliary atresia with Kasai portoenterostomy and liver transplantation: a review. *HEPATOLOGY* 1994;20:41S-48S.
187. Van-der-Werf W-J, D'Alessandro AM, Knechtle SJ, Pilli G, Hoffmann RM, Judd RH, et al. Infant pediatric liver transplantation results equal those for older pediatric patients. *J Pediatr Surg* 1998;33:20-23.
188. Laurent J, Gauthier F, Bernard O, Hadchouel M, Odievre M, Valayer J, et al. Long-term outcome after surgery for biliary atresia. Study of 40 patients surviving for more than 10 years. *Gastroenterology* 1990;99:1793-1797.
189. Woodle ES, Millis JM, So SK, McDiarmid SV, Busuttil RW, Esquivel CO, et al. Liver transplantation in the first three months of life. *Transplantation* 1998;66:606-609.
190. Diem HV, Evrard V, Vinh HT, Sokal EM, Janssen M, Otte JB, et al. Pediatric liver transplantation for biliary atresia: results of primary grafts in 328 recipients. *Transplantation* 2003;75:1692-1697.
191. Sandler AD, Azarow KS, Superina RA. The impact of a previous Kasai procedure on liver transplantation for biliary atresia. *J Pediatr Surg* 1997;32:416-419.
192. Alagille D. Alagille syndrome today. *Clin Invest Med* 1996;19:325-330.
193. Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut* 2001;49:431-435.
194. Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *HEPATOLOGY* 1999;29:822-829.
195. Molmenti EP, Squires RH, Nagata D, Roden JS, Molmenti H, Fasola CG, et al. Liver transplantation for cholestasis associated with cystic fibrosis in the pediatric population. *Pediatr Transplant* 2003;7:93-97.
196. Balistreri WF. Intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr* 2002;35:S17-S23.
197. Bezerra JA, Balistreri WF. Intrahepatic cholestasis: order out of chaos. *Gastroenterology* 1999;117:1496-1498.
198. Kurbegov AC, Setchell KD, Haas JE, Mierau GW, Narkewicz M, Bancroft JD, et al. Biliary diversion for progressive familial intrahepatic cholestasis: improved liver morphology and bile acid profile. *Gastroenterology* 2003;125:1227-1234.
199. Ismail H, Kalicinski P, Markiewicz M, Jankowska I, Pawlowska J, Kluge P, et al. Treatment of progressive familial intrahepatic cholestasis: liver transplantation or partial external biliary diversion. *Pediatr Transplant* 1999;3:219-224.
200. Lykavieris P, van Mil S, Cresteil D, Fabre M, Hadchouel M, Klomp L, et al. Progressive familial intrahepatic cholestasis type 1 and extrahepatic features: no catch-up of stature growth, exacerbation of diarrhea, and appearance of liver steatosis after liver transplantation. *J Hepatol* 2003;39:447-452.
201. Kayler LK, Rasmussen CS, Dykstra DM, Punch JD, Rudich SM, Magee JC, et al. Liver transplantation in children with metabolic disorders in the United States. *Am J Transplant* 2003;3:334-339.
202. Marcus N, Teckman JH, Perlmutter DH. Alpha1-antitrypsin deficiency: from genotype to childhood disease. *J Pediatr Gastroenterol Nutr* 1998;27:65-74.
203. Sveger T. The natural history of liver disease in alpha 1-antitrypsin deficient children. *Acta Paediatr Scand* 1988;77:847-851.
204. Sveger T, Eriksson S. The liver in adolescents with alpha 1-antitrypsin deficiency. *HEPATOLOGY* 1995;22:514-517.

205. Perlmutter DH. Alpha-1-antitrypsin deficiency. *Semin Liver Dis* 1998; 18:217-225.
206. Sveger T. Liver disease in alpha-1-antitrypsin deficiency detected by screening of 200,000 infants. *New Engl J Med* 1976;294:1316-1321.
207. Volpert D, Molleston JP, Perlmutter DH. Alpha-1-antitrypsin deficiency-associated liver disease progresses slowly in some children. *J Pediatr Gastroenterol Nutr* 2000;31:258-263.
208. Elzouki AN, Erikssohn S. Risk of hepatobiliary disease in adults with severe alpha-1-antitrypsin deficiency (PiZZ): is chronic viral hepatitis B or C an additional risk factor for cirrhosis and hepatocellular carcinoma? *Eur J Gastroenterol Hepatol* 1996;8:989-994.
