Liver Transplantation

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Liver transplantation has revolutionized the care of patients with end-stage liver disease. Liver transplantation is indicated for acute or chronic liver failure from any cause. Because there are no randomized controlled trials of liver transplantation versus no therapy, the efficacy of this surgery is best assessed by carefully comparing postoperative survival with the known natural history of the disease in question. The best examples of this are in primary biliary cirrhosis and primary sclerosing cholangitis, for which well-validated disease-specific models of natural history are available. There are currently relatively few absolute contraindications to liver transplantation. These include severe cardiopulmonary disease, uncontrolled systemic infection, extrahepatic malignancy, severe psychiatric or neurological disorders, and absence of a viable splanchnic venous inflow system. One of the most frequently encountered contraindications to transplantation is ongoing destructive behavior caused by drug and alcohol addiction. The timing of the surgery can have a profound impact on the mortality and morbidity of patients undergoing liver transplantation. Because of the long waiting lists for donor organs, the need to project far in advance when transplantation might be required has proven to be one of the greatest challenges to those treating patients with end-stage liver disease. Three important questions must be addressed in a patient being considered for liver transplantation: (1) when should the patient be referred for possible transplantation? (2) when should the patient be listed for transplantation? and (3) when is the patient too sick to have a reasonable chance of surviving the perioperative period?

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These guidelines provide a data-supported approach to the treatment of patients considered for liver transplantation. They are based on the following data: (1) a formal review and analysis of the recent published world literature on liver transplantation (Medline search from 1990 to 1998); (2) the American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines[1]; (3) several published and draft guidelines, including the American Association for the Study of Liver Diseases' Policy Statement on Development and Use of Practice Guidelines and the American Gastroenterological Association's Policy Statement on Guidelines[2]; and (4) 15 years' experience on the part of the author in the clinical care and education of patients before and after liver transplantation.

These guidelines, intended for use by physicians, suggest preferred approaches to the diagnostic, therapeutic, and preventative aspects of care. These guidelines are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in almost every case.[1]

Specific recommendations are based on relevant published information. In an attempt to standardize recommendations, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases modified the categories of the Quality Standards of the Infectious Diseases Society of America.[3] These categories are reported with each recommendation, using the letters A through E to determine the strength of recommendation and Roman numerals I through III to determine quality of evidence on which recommendations are based, as follows: A, survival benefit; B, improved diagnosis; C, improvement in quality of life; D, improved relevant pathophysiological parameters; E, impacts on costs of health care; I, evidence from multiple well-designed, randomized, controlled trials, each involving a number of participants to be of sufficient statistical power; II, evidence from at least one large, well-designed clinical trial with or without randomization from cohort or case-control analytic studies or from well-designed meta-analyses; III, evidence based on clinical experience, descriptive studies, or reports of expert committees; and, IV, not rated.

Introduction

Because of logistic restraints, no randomized trials have been performed to prove the efficacy of liver transplantation. However, various registries provide a wealth of information concerning the outcome of liver transplantation for various conditions. These guidelines have been developed to reflect a consensus from the literature and outcomes data comparing transplant results with the natural history of selected disease states, as well as the views of most experts involved in liver transplantation.

Background

Liver transplantation has revolutionized the care of patients with end-stage liver disease. Before transplantation, patients with advanced liver disease were doomed to death within months to years. These patients now have the opportunity for extended survival with excellent quality of life after transplantation.[4] The exponential increase in transplantations over the past two decades appears to have impacted favorably on chronic liver disease mortality in the United States.[5] Nevertheless, many issues remain, including specific indications and contraindications to transplantation, the optimum timing of the surgery, 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 most frequent indications for liver transplantation include: (1) chronic liver failure from cholestatic disorders (e.g., primary biliary cirrhosis [PBC], sclerosing cholangitis [PSC], and extrahepatic biliary atresia); chronic hepatitis (e.g., hepatitis B, hepatitis C, and autoimmune hepatitis); alcoholic liver disease; metabolic diseases (e.g., Wilson's disease, hereditary tyrosinemia type I, hereditary hemochromatosis, alpha$_1$-antitrypsin deficiency, nonalcoholic steatohepatitis); and cirrhosis of unknown cause (cryptogenic cirrhosis); (2) acute liver failure (fulminant hepatic failure [FHF]) of any cause; (3) hepatocellular carcinoma [HCC]; and (4) other indications.

Other less common indications for which liver transplantation may be required include end-stage liver disease secondary to a variety of metabolic conditions (for example, erythropoietic protoporphyria, cystic fibrosis, glycogen storage diseases, and progressive familial intrahepatic cholestasis [Byler's disease]) and metabolic disorders that cause such profound extrahepatic manifestations that transplantation of an anatomically normal liver may be justified (hereditary oxalosis, Crigler-Najjar syndrome, familial amyloidosis, and hyperammonemic syndromes). Other infrequent indications for liver transplantation include liver failure from hepatic vein occlusion (Budd-Chiari syndrome and veno-occlusive disease) and polycystic disease.

