

Update On Liver Transplantation: Indications, Organ Allocation, and Long-Term Care

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Abstract

Liver transplantation (LT) is definitive treatment for patients with acute liver failure and end-stage liver disease and in a subset of primary hepatic malignancies. For patients who successfully undergo LT, the probability of long-term graft and recipient survival is generally excellent, with a high likelihood of return to a relatively normal lifestyle. This article will review current indications, contraindications and postoperative care in LT. With the number of potential recipients far exceeding the number of deceased donor organs, new strategies are being explored to increase access to LT, including: splitting cadaveric donor livers, the use of living donors, and the adoption of the Model for End-Stage Liver Disease (MELD) scoring system, which is based on a mathematical formula to stratify patients in greatest need of transplantation. The allocation of deceased donor organs will, however, remain a contentious issue unless the donor pool is greatly expanded.

Key Words: Liver transplantation.

Introduction

ALTHOUGH THE FIRST HUMAN liver transplantation (LT) was done in 1963 (1), it has been only in the last two decades that orthotopic liver transplant (OLT) has achieved one-year survival rates of 80–90% (2). According to the United Network for Organ Sharing (UNOS), there are currently more than 17,000 patients on the national waiting list for OLT, but in 2005, only 5,435 liver transplants were performed (3). Thus, many patients die while awaiting organ transplant. This large disparity between the number of available deceased donor organs and qualified recipients awaiting OLT has created an ongoing debate regarding selection criteria, timing of OLT, and attempts to expand the donor pool as mortality for listed patients rises.

There are related issues as well. For example, transplant may not cure the underlying liver disease, and recurrent liver disease after LT remains a major challenge.

Indications and Contraindications

LT is indicated for most causes of acute or chronic liver disease. Cirrhosis accounts for more than 80% of transplants performed in adults, with hepatitis C and alcoholism being the two most common diagnoses (2). Other indications include the cholestatic liver disorders (primary biliary cirrhosis, sclerosing cholangitis, biliary atresia), chronic hepatitis (hepatitis B, autoimmune hepatitis), metabolic diseases (Wilson's disease, nonalcoholic steatohepatitis), fulminant hepatic failure (FHF), and non-metastatic hepatocellular carcinoma (Fig. 1). Major pediatric indications for LT include biliary atresia and metabolic liver disease.

Acceptable tumor dimensions for patients with hepatocellular carcinoma (HCC) under consideration for OLT are either a single lesion less than 5 cm, or if multiple, two or three lesions with the largest not greater than 3 cm in diameter (4). Survival rates for these patients are comparable to those for cirrhosis leading to transplant without a complicating HCC. Preoperative metastatic work-

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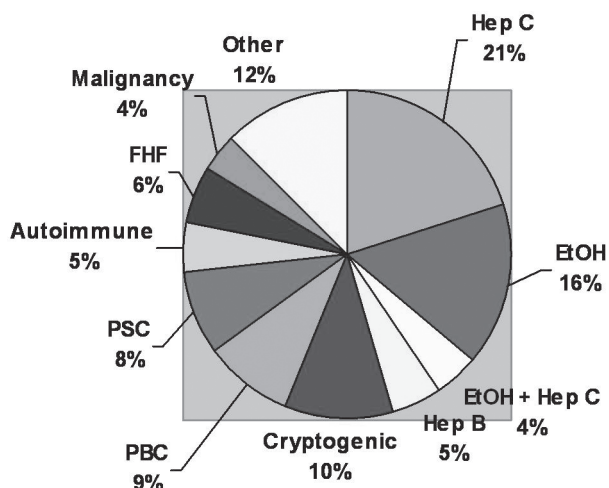


Fig. 1. Indications for liver transplant.

HepC = hepatitis C, PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; EtOH = alcohol; FHF = fulminant hepatic failure.

up includes bone scan, chest CT with an absence of vascular invasion (suggested for instance by an occluded portal vein). Not infrequently, a small “incidental” HCC is discovered in the native liver following OLT. These tumors are typically less than 2 cm in diameter, had not been detected by preoperative imaging, and do not affect survival.