209. Esquivel CO, Vicente E, Van Thiel DH, Gordon R, Marsh W, Makowka L, et al. Orthotopic liver transplantation for alpha-1-antitrypsin deficiency: an experience in 29 children and ten adults. *Transplant Proc* 1987;19:3798-3802.
210. Vennarecci G, Gunson BK, Ismail T, Hubscher SG, Kelly DA, McMaster P, et al. Transplantation for end stage liver disease related to alpha-1 antitrypsin. *Transplantation* 1996;61:1488-1495.
211. Francavilla R, Castellana SP, Hadzic N, Chambers SM, Portmann B, Tung J, et al. Prognosis of alpha-1-antitrypsin deficiency-related liver disease in the era of paediatric liver transplantation. *J Hepatol* 2000;32: 986-992.
212. Prachalias AA, Kalife M, Francavilla R, Muiesan P, Dhawan A, Baker A, et al. Liver transplantation for alpha-1-antitrypsin deficiency in children. *Transpl Int* 2000;13:207-210.
213. Schilsky ML, Scheinberg IH, Sternlieb I. Prognosis of Wilsonian chronic active hepatitis. *Gastroenterology* 1991;100:762-767.
214. Schilsky ML. Wilson disease: genetic basis of copper toxicity and natural history. *Semin Liver Dis* 1996;16:83-95.
215. Roberts EA, Schilsky ML. A practice guideline on Wilson disease. *HEPATOLOGY* 2003;37:1475-1492.
216. Sokol RJ, Francis PD, Gold SH, Ford DM, Lum GM, Ambruso DR. Orthotopic liver transplantation for acute fulminant Wilson disease. *J Pediatr* 1985;107:549-552.
217. Bellary S, Hassanein T, Van-Thiel DH. Liver transplantation for Wilson's disease. *J Hepatol* 1995;23:373-381.
218. Schumacher G, Mueller AR, Platz KP, Neuhaus R, Bechstein WO, Becker M, et al. Neurologic symptoms improve in patients with Wilson's disease despite immunosuppression. *Transplant Proc* 1996;28:3099-3100.
219. Guarino M, Stracciari A, D'Alessandro R, Pazzaglia P. No neurological improvement after liver transplantation for Wilson's disease. *Acta Neurol Scand* 1995;92:405-408.
220. Eghtesad B, Nezakatgoo N, Geraci LC, Jabbar N, Irish WD, Marsh W, et al. Liver transplantation for Wilson's disease: a single-center experience. *Liver Transpl Surg* 1999;5:467-474.
221. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980;55:434-438.
222. Sheth SG, Gordon FD, Chopra S. Nonalcoholic steatohepatitis. *Ann Intern Med* 1997;126:137-145.
223. Baldrige AD, Perez-Atayde AR, Graeme-Cook F, Higgins L, Lavine JE. Idiopathic steatohepatitis in childhood: a multicenter retrospective study. *J Pediatr* 1995;127:700-704.
224. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001;120: 1183-1192.
225. Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. *HEPATOLOGY* 2002;35:373-379.
226. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *HEPATOLOGY* 2003;37:917-923.
227. Charlton M, Kasparova P, Weston S, Lindor K, Maor-Kendler Y, Wiesner RH, et al. Frequency of nonalcoholic steatohepatitis as a cause of advanced liver disease. *Liver Transpl* 2001;7:608-614.
228. Lindor KD, Kowdley KV, Heathcote EJ, Harrison ME, Jorgensen R, Angulo P, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. *HEPATOLOGY* 2004;39:770-778.
229. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *HEPATOLOGY* 1999;29:664-669.
230. Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002;123:134-140.
231. Ratzu V, Bonyhay L, Di M, V, Charlotte F, Cavallaro L, Sayegh-Tainturier MH, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. *HEPATOLOGY* 2002;35:1485-1493.
232. Contos MJ, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl* 2001;7:363-373.
233. Ong J, Younossi ZM, Reddy V, Price LL, Gramlich T, Mayes J, et al. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. *Liver Transpl* 2001;7:797-801.
234. Duchini A, Brunson ME. Roux-en-Y gastric bypass for recurrent nonalcoholic steatohepatitis in liver transplant recipients with morbid obesity. *Transplantation* 2001;72:156-159.