Outcome After Transplantation

Given the absence of randomized controlled trials of transplantation versus conservative management, the role of transplantation can best be addressed by comparing the outcome of transplantation with the natural history of the disease in question. The most useful studies comparing results of liver transplantation with natural history have used prognostic models for specific disease states. The best examples of this approach have been in patients with such cholestatic disorders as PBC and PSC.

Cholestatic Disorders

PBC. A chronic destructive disorder of interlobular bile ducts that can progress to cirrhosis and liver failure over several decades, PBC most commonly affects women in the fourth to seventh decades of life. Ursodeoxycholic acid therapy may improve survival and delay the need for transplantation.[6] However, there is no other proven treatment for PBC, and if not undergoing transplantation, many patients ultimately die of hepatic failure.

Most liver transplant centers now report 1-year survival rates of 85% to 90% and 5-year survival rates of 70% to 80% in patients with PBC.[7,8] When the outcome of patients with PBC after liver transplantation is compared with their estimated prognosis using the Mayo Clinic model, transplantation dramatically improves survival.[7] The survival benefit of transplantation is evident as soon as 3 months after surgery, with 2-year survival of patients who underwent transplantation more than twice that predicted for those treated conservatively.[9] These results, independently confirmed by other groups, provide the most compelling evidence that liver transplantation improves survival among patients with chronic liver disease.[7]

PSC. 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.[10] Direct radiographic visualization of the bile ducts by endoscopic, percutane-

ous, or operative cholangiography is required for accurate diagnosis.

The natural history of patients with PSC is quite variable. Some asymptomatic patients survive for prolonged periods of time without developing significant complications of the disease.[11] However, the majority of patients with symptomatic PSC have a progressive disease that typically results in liver failure within 10 to 12 years.[12] No specific treatment has been shown to improve survival in patients with PSC.[12]

In recent series, transplant outcomes for patients with PSC equal or surpass those reported for PBC, with 3-year survival rates greater than 90%.[13] Using disease-specific prognostic models developed for PSC, survival after liver transplantation has been far superior to that predicted for patients treated conservatively.[14-16]

Recommendations

Liver transplantation is indicated for appropriately selected patients with advanced PBC or PSC (rating, II A, III CD).

Childhood cholestatic disorders. Chronic cholestasis in children can result from a variety of conditions, including extrahepatic biliary atresia, alpha$_1$-antitrypsin deficiency, various types of intrahepatic cholestasis, and PSC. Extrahepatic biliary atresia is the most common cause of chronic childhood cholestasis. Children with this disorder account for more than 50% of all pediatric liver transplantations.

Extrahepatic biliary atresia is a destructive inflammatory process of unknown cause that results in fibrosis and obliteration of the intrahepatic and extrahepatic bile ducts. If untreated, death usually ensues within the first 1 to 2 years of life.[17] There is no effective medical therapy for children with extrahepatic biliary atresia. However, if the diagnosis can be established within the first few months of life, anastamosis of bile duct remnants in the porta hepatis to a loop of bowel (Kasai portoenterostomy) can result in survival into childhood in as many as 70% of infants.[18] As a consequence, portoenterostomy performed within the first 3 months of life by an experienced surgeon is considered the treatment of choice for children with extrahepatic biliary atresia. However, if the diagnosis is delayed beyond 3 months, successful results from the Kasai procedure are dramatically reduced. Children who are not offered surgery because of a delay in diagnosis, as well as those with unsuccessful Kasai procedures, require liver transplantation. Small children who need a transplant within the first 6 months of life can successfully undergo transplantation using a reduced-size donor organ or a portion of the liver from a living related donor.[19,20] In addition, most children with successful Kasai procedures develop cirrhosis and progressive portal hypertension over a period of years. These children also require liver transplantation to have any hope of long-term survival.[17]

There are no controlled studies directly comparing liver transplantation with the Kasai procedure. 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 are diminished surgical mortality and reduction in severe postoperative viral infections and lymphoproliferative disorders.[21] These benefits must be weighed against the increased blood loss, longer surgical time, and increased perioperative complications of transplantation in children with a previous portoenterostomy.[22] However, recent surgical series do not suggest increased perioperative mortality in such children.[22]

Other less common causes of chronic cholestasis in children include syndromic (Alagille's syndrome) and nonsyndromic types of intrahepatic cholestasis, as well as PSC in adolescents. Approximately 20% of children with Alagille's syndrome develop cirrhosis. Although the number of transplantations performed for these conditions are limited, the results appear to approximate those seen for other chronic cholestatic conditions, and in many children, growth is accelerated after successful transplantation.[23]

Recommendations

Liver transplantation is indicated in appropriately selected children with extrahepatic biliary atresia if the diagnosis is delayed beyond 3 months after birth, portoenterostomy is unsuccessful, or intractable portal hypertension or liver failure develop despite a successful Kasai procedure (rating, III AC).