There are relatively few absolute contraindications to OLT. Although organ allocation is centralized, many contraindications to listing for LT are center-specific. In most transplant centers a selection committee composed of hepatologists, transplant surgeons, transplant coordinators, psychiatrists and social workers determines the overall suitability of the transplant candidate. Most generally accepted absolute contraindications to transplantation are noted in Table 1. Centers are now increasingly offering LT to carefully selected older patients and HIV-infected individuals in the absence of AIDS, as part of newer protocols.

Listing and Timing of Transplantation

One of the key issues in LT is appropriate timing of transplant. Any patient with documented FHF is a potential candidate for liver transplantation. The term “fulminant hepatic failure” refers to the rapid development of severe acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver or had well-compensated liver disease. For FHF, underlying etiology is the single best predictor of outcome without OLT (5). The King’s College Criteria are used by many centers to predict outcome

TABLE 1
Contraindications to Liver Transplantation

Anatomic abnormality precluding liver transplantation
Malignancy outside the liver
Untreated sepsis
Advanced cardiopulmonary disease
Active alcohol and drug use
AIDS

of FHF and the need for OLT (Table 2; 5). Early referral of these patients to a transplant center is critical to offer the best chance of survival. Patients with fulminant hepatic failure are given the highest priority on the transplant list (UNOS Status 1).

The presence of cirrhosis alone is not sufficient to warrant transplantation. Although the high level of morbidity and mortality in chronic liver disease is related to complications of cirrhosis, the well-compensated cirrhotic patient can remain stable for many years. Fattovich et al. reported a 91% 5-year survival rate in a cohort of 384 cirrhotic hepatitis C virus (HCV) patients. Predictors of decompensation included age >54, presence of stigmata of chronic liver disease, platelets <130, and bilirubin >17 mmol/L (6). However, once an index manifestation of decompensation had occurred (variceal bleed, ascites, etc.), survival dropped to 50% at 5 years, suggesting that referral for LT should be considered once an index complication has occurred. Although variceal bleeding is the most dramatic and immediately life-threatening presentation of cirrhosis, the onset of ascites or hypoalbuminemia also predicts diminished long-term

TABLE 2
Criteria for Liver Transplantation in Fulminant Hepatic Failure
(Criteria of King’s College, London)

1. Acetaminophen toxicity patients
 - A. pH < 7.3 OR
 - B. Prothrombin time > 6.5 (INR) and serum creatinine >3.4 mg/dL
2. Other patients
 - A. Prothrombin time >6.5 (INR) OR
 - B. Any three of the following variables:
 1. Age <10 yrs or >40 yrs
 2. Etiology: non-A, non-B hepatitis; halothane hepatitis; idiosyncratic drug reaction
 3. Duration of jaundice before encephalopathy > 7 days
 4. Prothrombin time > 3.5 (INR)
 5. Serum bilirubin >17.6 mg/dL

Adapted with permission from O’Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; 97(2):439–445 (5).

INR = international normalized rate for prothrombin time.

survival. The development of hepatorenal syndrome is an ominous marker that signals the need for immediate transplant evaluation. Thus, the patient with evidence of progression of cirrhosis should be offered the option of referral to a transplant hepatologist for an opinion regarding further management (Table 3; 7).

In addition to referral for LT evaluation, prevention and management of several other complications of cirrhosis need to be considered (Table 4).

The ideal time for LT for chronic liver disease is when the patient has less than 50% chance of surviving 1–2 years but before he or she develops multi-organ complications. Once multi-organ system failure occurs, the survival rate is only 20–30% after transplantation (8). The prognosis of patients with cirrhosis is currently defined using both disease-specific and non-disease-specific clinical tools. The Child-Turcotte-Pugh score has been most frequently used to assess prognosis of cirrhotic patients until recently (Table 5; 9).