235. Charlton MR, Kondo M, Roberts SK, Steers JL, Krom RA, Wiesner RH. Liver transplantation for cryptogenic cirrhosis. *Liver Transpl Surg* 1997; 3:359-364.
236. Heneghan MA, Zolfino T, Muiesan P, Portmann BC, Rela M, Heaton ND, et al. An evaluation of long-term outcomes after liver transplantation for cryptogenic cirrhosis. *Liver Transpl* 2003;9:921-928.
237. Ayata G, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, et al. Cryptogenic cirrhosis: clinicopathologic findings at and after liver transplantation. *Hum Pathol* 2002;33:1098-1104.
238. Mainous AG III, Gill JM, Pearson WS. Should we screen for hemochromatosis? An examination of evidence of downstream effects on morbidity and mortality. *Arch Intern Med* 2002;162:1769-1774.
239. Asberg A, Hveem K, Kruger O, Bjerre KS. Persons with screening-detected haemochromatosis: as healthy as the general population? *Scand J Gastroenterol* 2002;37:719-724.
240. Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110:1107-1119.
241. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and noncirrhotic patients with primary hemochromatosis. *New Engl J Med* 1985;313: 1256-1262.
242. Kowdley KV, Hassanein T, Kaur S, Farrell FJ, Van-Thiel DH, Keeffe EB, et al. Primary liver cancer and survival in patients undergoing liver transplantation for hemochromatosis. *Liver Transpl Surg* 1995;1:237-241.
243. Ludwig J, Hashimoto E, Porayko MK, Moyer TP, Balduz WP. Hemosiderosis in cirrhosis: a study of 447 native livers. *Gastroenterology* 1997; 112:882-888.
244. Deugnier Y, Turlin B, le Quilleuc D, Moirand R, Loreal O, Messner M, et al. A reappraisal of hepatic siderosis in patients with end-stage cirrhosis: practical implications for the diagnosis of hemochromatosis. *Am J Surg Pathol* 1997;21:669-675.
245. Cotler SJ, Bronner MP, Press RD, Carlson TH, Perkins JD, Emond MJ, et al. End-stage liver disease without hemochromatosis associated with elevated hepatic iron index. *J Hepatol* 1998;29:257-262.
246. Fiel MI, Schiano TD, Bodenheimer HC, Thung SN, King TW, Varma CR, et al. Hereditary hemochromatosis in liver transplantation. *Liver Transpl Surg* 1999;5:50-56.
247. Brandhagen DJ, Alvarez W, Therneau TM, Kruckeberg KE, Thibodeau SN, Ludwig J, et al. Iron overload in cirrhosis-HFE genotypes and outcome after liver transplantation. *HEPATOLOGY* 2000;31:456-460.

248. Kilpe VE, Krakauer H, Wren RE. An analysis of liver transplant experience from 37 transplant centers as reported to Medicare. *Transplantation* 1993;56:554-561.
249. Farrell FJ, Nguyen M, Woodley S, Imperial JC, Garcia KR, Man K, et al. Outcome of liver transplantation in patients with hemochromatosis. *HEPATOLOGY* 1994;20:404-410.
250. Tung BY, Farrell FJ, McCashland TM, Gish RG, Bacon BR, Keeffe EB, et al. Long-term follow-up after liver transplantation in patients with hepatic iron overload. *Liver Transpl Surg* 1999;5:369-374.
251. Stuart KA, Fletcher LM, Clouston AD, Lynch SV, Purdie DM, Kerlin P, et al. Increased Hepatic iron and cirrhosis: no evidence for an adverse effect on patient outcome following liver transplantation. *HEPATOLOGY* 2000;32:1200-1207.
252. Keeffe EB. Liver transplantation in patients with hepatic iron overload: favorable or unfavorable outcome? *HEPATOLOGY* 2000;32:1396-1398.
253. Poulos JE, Bacon BR. Liver transplantation for hereditary hemochromatosis. *Dig Dis Sci* 1996;14:316-322.
254. Brandhagen DJ. Liver transplantation for hereditary hemochromatosis. *Liver Transpl* 2001;7:663-672.
255. Crawford DH, Fletcher LM, Hubscher SG, Stuart KA, Gane E, Angus PW, et al. Patient and graft survival after liver transplantation for hereditary hemochromatosis: implications for pathogenesis. *HEPATOLOGY* 2004;39:1655-1662.