Chronic Hepatitis

Chronic hepatitis from a number of causes can progress to end-stage liver disease. The most common of these are chronic hepatitis C, chronic hepatitis B, and autoimmune hepatitis.

Hepatitis C. Approximately 3.9 million Americans are chronically infected with hepatitis C.[24] It is estimated that 20% of the patients develop cirrhosis within 20 years after developing this chronic infection.[25] Chronic alcohol abuse appears to accelerate this process.[26] Although patients with well-compensated cirrhosis have an estimated 10-year survival rate greater than 80%, once complications develop, the 5-year survival rate decreases to less than 50%.[27] Patients with

cirrhosis also have a 1% to 4% risk for developing HCC each year.[28] Current therapy with interferon and other antiviral agents results in sustained virological and histological remission of disease in only a minority of patients.[29-31] Antiviral treatment of patients who have cirrhosis and evidence of hepatic failure is not recommended.[32]

It is estimated that end-stage liver disease secondary to chronic hepatitis C virus infection accounts for 8,000 to 10,000 deaths annually in the United States.[24] As a result, this condition has become the leading reason for liver transplantation in adults. Although persisent viremia with hepatitis C virus is virtually universal after liver transplantation, postoperative survival is similar to that seen for patients who undergo transplantation for all conditions, with 7-year survival rates of approximately 60%.[33-35] However, longer term prospective trials to address natural history and postoperative antiviral treatment of persistent hepatitis C after transplantation are needed.

Hepatitis B. The natural history of patients with chronic hepatitis B is variable. Some patients develop progressive liver injury, cirrhosis, and HCC. The prognosis of individual patients is closely related to the severity of histological injury and the presence of ongoing viral replication. For example, the 5-year survival rate of hepatitis B e antigen–positive patients with cirrhosis is only 50%.[36,37]

Approximately 30% to 40% of the patients with chronic hepatitis B who are hepatitis B e antigen positive have a sustained virological response to treatment with interferon therapy.[38] Although occasional patients with decompensated cirrhosis have responded to low-dose interferon therapy, such treatment is not recommended outside of carefully controlled trials because life-threatening infections and severe neuropsychiatric complications are common.[39] A variety of newer antiviral agents are being tested in patients with chronic hepatitis B. Their efficacy and safety remain to be determined.[40,41]

The early results of liver transplantation for hepatitis B were discouraging. Although perioperative survival was the same as for other conditions, many patients who underwent transplantation for cirrhosis secondary to chronic hepatitis B developed rapidly progressive recurrent disease (fibrosing cholestatic hepatitis) that resulted in death within 12 to 18 months after transplantation.[42,43] Attempts at retransplantation often accelerated this process. As a result, by the early 1990s, many programs refused to offer transplants to patients with chronic hepatitis B.

The recognition that continuous administration of hepatitis B immune globulin (HBIG) could diminish both the reinfection rate and the severity of recurrent hepatitis B dramatically altered the outlook on transplantation for patients with chronic hepatitis B. It also became apparent that patients with FHF secondary to hepatitis B and patients coinfected with delta virus were less likely to have recurrent hepatitis B virus infection after transplantation.[44] With the use of continuous HBIG, short-term survival of patients who undergo transplantation for chronic hepatitis B approximates that of patients who undergo transplantation for other conditions.[44] However, HBIG is costly and must be administered for the lifetime of the patient. For this reason, other strategies using nucleoside analogues for hepatitis B are being explored by many transplant centers.[45,46]

Autoimmune hepatitis. This condition of unknown cause affecting primarily women can result in progressive inflammation and fibrosis of the liver, with subsequent cirrhosis and hepatic failure. Patients with autoimmune hepatitis may initially present with severe jaundice, ascites, and hepatic encephalopathy or more insidiously with chronic mild abnormalities of liver function test results. Corticosteroid therapy is associated with clinical remission of disease in 80% of the patients, prolongs immediate survival, and results in 10-year survival rates of 90%.[47,48] Nevertheless, some patients develop intractable portal hypertension and slowly progressive liver failure despite biochemical response to treatment.

Liver transplantation is the only effective treatment for patients with severe autoimmune hepatitis in whom immunosuppressive therapy fails or who develop advanced decompensated disease despite treatment. Outcome after liver transplantation is excellent, with reported 5-year survival rates greater than 90% in adults.[49] However, the outcome in children may be less favorable.[50]

Recommendations

Liver transplantation is indicated for appropriately selected patients with decompensated cirrhosis secondary to chronic hepatitis C, hepatitis B, or autoimmune hepatitis. Patients undergoing transplantation for hepatitis B need specialized management to prevent severe recurrent disease after transplantation (rating, III ACD).