Model for End-Stage Liver Disease (MELD) Score

In 1998, the Department of Health and Human Services re-defined policies and principles for organ allocation, to create an equitable system that optimizes potential outcomes for all potential recipients. In 2002, the Organ Procurement and Transplantation Network (OPTN) along with UNOS endorsed the development of a new system

TABLE 3
Biochemical and Clinical Indications for Liver Transplantation in Chronic Liver Disease

- | |
|---|
| 1. Cholestatic liver disease |
| A. Bilirubin >10 mg/dL |
| B. Intractable pruritus |
| C. Progressive bone disease |
| D. Recurrent bacterial cholangitis |
| 2. Hepatocellular liver disease |
| A. Serum albumin <3.0 g/dL |
| B. Prothrombin time >3 seconds above control |
| 3. Both cholestatic and hepatocellular liver diseases |
| A. Recurrent or severe hepatic encephalopathy |
| B. Refractory ascites |
| C. Spontaneous bacterial peritonitis |
| D. Recurrent portal hypertensive bleeding |
| E. Severe chronic fatigue and weakness |
| F. Progressive malnutrition |
| G. Development of hepatorenal syndrome |
| H. Detection of small hepatocellular carcinoma |

Adapted with permission from Keefe EB. Selection of patients for liver transplantation. In: Maddrey WC, Sorrell MF, editors. *Transplantation of the liver*. 2nd ed. Norwalk (CT): Appleton & Lange, 1995. pp. 13–60 (7).

TABLE 4
Management of Patients with Compensated Cirrhosis

Endoscopic screening of varices
Prophylaxis of variceal bleeding
Prophylaxis of bacterial peritonitis
Screening and treatment of osteoporosis
Treatment of vitamin deficiencies
Screening of hepatocellular carcinoma
Screening and treatment of diabetes
Vaccinations: hepatitis A, B, influenza, pneumococcus

TABLE 5
Child-Turcotte-Pugh Classification: Class A=5–6; Class B=7–9; Class C=10–15

	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2–3	>3
Ascites	Absent	Slight	Moderate
Prothrombin time (seconds)	<4	4–6	>6
(INR <1.7) (INR 1.7–2.3) (INR >2.3) prolonged)/INR			
Encephalopathy grade	None	1–2	3–4
Albumin (g/dL)	>3.5	2.8–3.5	<2.8

Adapted with permission from Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. *The liver and portal hypertension*. Philadelphia (PA): WB Saunders; 1964; 50:1–85 (9).

INR = international normalized rate for prothrombin time.

based on the Model for End-Stage Liver Disease score for patients who do not have status 1 or are in fulminant liver failure.

The MELD score was originally developed to assess the prognosis of cirrhosis patients undergoing transjugular intrahepatic portosystemic shunt (10), but has been validated in several patient populations to provide a reliable estimate of short-term survival of patients with end-stage liver disease awaiting liver transplantation. The MELD score incorporates values for serum bilirubin, serum creatinine, and international normalized ratio for prothrombin time (INR) in a log-transformed equation to estimate likelihood of 3-month survival. The formula for the MELD score and 3-month mortality is available on the Internet at www.mayo.edu/int-med/gi/model/mayomdl.htm (Table 6; 10).

The potential advantages of the MELD score over the Child-Turcotte-Pugh score are its use of only objective parameters, in contrast to the Child-Turcotte-Pugh score, which incorporates subjective parameters such as the presence of hepatic encephalopathy and ascites. Higher MELD scores have been associated with decreased survival

TABLE 6
Model for End-Stage Liver Disease Score

MELD score	Three-Month Mortality (Hospitalized Patients)
≤ 9	4%
10–19	27%
20–29	76%
30–39	83%
≥ 40	100%

Adapted with permission from Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33(2):464–470 (10).

MELD = $3.8 \cdot \log_e(\text{Bilirubin}[\text{mg/dL}]) + 11.2 \cdot \log_e(\text{INR}) + 9.6 \cdot \log_e(\text{Creatinine}[\text{mg/dL}]) + 6.4 \cdot (\text{Etiology: } 0 \text{ if Cholestatic or Alcohol, } 1 \text{ Otherwise})$

rates. Three-month survival is less than 20% for patients with a MELD score of 40. The driving force of this system is disease severity, and there is no inherent benefit to early referral. In fact, referral too early may waste time and resources and cause the patient anxiety. A Child-Turcotte-Pugh Score of 7, a MELD score of 10 or any complication of portal hypertension, such as ascites or variceal bleeding, is an appropriate indication for transplant evaluation.