256. Murray KF, Kowdley KV. Neonatal hemochromatosis. *Pediatrics* 2001;108:960-964.
257. Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). *J Inher Metab Dis* 1998;21:507-517.
258. Mohan N, McKiernan P, Preece MA, Green A, Buckels J, Mayer AD, et al. Indications and outcome of liver transplantation in tyrosinaemia type 1. *Eur J Pediatr* 1999;158(Suppl 2):S49-S54.
259. Matern D, Starzl TE, Arnaout W, Barnard J, Bynon JS, Dhawan A, et al. Liver transplantation for glycogen storage disease types I, III, and IV. *Eur J Pediatr* 1999;158(Suppl 2):S43-S48.
260. Suhr OB, Ericzon BG, Friman S. Long-term follow-up of survival of liver transplant recipients with familial amyloid polyneuropathy (Portuguese type). *Liver Transpl* 2002;8:787-794.
261. Adams D, Samuel D, Goulon-Goeau C, Nakazato M, Costa PM, Feray C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. *Brain* 2000;123(Pt 7):1495-1504.
262. Latta K, Brodehl J. Primary hyperoxaluria type I. *Eur J Pediatr* 1990;149:518-522.
263. van Woerden CS, Groothoff JW, Wanders RJ, Davin JC, Wijburg FA. Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. *Nephrol Dial Transplant* 2003;18:273-279.
264. Langman CB. The optimal approach to the patient with oxalosis. *Adv Ren Replace Ther* 2001;8:214-222.
265. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH. Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. *New Engl J Med* 1994;331:1553-1558.
266. Cibrik DM, Kaplan B, Arndorfer JA, Meier-Kriesche HU. Renal allograft survival in patients with oxalosis. *Transplantation* 2002;74:707-710.
267. Kayler LK, Merion RM, Lee S, Sung RS, Punch JD, Rudich SM, et al. Long-term survival after liver transplantation in children with metabolic disorders. *Pediatr Transplant* 2002;6:295-300.
268. Yorifuji T, Muroi J, Uematsu A, Nakahata T, Egawa H, Tanaka K. Living-related liver transplantation for neonatal-onset propionic acidemia. *J Pediatr* 2000;137:572-574.
269. van't Hoff W, McKiernan PJ, Surtees RA, Leonard JV. Liver transplantation for methylmalonic acidemia. *Eur J Pediatr* 1999;158(Suppl 2):S70-S74.
270. Chakrapani A, Sivakumar P, McKiernan PJ, Leonard JV. Metabolic stroke in methylmalonic acidemia five years after liver transplantation. *J Pediatr* 2002;140:261-263.
271. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;19:329-338.
272. Cha CH, Ruo L, Fong Y, Jarnagin WR, Shia J, Blumgart LH, et al. Resection of hepatocellular carcinoma in patients otherwise eligible for transplantation. *Ann Surg* 2003;238:315-321.
273. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;35:421-430.
274. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *HEPATOLOGY* 1999;30:1434-1440.
275. Castells A, Bruix J, Bru C, Fuster J, Vilana R, Navasa M, et al. Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. *HEPATOLOGY* 1993;18:1121-1126.
276. Curley SA, Izzo F, Ellis LM, Nicolas VJ, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. *Ann Surg* 2000;232:381-391.
277. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734-1739.
278. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *HEPATOLOGY* 2002;35:1164-1171.
279. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *HEPATOLOGY* 2003;37:429-442.
280. Iwatsuki S, Gordon RD, Shaw BW Jr., Starzl TE. Role of liver transplantation in cancer therapy. *Ann Surg* 1985;202:4:401-407.
281. Bismuth H, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 1999;19:311-322.
282. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New Engl J Med* 1996;334:693-699.
283. Sharma P, Balan V, Hernandez JL, Harper AM, Edwards EB, Rodriguez-Luna H, et al. Liver transplantation for hepatocellular carcinoma: the MELD impact. *Liver Transpl* 2004;10:36-41.
284. Yoo HY, Patt CH, Geschwind JF, Thuluvath PJ. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. *J Clin Oncol* 2003;21:4329-4335.