Alcoholic Liver Disease

Alcoholic liver disease is the most common cause of cirrhosis and end-stage liver disease in the United States and in most developed countries. It is estimated that 12,000 deaths occur annually from alcoholic liver

disease in the United States.[51] Abstinence is the only effective treatment for most patients, and even among patients with cirrhosis, it is associated with a dramatic increase in survival.[52,53] As a result, many patients with apparently far-advanced alcoholic liver disease can recover to the degree that transplantation is not required. Unfortunately, there is no effective means of predicting which patients will have such a dramatic response to abstinence.

The outcome after liver transplantation for alcoholic liver disease is similar to that of patients who undergo transplantation for most other conditions, with 7-year survival rates of 60%.[54-56] Rejection, graft failure, and the need for retransplantation are less common in patients with alcoholic liver disease than among patients who undergo transplantation for other conditions.[57] Although complete abstinence rates vary considerably from center to center, graft loss as a consequence of destructive drinking after transplantation is uncommon.[58-61]

More than 85% of the transplant programs in the United States require 6 months of abstinence before transplantation, and careful evaluation by professional counselors is important to directly address the addiction to alcohol.[62] Successful completion and adherence to a formal treatment program may be necessary.[63] The reasons for this are twofold: (1) to allow patients every opportunity for spontaneous recovery to avoid the need for unnecessary transplantation, and (2) to minimize the risk for self-destructive drinking after transplantation.

Recommendations

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

Metabolic Diseases

A variety of metabolic diseases can result in progressive liver injury and cirrhosis. The most common of these are hereditary hemochromatosis, alpha$_1$-antitrypsin deficiency, and Wilson's disease.

Heriditary hemochromatosis. The most common inherited disorder among persons of Northern European descent, this autosomal recessive disorder has an estimated disease prevalence of 1:200 to 1:300 among whites. Chronic iron accumulation over many years can result in cirrhosis, HCC, cardiomyopathy, diabetes mellitus, arthritis, and hypogonadism. If diagnosed before the development of cirrhosis, iron depletion with long-term phlebotomy results in a normal life expectancy.[64] However, if the diagnosis is delayed until after the development of cirrhosis, survival is diminished and the risk for HCC is increased despite adequate iron depletion.[65]

Liver transplantation is the only treatment for patients with decompensated cirrhosis from hemochromatosis. Unfortunately, the results have been disappointing. Postoperative survival is significantly less than that for patients who undergo transplantation for other conditions.[66-68] Although not well characterized, these suboptimal results appear to result from a high rate of postoperative infection and occasional deaths from cardiomyopathy.[69,70]

Recommendations

Liver transplantation is indicated for carefully selected patients with hereditary hemochromatosis. However, because the results have been disappointing, more research is needed to determine the optimum use of transplantation in these patients (rating, III D).

Alpha$_1$-antitrypsin deficiency. This deficiency is the most common inherited cause of liver disease for which liver transplantation is performed in children.[71] Although the frequency of this codominant recessive disorder is 1:2,000 to 1:7,000, only a minority of individuals with the PiZZ phenotype develop liver disease.[72] Children with alpha$_1$-antitrypsin deficiency often present with neonatal cholestasis. In most of these children, the jaundice gradually resolves, but within the first decade of life, 25% develop cirrhosis. Another 25% present with cirrhosis during the second decade of life. Cirrhosis secondary to alpha$_1$-antitrypsin deficiency can have its first presentation at any age.[73,74]

Liver transplantation is the only treatment for decompensated cirrhosis secondary to alpha$_1$-antitrypsin deficiency. After transplantation, the donor alpha$_1$-antitypsin phenotype is expressed. Serum levels of alpha$_1$-antitrypsin return to normal range within weeks after transplantation. Although reported series are small, the long-term outcome of these patients after liver transplantation appears to be excellent.[75,76]

Recommendations

Selected patients with severe liver disease secondary to alpha$_1$-antitrypsin deficiency should be considered for liver transplantation (rating, III ACD).

Wilson's disease. Wilson's disease is an autosomal recessive disorder of copper excretion that can result in

either severe acute or chronic hepatitis with liver failure.[77,78] Other complications of the disease include neurological dysfunction, hemolytic anemia, and renal involvement. Most patients presenting with chronic liver disease respond dramatically to chelation therapy with penicillamine or trientene and have long-term sustained remissions of the disease.[79] In contrast, patients who present with FHF invariably die unless urgent liver transplantation can be performed. Liver transplantation is the only treatment for patients with FHF, those with chronic liver disease who fail to respond to chelation therapy, or for recurrent disease in patients who discontinue treatment.[80-82]

Liver transplantation usually reverses the metabolic abnormalities associated with Wilson's disease; however, long-standing neurological dysfunction may not improve in some patients.[83-85] Survival rates 1 year after transplantation have ranged from 70% to 90%. Although the reported series are small, long-term survival appears to be excellent. Copper chelation therapy is not required after transplantation.