An analysis of the impact on deaths on the waiting list, early patient and graft survival, and waiting list registrations in the MELD era has been recently reported. Freeman et al. noted a 12% reduction in the number of newly listed patients (mainly those with low MELD scores), a 3.5% reduction in deaths while on the waiting list, and unchanged early graft and patient survival as compared to the previous allocation system (11).

The MELD score at which a patient will realistically receive a donor liver varies by region and organ demand. Providers need to know the average MELD score at time of transplant for each blood group in their region, in order to determine the appropriate timing for referral.

Pretransplant Evaluation

The objective of the pretransplant evaluation is to assess whether the patient will be able to tolerate the stress of the surgery, the immunosuppression and the highly demanding post-transplant care, as well as to confirm that the patient requires LT. Each patient undergoes extensive cardiopulmonary and psychosocial evaluation as well as screening for occult infection and neoplasia. Initial assessment should also include a teaching session for the pa-

tient and his or her family; this session should include a discussion of the risks and benefits of transplantation, including the potential for poor outcomes and the need to comply with follow-up appointments and medication regimens (12).

Careful psychiatric evaluation must be done on patients with a history of alcohol or drug abuse in order to prevent relapse after transplantation (13, 14). The impact of drug or alcohol use after transplant is still under investigation. However, recidivism has been found for as many as 30% of alcoholics after transplantation and for 20% of patients on a methadone maintenance program (15, 16); recidivism can have an effect on graft function, medical compliance and long-term survival (14).

Advances in Immunosuppression

Post-transplantation immunosuppression consists of “induction” and “maintenance” regimens, as well as treatment protocols for acute cellular rejection (ACR). Acute cellular rejection develops in approximately 70% of liver transplant recipients treated with cyclosporine-based or tacrolimus-based immunosuppression (17). ACR is most frequent 5–14 days following transplantation, but may present later, often in association with inadequate immunosuppression. Early in the post-transplant period, intravenous corticosteroids are used and tapered rapidly over several days with more long-term use of oral steroids. At most centers, maintenance immunosuppression is based on a calcineurin inhibitor (cyclosporine or tacrolimus) started immediately postoperatively with corticosteroids. The induction regimen typically includes high-dose steroids with initial introduction of cyclosporin or tacrolimus. Calcineurin inhibitors bind to intracellular proteins, inhibiting the phosphatase activity of calcineurin, resulting in inhibition of gene transcription for the synthesis of lymphokines such as interleukin (IL)-2. Calcineurin inhibitors have significant side effects including neurotoxicity, nephrotoxicity, hypertension and diabetes (Table 7). Mycophenolate mofetil (an inhibitor of inosine monophosphate dehydrogenase) or azathioprine (an inhibitor of DNA and RNA synthesis) may be used as adjuvant agents in order to allow lower doses of the calcineurin inhibitors in an effort to reduce toxicity. Maintenance immunosuppression in the stable patient generally permits lower therapeutic levels of tacrolimus or cyclosporine. Complete withdrawal of oral corticosteroids within 6–12 months of OLT has become standard in non-autoimmune-mediated liver disease, especially in patients transplanted for chronic viral hepatitis.

TABLE 7
Side Effects of Immunosuppression

Tacrolimus	Cyclosporine	Prednisone
Nephrotoxicity	Nephrotoxicity	Osteoporosis
Tremor	Tremor	Osteonecrosis
Hypertension	Hypertension	Diabetes
Headache	Headache	Hyperlipidemia
Gastrointestinal symptoms	Hirsutism	Hirsutism
Alopecia	Gingival hyperplasia	Hypertension
Diabetes		Cushingoid habitus

Sirolimus (Rapamycin) is a new immunosuppressive agent, which is structurally similar to tacrolimus but acts by inhibiting lymphocyte proliferation. In preliminary studies, it appeared less nephrotoxic than tacrolimus, and when used in combination with tacrolimus or cyclosporine it may allow use of lower levels of the calcineurin inhibitors (18). However, enthusiasm for its use in OLT has been tempered by potentially severe side effects, including delayed wound healing and vascular complications (19). Its role in OLT recipients is still not well defined.