285. Srinivasan P, McCall J, Pritchard J, Dhawan A, Baker A, Vergani GM, et al. Orthotopic liver transplantation for unresectable hepatoblastoma. *Transplantation* 2002;74:652-655.
286. El Serag HB, Davila JA. Is fibrolamellar carcinoma different from hepatocellular carcinoma? A US population-based study. *HEPATOLOGY* 2004;39:798-803.
287. Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. *Cancer* 1999;85:562-582.
288. Ben-Haim M, Roayaie S, Ye MQ, Thung SN, Emre S, Fishbein TA, et al. Hepatic epithelioid hemangioendothelioma: resection or transplantation, which and when? *Liver Transpl Surg* 1999;5:526-531.
289. Sharif K, English M, Ramani P, Alberti D, Otte JB, McKiernan P, et al. Management of hepatic epithelioid haemangio-endothelioma in children: what option? *Br J Cancer* 2004;90:1498-1501.
290. Goldstein RM, Stone M, Tillery GW, Senzer N, Levy M, Husberg BS, et al. Is liver transplantation indicated for cholangiocarcinoma? *Am J Surg* 1993;166:768-771.
291. Hassoun Z, Gores GJ, Rosen CB. Preliminary experience with liver transplantation in selected patients with unresectable hilar cholangiocarcinoma. *Surg Oncol Clin N Am* 2002;11:909-921.
292. Trey C, Lipworth L, Chalmers TC, Davidson CS, Gottlieb LS, Popper H, et al. Fulminant hepatic failure. Presumable contribution to halothane. *New Engl J Med* 1968;279:798-801.
293. Lee WM. Acute liver failure in the United States. *Semin Liver Dis* 2003;23:217-226.

294. Lee WM. Management of acute liver failure. *Semin Liver Dis* 1996;16:369-378.
295. O'Grady JG, Gimson AES, O'Brien CJ, Pucknell A, Hughes RD, Williams R. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. *Gastroenterology* 1988;94:1186-1192.
296. O'Grady J, Alexander G, Hayllar K. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439-445.
297. Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. *Crit Care Med* 2003;31:299-305.
298. Bismuth H, Samuel D, Castaing D, Williams R, Pereira SP. Liver transplantation in Europe for patients with acute liver failure. *Semin Liver Dis* 1997;16:415-425.
299. McCashland TM, Shaw BW Jr., Tape E. The American experience with transplantation for acute liver failure. *Semin Liver Dis* 1996;16:427-433.
300. Farmer DG, Anselmo DM, Ghobrial RM, Yersiz H, McDiarmid SV, Cao C, et al. Liver transplantation for fulminant hepatic failure: experience with more than 200 patients over a 17-year period. *Ann Surg* 2003;237:666-675.
301. Ellis A, Wendon J. Circulatory, respiratory, cerebral, and renal derangements in acute liver failure: pathophysiology and management. *Semin Liver Dis* 1996;16:379-388.
302. McCormick PA, Treanor D, McCormack G, Farrell M. Early death from paracetamol (acetaminophen) induced fulminant hepatic failure without cerebral oedema. *J Hepatol* 2003;39:547-551.
303. Acharya J, Westwood NB, Sawyer BM, Messinezy M, Burroughs AK, Mehta AB, et al. Identification of latent myeloproliferative disease in patients with Budd-Chiari syndrome using X-chromosome inactivation patterns and in vitro erythroid colony formation. *Eur J Haematol* 1995;55:315-321.
304. Deltenre P, Denninger MH, Hillaire S, Guillin MC, Casadevall N, Briere J, et al. Factor V Leiden related Budd-Chiari syndrome. *Gut* 2001;48:264-268.
305. Denninger MH, Chait Y, Casadevall N, Hillaire S, Guillin MC, Bezaud A, et al. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. *HEPATOLOGY* 2000;31:587-591.
306. Ganger DR, Klapman JB, McDonald V, Matalon TA, Kaur S, Rosenblate H, et al. Transjugular intrahepatic portosystemic shunt (TIPS) for Budd-Chiari syndrome or portal vein thrombosis: review of indications and problems. *Am J Gastroenterol* 1999;94:603-608.
307. Burroughs AK, Patch D. Transjugular intrahepatic portosystemic shunt. *Semin Liver Dis* 1999;19:457-473.
308. Orloff MJ, Daily PO, Orloff SL, Girard B, Orloff MS. A 27-year experience with surgical treatment of Budd-Chiari syndrome. *Ann Surg* 2000;232:340-352.