Recommendations

Liver transplantation is indicated in selected patients with Wilson's disease who present with FHF and in those with chronic liver disease who fail to respond to chelation therapy or who relapse after discontinuing therapy (rating, III ACD).

Hepatobiliary Malignancies

HCC. HCC is an uncommon but often fatal complication of cirrhosis from any cause. Patients with chronic hepatitis B, chronic hepatitis C, and hemochromatosis are at particularly high risk for developing HCC. In addition, almost all children with tyrosinemia surviving to early childhood develop HCC. Although primary hepatic resection has been considered the treatment of choice for HCC, 5-year survival rates in patients with cirrhosis are only 25% to 60%, and less than half these patients are free of tumor.[86] Furthermore, most patients referred for resection are rejected because the tumor is nonresectable or hepatic reserve is considered inadequate.[87] Percutaneous alcohol injection is effective in tumors less than 3 cm in size but is far less successful for larger tumors.[88-90] Other treatment modalities, such as chemotherapy and tumor embolization, may be useful in individual patients but have not been shown to improve survival in patients with HCC.[90,91]

The early results of liver transplantation for nonresectable HCC were quite discouraging.[92-94] Despite having extremely good quality of life after transplantation, within 2 years, 90% of the patients developed recurrent disease, often within the engrafted liver. In contrast, patients with small hepatomas discovered during the transplant evaluation or at pathological dissection of the resected liver have done well, with only occasional recurrent disease. Historic experience suggests that the best HCC candidates for transplantation are those with a single lesion less than 5 cm in diameter or, if more than one lesion is present, no lesion greater than 3 cm in diameter.[86,95] However, patients with large epitheliomas or fibrolamellar hepatomas usually do well.[93] If patients are to undergo successful transplantation, they should have no radiologic evidence of vascular invasion or metastatic disease.[96]

Unfortunately, because of the long waiting list for liver transplantation, many patients with small HCCs who are optimum candidates for transplantation develop progressive disease before an appropriate donor organ can be found.

Numerous retrospective series have shown the superiority of liver transplantation over primary surgical resection in patients with cirrhosis, even for small tumors.[97,98] However, no series has prospectively compared the results of placing patients on a transplant waiting list versus immediate surgical resection. Control of tumors during the transplant waiting period has been attempted with chemotherapy, tumor embolization, and alcohol injection, but these approaches have not been proven to be beneficial in well-controlled randomized trials.[98]

Cholangiocarcinoma. The outcome of liver transplantation for cholangiocarcinoma has been particularly frustrating. Even small tumors with no evidence of local invasion have almost invariably recurred within a few years after transplantation.[99]

Metastatic tumors. The results of performing liver transplantation for nonresectable metastatic tumors to the liver have been predictably disappointing.[93] The only exception has been slow-growing neuroendocrine tumors that produce devastating extrahepatic manifestations.[100]

Recommendations

Liver transplantation can be very effective treatment for patients with cirrhosis in whom HCC is confined to the liver. The best candidates for transplantation are those with single tumors less than 5 cm in size or multiple tumors, each less than 3 cm in size. Patients with radiologic evidence of vascular invasion or metastatic disease are not candidates for transplantation. Because of the extraordinary risk for HCC, children

with tyrosinemia should be considered for transplantation at an early age. Patients with cholangiocarcinoma or metastatic tumors (excluding neuroendocrine tumors) should not undergo liver transplantation except in carefully controlled trials (rating, III AC).

FHF

FHF is defined as the development of hepatic encephalopathy and profound coagulopathy within 8 weeks of the onset of symptoms in patients without preexisting liver disease.[101] 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, and Wilson's disease.[102-104] In many cases, the precise cause is never discovered.[105,106]

A subset of patients have a delayed onset of hepatic decompensation that occurs from 8 weeks to 6 months after the onset of symptoms. This clinical syndrome has been variously referred to as subacute hepatic failure, late-onset hepatic failure, subacute hepatic necrosis, or subfulminant hepatic failure.[107] These patients rarely recover without transplantation.

There is no specific therapy for FHF.[108] However, if given appropriate critical care support, many patients spontaneously recover. In the vast majority of these patients, recovery is complete, with no evidence of residual liver injury. The prognosis for spontaneous recovery depends on the patient's age, underlying cause, and severity of liver injury.[109,110] Children younger than 10 years of age and adults aged older than 40 years rarely recover spontaneously from FHF.

Although most patients with FHF are young with no preexisting liver injury, survival after liver transplantation for FHF has been somewhat disappointing.[111,112] In part, this is caused by the rapid development of cerebral edema and multiorgan failure within days to weeks of clinical presentation.[103,113] Many of these patients receive marginal or even blood type group A, group B, group O–incompatible organs because of the extremely narrow window of time in which transplantation can be performed. Nevertheless, this is the only viable therapeutic option for many patients with this rapidly fatal condition.