First-line therapy for acute cellular rejection, which is critical in the initial few months after transplant, generally consists of high doses of intravenous corticosteroids tapered over several days (20). Approximately 70–80% of rejection episodes respond to bolus doses of methylprednisolone (21, 22). Acute rejection not responsive to steroids may require addition of other agents, including mycophenolate mofetil, higher levels of tacrolimus, or muromonab-CD3 (OKT3), a monoclonal preparation of antibodies directed against CD3 cells. Chronic rejection typically develops later in the post-OLT course and is characterized by vanishing bile ducts (ductopenia). It may respond to a high dose of tacrolimus but can lead to the need for retransplantation.

Other agents currently undergoing investigation as induction therapy include daclizumab, a humanized monoclonal antibody, basiliximab, a murine-human chimeric antibody, and FTY720, a synthetic analogue of myriocin that inhibits lymphocyte and chemokine actions.

Early Post-transplant Course

Because of the complexity of LT and the often markedly decompensated state of OLT recipients, invasive monitoring in the setting of an intensive care unit is necessary in the first few postoperative days. Markedly abnormal liver biochemistries are

typical during the initial 48–72 postoperative hours and reflect a number of insults to the graft, including ischemia following harvesting, preservation, and subsequent reperfusion. However, the overall trend in serum aminotransferase levels should be downward, with a corresponding improvement in coagulopathy and a falling serum bilirubin level. Hepatic artery thrombosis needs to be excluded promptly by Doppler ultrasound and sometimes requires urgent retransplantation. Primary nonfunction of the graft is also an indication for urgent retransplantation.

Within the first week after OLT, liver biochemistries should steadily improve as ischemia and reperfusion damage resolve. Acute cellular rejection becomes an important and frequent cause of graft dysfunction at 1 week and beyond. ACR is suggested by a rise in serum aminotransferase, alkaline phosphatase and bilirubin levels, but the diagnosis requires confirmation by a liver biopsy.

The timing of various infectious complications following liver transplantation is shown in Fig. 2 (23, 24).

Neurologic dysfunction can present in the early-post LT phase, as well as hyperglycemia and renal impairment. They may reflect a number of factors but are mainly related to the toxic effects of cyclosporine and tacrolimus.

After discharge, patients are seen at weekly intervals during the first postoperative month. The liver biochemistries should fall to normal levels within a few weeks following OLT. Any graft dysfunction is an indication for prompt liver biopsy, because ACR remains a concern during this time; in addition, cytomegalovirus (CMV) (25) and early HCV infection recurrence become important considerations three or more weeks after OLT. The guidelines in terms of prophylaxis strategies after LT are shown in Table 8.

The Timeline of Post-transplant Infections

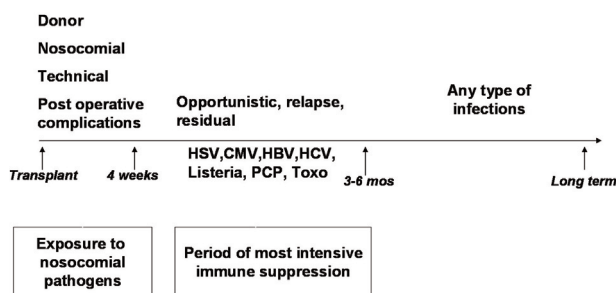


Fig. 2. The timeline of post-transplant infections.

HSV = herpes simplex virus; CMV = cytomegalovirus; HBV = hepatitis B virus; HCV = hepatitis C virus; PCP = pneumocystis carinii pneumonia; Toxo = toxoplasmosis.

TABLE 8
Infectious Diseases Guidelines

Prophylaxis Strategy	
Antibacterial	
Without significant infection history	ampicillin/sulbactam (before LT and for 48 hours after LT)
History of significant infection	vancomycin (before LT and for 48 hours after LT)
Antifungal	
In high-risk patients (re-transplants, FHF, renal failure, prolonged surgery)	IV fluconazole × 7 days followed by PO clotrimazole × 1 month
Low-risk patients	PO clotrimazole troche × 1 month
PCP	
	PO trimethoprim / sulfamethoxazole (TMP/SMX) × 3 months or atovaquone or pentamidine in allergics or intolerants to TMP/SMX
CMV	
CMV recipient + /donor + or -	PO valganciclovir 450 mg/d × 3 months
CMV recipient - / donor +	PO valganciclovir 900 mg/d × 3 months
CMV recipient -/ donor -	PO valacyclovir 500 mg/d × 3 months

LT = lung transplantation, PCP = pneumocystis carinii pneumonia, FHF = fulminant hepatic failure, TMP = trimethoprim, SMX = sulfamethoxazole, CMV = cytomegalovirus.