309. Slakey DP, Klein AS, Venbrux AC, Cameron JL. Budd-Chiari syndrome: current management options. *Ann Surg* 2001;233:522-527.
310. Emre A, Kalayci G, Ozden I, Bilge O, Acarli K, Kaymakoglu S, et al. Mesoatrial shunt in Budd-Chiari syndrome. *Am J Surg* 2000;179:304-308.
311. Saigal S, Norris S, Srinivasan P, Muiesan P, Rela M, Heaton N, et al. Successful outcome of orthotopic liver transplantation in patients with preexisting malignant states. *Liver Transpl* 2001;7:11-15.
312. Ringe B, Lang H, Oldhafer K-J, Gebel M, Flemming P, Georgii A, et al. Which is the best surgery for Budd-Chiari syndrome: venous decompression or liver transplantation? A single-center experience with 50 patients. *HEPATOLOGY* 1995;21:1337-1344.
313. Srinivasan P, Rela M, Prachalias A, Muiesan P, Portmann B, Mufti GJ, et al. Liver transplantation for Budd-Chiari syndrome. *Transplantation* 2002;73:973-977.
314. Mahmoud AE, Helmy AS, Billingham L, Elias E. Poor prognosis and limited therapeutic options in patients with Budd-Chiari syndrome and portal venous system thrombosis. *Eur J Gastroenterol Hepatol* 1997;9:485-489.
315. Langnas AN. Budd-Chiari syndrome: decisions, decisions. *Liver Transpl Surg* 1997;3:443-445.
316. Olzinski AT, Sanyal AJ. Treating Budd-Chiari Syndrome: making rational choices from a myriad of options. *J Clin Gastroenterol* 2000;30:155-161.
317. Sutcliffe R, Maguire D, Ramage J, Rela M, Heaton N. Management of neuroendocrine liver metastases. *Am J Surg* 2004;187:39-46.
318. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. *Surg Oncol Clin N Am* 2003;12:231-242.
319. Olausson M, Friman S, Cahlin C, Nilsson O, Jansson S, Wangberg B, et al. Indications and results of liver transplantation in patients with neuroendocrine tumors. *World J Surg* 2002;26:998-1004.
320. Florman S, Toure B, Kim L, Gondolesi G, Roayaie S, Krieger N, et al. Liver transplantation for neuroendocrine tumors. *J Gastrointest Surg* 2004;8:208-212.
321. Jeyarajah DR, Gonwa TA, Testa G, Abbasoglu O, Goldstein R, Husberg BS, et al. Liver and kidney transplantation for polycystic disease. *Transplantation* 1998;66:529-532.
322. Chui AK, Koorey D, Pathania OP, Rao AR, McCaughan GW, Sheil AG. Polycystic disease: a rare indication for combined liver and kidney transplantation. *Hong Kong Med J* 2000;6:116-118.
323. Koyama I, Fuchinoue S, Urashima Y, Kato Y, Tsuji K, Kawase T, et al. Living related liver transplantation for polycystic liver disease. *Transpl Int* 2002;15:578-580.
324. Azoulay D, Linhares MM, Huguet E, Delvart V, Castaing D, Adam R, et al. Decision for retransplantation of the liver: an experience- and cost-based analysis. *Ann Surg* 2002;236:713-721.
325. Biggins SW, Beldecos A, Rabkin JM, Rosen HR. Retransplantation for hepatic allograft failure: prognostic modeling and ethical considerations. *Liver Transpl* 2002;8:313-322.
326. Yoo HY, Maheshwari A, Thuluvath PJ. Retransplantation of liver: primary graft nonfunction and hepatitis C virus are associated with worse outcome. *Liver Transpl* 2003;9:897-904.
327. Sieders E, Peeters PM, TenVergert EM, de Jong KP, Porte RJ, Zwaveling JH, et al. Retransplantation of the liver in children. *Transplantation* 2001;71:90-95.
328. Yao FY, Saab S, Bass NM, Hirose R, Ly D, Terrault N, et al. Prediction of survival after liver retransplantation for late graft failure based on preoperative prognostic scores. *HEPATOLOGY* 2004;39:230-238.