Recommendations

Patients with suspected FHF should be referred to a transplant center as quickly as possible. Patients with FHF with progressive encephalopathy and coagulopathy should receive the highest priority for liver transplantation (rating, III ACD).

Contraindications to Transplantation

There are few absolute medical or surgical contraindications to liver transplantation. There is no specific age limitation to successful transplantation.[114,115] Patients must have adequate cardiac and pulmonary function to tolerate major surgery. Patients with cirrhosis can develop significant hypoxia or pulmonary hypertension.[116] Moderate abnormalities of gas exchange or pulmonary pressures are not a deterrent to successful transplantation.[117,118] However, patients with severe hypoxia or right atrial pressure greater than 60 mm Hg rarely survive surgery and the perioperative recovery period.[118] Uncontrolled systemic infection is an obvious contraindication to high-dose immunosuppressive therapy. In addition, the prognosis of other serious medical conditions should be reasonable if transplantation is to be contemplated. Patients with extrahepatic malignancies other than squamous cell skin carcinoma should be deferred for at least 2 years after completion of curative therapy before transplantation is attempted.[119] Finally, significant psychiatric or neurological disorders must be under excellent medical control with assurance that the patient can be compliant after transplantation.

Absence of a viable splanchnic venous inflow system is the most commonly encountered surgical contraindication to liver transplantation. Thrombosis of the main portal vein can be successfully bypassed; however, if the entire portal venous system is occluded, attempts at transplantation have rarely been successful.[120,121]

The final and most frequently encountered contraindication to transplantation is ongoing destructive behavior caused by drug and alcohol addiction. Medical compliance should be effectively addressed before patients are considered for transplantation.

Selection of Patients for Transplantation

It is estimated that 26,000 deaths occur annually from liver disease in the United States.[51] Although the absolute number of donors has increased over the past decade, it has been overwhelmed by the number of potential recipients listed for transplantation. Because of this rapidly escalating discrepancy between supply and demand for donor organs, most patients with end-stage liver disease cannot be offered the opportunity for liver transplantation. As a result, patients to be considered for transplantation must be carefully selected if optimum use of scarce donor organs is to occur.

To be accepted for liver transplantation, patients should have no obvious medical or surgical contraindi-

cations to successful surgery. In addition, they must understand and comply with continuous therapy with immunosuppressive medications and other treatments necessary for successful long-term outcome after surgery. They need significant support from family or friends during the early postoperative period, particularly immediately after discharge from the hospital. In particular, children undergoing liver transplantation need a stable home environment.

Any form of addictive behavior must be addressed frankly and be well controlled before patients are accepted for transplantation. This may require extensive counseling, inpatient or outpatient treatment programs, and well-verified periods of abstinence.

Recommendations

Patients should only be considered for transplantation if they have a reasonable chance of surviving the perioperative period. Those selected must be able to comply with long-term medication therapy and refrain from addictive forms of behavior. They should have no other major medical illness significantly curtailing life expectancy (rating, III ACE).

Timing of Transplantation

Timing of the surgery can have a profound impact on both the mortality and morbidity of liver transplantation. When patients receive a transplant before they develop multisystem complications of end-stage liver disease, perioperative survival is excellent.[122,123] In contrast, debilitated patients with multiorgan failure before transplantation have only a 20% to 30% chance of surviving and often require weeks to months of postoperative hospitalization.[123] This dilemma underlies the ongoing debate about the optimum allocation of donor organs.

The need to project far in advance when transplantation might be required is one of the major challenges in treating patients with severe acute and chronic liver diseases. This has forced transplant physicians to develop better means of determining prognosis at various stages of these illnesses and to pose a series of critical clinical questions about each patient considered for liver transplantation.

Prognostic Tools in Acute and Chronic Liver Disease

One of the first challenges has been to develop accurate, well-accepted, and widely available means to effectively determine the prognosis of patients at various stages of disease. A number of pharmacological approaches to determining liver function have been explored, including caffeine breath tests, monoethylglycinexylidide (MEGX) clearance, and indocyanine green clearance. However, none appears superior to simple clinical tests in determining the prognosis of patients with end-stage liver disease.[124]

Prognostic tools in chronic liver disease. The clinical tools most widely used to determine prognosis in patients with chronic liver diseases include disease-specific indices for PBC and PSC and the Child-Turcotte-Pugh (CTP) classification, as well as the clinical impact of specific complications of cirrhosis on patient survival.