Fungal infections pose a major threat to the LT recipient, particularly in the setting of marked debilitation, intensive immunosuppression for rejection, or retransplantation. Major sites of infection are mucocutaneous (oral and esophageal), pulmonary, and intracerebral. Despite prolonged therapy with amphotericin or more recently with itraconazole, a fatal outcome is usual.

Long-Term Primary Care Management Issues

As the number of LT recipients continues to increase, and the five-year survival rate exceeds 70%, the non-transplant physician is playing a larger role in the care of these patients. Along with general preventative medicine, primary care management issues specifically related to immunosuppressive therapy include obesity, hyperlipidemia, hypertension, diabetes, osteoporosis, and screening for malignancy.

Routine health maintenance, as recommended by the US Preventive Services Task Force (26), should be applied to post-LT patients. This includes annual physical exams and age—appropriate screening for cholesterol, hypertension, breast cancer, colon cancer, cervical cancer, skin cancer and diabetes.

Patients frequently experience weight gain and obesity after LT (27). Body weight tends to increase during the two years after transplantation, before stabilizing. Excessive weight gain is frequent and 20–40% of patients become obese (body weight >30 kg/m²). Reasons for weight gain include use of prednisone, appetite stimulation by the anti-rejection regimens and an increased sense of well being after long-term chronic illness, often with a lack of pre-LT dietary restriction. Appropriate dietary counseling and an exercise program should be initiated.

Hyperlipidemia, with a mixed profile of elevated cholesterol and triglyceride levels, is noted in up to 30% of OLT recipients (28). Elevated lipid levels may be associated with allograft vasculopathy. The etiology of hyperlipidemia is multifactorial, including obesity, medications (cyclosporine inhibition of bile acid synthesis, influence of sirolimus), and pre-transplant-related risk factors. Treatment of obesity and diabetes as well as dietary and lifestyle modification are the first-line measures. For many patients, hyperlipidemia improves over time if the maintenance doses of steroids and cyclosporine are at low levels (29). Thus, medical treatment is rarely indicated early in the course when steroid doses are relatively high. If serum lipids do not fall, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors can be safely prescribed (30). Myositis, rhabdomyolysis and hepatotoxicity are uncommon side effects. Choice of agent is dependent on cost and degree of hyperlipidemia. Nicotinic acid can decrease glucose tolerance and raise uric acid levels, leading to symptomatic gout in some patients. Bile-acid binders lower cholesterol but tend to raise triglyceride levels and impair the absorption of cyclosporine. Gemfibrozil may be considered for the treatment of refractory hypertriglyceridemia. However, its combination with a statin is contraindicated due to an increased risk of rhabdomyolysis.

Systemic hypertension develops in 55–85% of patients within the first year after LT (31). Hypertension is multifactorial but can be attributed partly to the immunosuppressive regimen, especially the calcineurin inhibitors and steroids (32, 33). The prevalence of hypertension increases with length of time from transplant. Initial treatments of hypertension include dietary sodium restriction and, if possible, dose reduction of calcineurin inhibitors and prednisone. In a majority of cases, antihypertensive medication is required, and calcium channel blockers have proven effective, without significant nephrotoxicity. Diltiazem and verapamil may elevate cyclosporine and tacrolimus levels. If blood

pressure control is not adequate with a calcium channel blocker, a beta-blocker such as labetalol, diuretics, and angiotensin-converting enzyme inhibitors (such as enalapril and captopril) or angiotensin II receptor antagonist may be required.