The Mayo Clinic prognostic model for PBC is the best validated tool for determining the prognosis of groups of patients with chronic liver disease.[125] It does not require such invasive procedures as liver biopsy and can be repeated over time.[126] However, it requires the use of a programmed calculator or computer. Furthermore, neither variceal bleeding nor ursodeoxycholic acid therapy were included in the design of the model. A number of disease-specific models also have been developed for PSC.[14,15] However, each requires a liver biopsy. As a result, they cannot be used in patients with contraindications to biopsy and cannot be repeated over time to reassess the prognosis of individual patients. Furthermore, it is not clear whether these models add to such simple means of assessment as the CTP classification in determining the prognosis of individual patients with PSC.[127]

The CTP, designed to stratify the risk of portacaval shunt surgery in patients with cirrhosis with variceal bleeding, has recently gained favor as a simple method for determining the prognosis of patients with chronic liver disease.[128] Although never formally validated as a prognostic tool, it is useful as a rapid means of assessing the relative risk for mortality among groups of patients with cirrhosis. The CTP is as effective as MEGX and indocyanine green clearance in determining short-term prognosis among patients awaiting liver transplantation.[124] Although its limitations have been well described, the CTP has become widely adopted for risk stratifying of patients before transplantation because of its simplicity and ease of use.[129] However, it has not been validated in children.

More than a third of the patients with CTP scores greater than 10 (class C) who are waiting for transplantation can be expected to die within a year.[124,127] In contrast, patients with CTP scores of 7 to 9 have an 80% chance of surviving 5 years, and those with CTP scores of 5 to 6 have a 90% chance of surviving more than 5 years without transplantation.[127,130]

The development of ascites, variceal bleeding, he-

patic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome also can have a significant impact on the prognosis of patients with cirrhosis. The 5-year survival rate of patients who develop any of these complications is only 20% to 50% of that of patients with compensated cirrhosis.[27,131] The most ominous of these complications are spontaneous bacterial peritonitis and hepatorenal syndrome. Less than half of those who develop spontaneous bacterial peritonitis can be expected to survive a year, whereas the median survival among patients with hepatorenal syndrome is less than 2 weeks.[132,133]

Prognostic tools in FHF. The prognosis of individual patients with FHF varies widely. Some patients have an excellent chance of spontaneous recovery. Other patients have such a dismal prognosis that transplantation is their only hope for survival. Finally, some patients become so critically ill from multisystem disease that heroic therapeutic efforts are futile.

The underlying cause is the single most important predictor of outcome in patients with FHF.[134] Patients with fatty liver of pregnancy, acetaminophen ingestion, or hepatitis A have an excellent chance for spontaneous recovery. Patients with hepatitis B have an intermediate prognosis, whereas those with hepatotoxicity from drugs other than acetaminophen or FHF of unknown cause have less than a 20% chance of recovery without transplantation. Patients with fulminant Wilson's disease rarely recover spontaneously and need urgent transplantation if they are to survive.

Among patients with FHF caused by an overdose of acetaminophen, arterial pH less than 7.30 at the time of admission is highly predictive of a fatal outcome.[134] Among patients with admission pH values greater than 7.30, the triad of prothrombin international normalized ratio (INR) greater than 6.5, serum creatinine level greater than 3.5 mg/dL (300 μmol/L), and grade III or IV encephalopathy are the most ominous prognostic signs.[134,135]

In patients with FHF from other causes, prothrombin time INR values greater than 6.5 offer the most ominous prognosis. Most patients with values this high die unless transplantation can be performed urgently. Among patients with lesser degrees of prothrombin time prolongation, unfavorable cause, age younger than 10 years or older than 40 years, jaundice for greater than 7 days before encephalopathy, and bilirubin values greater than 18 mg/dL (300 μmol/L) are associated with a poor prognosis.[134,135]

The Acute Physiology, Age, and Chronic Health Evaluation (APACHE) prognostic index is a systematic method of assessing intensive care unit mortality in critically ill patients.[136] It offers considerable promise in assessing the severity of multisystem disease in patients with FHF and chronic liver disease.[137] In addition, it may be the best method available for systematically determining the futility of providing extraordinary care in patients with overwhelming systemic disease.

Prognosis-Based Timing of Transplantation

It is generally agreed that the ideal timing of liver transplantation occurs when patients have less than a 50% chance of surviving 1 to 2 years but before they develop multisystem disease. Unfortunately, because of the extended length of time many patients are forced to wait for an appropriate donor organ, the time at which transplantation can be offered is at best an approximation of this goal.[138] To provide patients the best chance for a successful outcome after liver transplantation, physicians must work together carefully from the time a serious acute or chronic liver disease is identified.

Three interdependent questions become the focal point of this planning: (1) when should patients be referred for possible transplantation? (2) when should they be placed on the donor waiting list? and (3) when should patients be declared too ill to have a reasonable chance of surviving surgery and the perioperative recovery period?

When should patients be referred for possible transplantation? Inappropriate early referral for transplantation can unnecessarily frighten patients and their families and foster confusion between patients and physicians. For example, patients with well-compensated cirrhosis (CTP scores of 5 to 6) who have not experienced such major complications as ascites or variceal hemorrhage have a 90% chance of surviving 5 to 10 years without transplantation.[27,127]

A far more lethal miscalculation occurs when referral is delayed to the point that patients have little or no chance of surviving until a donor organ can be obtained. Waiting until patients have developed intractable ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome before referral frequently results in death before transplantation.

Based on currently available knowledge of the natural history of liver diseases, it appears that a reasonable compromise between these two extremes is to refer patients for transplantation when they begin to show evidence of synthetic dysfunction or malnutrition or when the first complication of cirrhosis occurs. At this stage of disease, most patients can be expected

to survive the 1 to 2 years required for acquisition of a donor organ.

Patients with cirrhosis and hepatocellular malignancies should be referred as soon as the tumor is discovered if transplantation is to be considered.

Because patients with FHF can deteriorate quickly, they should be referred when a persistently elevated prothrombin time or the first alteration in mental status is identified. Early referral of these patients is necessary to minimize the risk of aspiration and other complications during transit.[112]

Recommendations

Patients with cirrhosis should be referred for transplantation when they develop evidence of synthetic dysfunction, experience their first major complication (ascites, variceal bleeding, or hepatic encephalopathy), or develop malnutrition. Children with chronic liver disease should be referred when they fall off their growth curves. If patients with cirrhosis and hepatocellular malignancies are to be considered for transplantation, they should be referred as soon as the tumor is recognized. Patients with potential FHF should be referred as soon as a persistently prolonged prothrombin time is identified or at the first sign of hepatic encephalopathy (rating, III ACE).

When should patients be listed for transplantation? There is general agreement that patients should not be placed on the transplant waiting list until their predicted chance of surviving 1 year is 90% or less.[139] Patients with cirrhosis and a CTP score of 7 or greater or any patient who has experienced gastrointestinal bleeding caused by portal hypertension or a single episode of spontaneous bacterial peritonitis, irrespective of CTP score, meet this criterion.[139]

Selected patients with cirrhosis with hepatocellular malignancies confined to the liver should be listed for transplantation irrespective of CTP score. However, if evidence of portal vein invasion or local or distal metastases occurs, these patients should be removed from the transplant waiting list and other options should be considered.

Patients with well-documented acetaminophen toxicity and arterial pH less than 7.3 should be listed immediately for transplantation.[137] Adult patients with FHF should be listed for transplantation at the onset of stage 2 hepatic encephalopathy.[139] The nature of FHF in children may mandate earlier listing. Although listed for transplantation, these patients should continue to receive careful observation because many, particularly those with acetaminophen overdose or hepatitis A, will recover spontaneously.

Recommendations

Adult patients with cirrhosis should be listed for transplantation once the CTP score is 7 or greater. Patients with FHF should be listed if the pH is less than 7.3 (acetaminophen toxicity) or if grade 2 hepatic encephalopathy develops (rating, III AC).

When are patients too sick to have a reasonable chance of surviving? Because of the rapidly progressive nature of the disease, only two thirds of the patients with FHF who meet the prognostic criteria for transplantation remain hemodynamically stable long enough to undergo surgery.[137] Many patients develop cerebral edema or multiorgan failure before a donor organ can be procured. Loss of oculovestibular reflexes and depressed cerebral perfusion pressures that cannot be easily controlled are almost invariably associated with irreversible brain stem damage.[140] Furthermore, patients who require continuous pressor support to maintain an adequate blood pressure cannot tolerate the rigors of major surgery. The APACHE III criteria may be a useful adjunct to clinical judgment in identifying these patients.[137]

Patients with severe chronic liver failure who require intubation have an extremely poor prognosis, with reported hospital mortality rates of 90% to 95%.[141] Patients with CTP scores greater than 10 who have evidence of advanced multisystem disease have the least chance of surviving. Although the majority of these patients will otherwise die, futile attempts at transplantation add greatly to the cost of the surgery and further diminish the limited supply of donor organs for more appropriate candidates. Unfortunately, there are no universally accepted criteria for identifying patients with chronic liver disease who are too ill to undergo the surgery.

Exceptional Situations

Certain patients need transplantation before they develop end-stage liver disease. For example, quality of life can be so profoundly affected by extrahepatic manifestations of certain liver diseases that transplantation is indicated irrespective of CTP score. Examples include children with severe defects in bilirubin or ammonia metabolism and patients with oxalosis, amyloidosis, or polycystic disease.

Summary and Conclusions

Liver transplantation offers the greatest hope for survival currently available for patients with severe acute and chronic liver diseases in whom other available forms of therapy have failed. To use the limited supply of donor organs judiciously, careful selection of patients to be considered for transplantation is required. The most difficult challenge in managing potential transplant candidates is optimizing the timing of surgery. This requires close cooperation of all physicians who treat these patients.

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