Impaired glucose tolerance and diabetes are common in cirrhotic patients due to peripheral insulin resistance, which predisposes them to post-transplant diabetes. The diabetogenic potential of immunosuppressives, mainly tacrolimus, cyclosporine and corticosteroids, as well as weight gain, are important exacerbating factors (34). For unclear reasons, the risk also appears to be increased in patients transplanted for hepatitis C (35). Patients who are diabetic prior to transplantation typically require insulin after the transplant, and 13–30% of patients develop *de novo* diabetes. The incidence of *de novo* diabetes is higher with tacrolimus than cyclosporine. Treatment of diabetes in post-OLT patients is based on the same principles on which treatment of the nontransplant patient is based. Diet, lifestyle modification, weight loss, and the addition of insulin or oral hypoglycemic agents may be indicated, glyburide being an initial choice. Metformin is best avoided. Side effects of the oral hypoglycemics should be monitored, including hepatotoxicity. Calcineurin inhibitor dose reduction and steroid withdrawal can be considered by the transplant team (29, 34).

Osteopenia is common in cirrhotic patients and typically is due to osteoporosis rather than osteomalacia, although the latter can occur in severely cholestatic patients. Bone disease occurs after liver transplantation (36). Factors implicated, apart from calcium and vitamin D deficiency, include low muscle mass, immobility, long-term corticosteroid use, poor nutrition, and alcohol abuse. After transplantation, rapid bone loss occurs in the first 3–6 months, but bone density increases to pretransplant levels by 6–12 months, and may show a trend toward further improvement thereafter (37). The rapid bone loss occurring in the first three months is primarily due to the high doses of corticosteroids used immediately after transplantation (38). The most important risk factor for symptomatic post-transplant bone disease is a low bone mass prior to transplant. For patients awaiting LT, serum calcium, phosphorus, thyroid function studies, and parathyroid hormone should be evaluated along with bone densitometry studies. In addition to calcium and vitamin D, calcitonin or bisphosphonates may be considered as supplements if bone density indicates osteoporosis or if long-term corticosteroids are used. Once-weekly oral dosing with alendronate or risedronate is well tolerated and convenient (39). Mo-

bilizing patients soon after surgery can help curb bone loss in the immediate post-transplant period.

As with other solid transplants, the incidence of malignancy is increased for liver transplant patients (40). Skin cancer, lymphoma, primarily non-Hodgkin's, and oropharyngeal cancers may be more common in the post-LT population. The overall incidence of post-transplant lymphoproliferative disease is 30–50 times higher than that in the general population (41). The risk is greatest in patients with high degrees of immunosuppression. Epstein-Barr virus infection is thought to be responsible for most post-transplant lymphomas (42). The underlying liver disease also may predispose patients to develop specific types of cancer after liver transplantation. Patients transplanted for primary sclerosing cholangitis who have inflammatory bowel disease remain at high risk for colonic dysplasia and colon cancer (43). The primary care physician and gastroenterologist, along with the transplant team, should perform routine examination and screening.

Recipients beyond 6 months after OLT should be vaccinated for influenza, pneumococcus, and tetanus. Live vaccines for illnesses such as measles, mumps, rubella, and live oral polio vaccine should not be given.

Recurrent Disease after Transplantation

With improved long-term post-OLT survival, disease recurrence has become more evident. In the early 1990s hepatitis B recurrence was observed in more than 80% of LT recipients, and accounted for 73% of all deaths of patients transplanted for this indication (44). Currently, effective antiviral prophylaxis with high-dose hepatitis B immunoglobulin (HBIG) (more recently combined with lamivudine and adefovir) has virtually eliminated HBV recurrence (45, 46). The overall survival of patients transplanted for HBV-related cirrhosis currently exceeds 80% at one year and 65% at three years (47). The major challenge now in managing HBV-infected patients perioperatively is to provide adequate immunoprophylaxis in a cost-effective manner, given the high cost of long-term HBIG use, especially when given intravenously. To reduce the costs of HBIG therapy, attempts have been made to substitute maintenance IV HBIG with IM administration. Combination therapy with HBIG and antiviral treatments can reduce reinfection rates to 10% with low doses of IM HBIG (48). Although reinfection rates have been dramatically reduced with HBIG prophylaxis and lamivudine, other issues, including viral resistance and optimal duration of therapy with HBIG, have yet to be resolved.

Cirrhosis due to hepatitis C virus is the most common indication for OLT in the United States. After transplantation, hepatitis C recurrence is nearly universal, with histological changes in 50–80% of patients (49). Virologic reinfection at the time of transplantation is not surprising, since almost all patients with HCV undergoing transplantation are viremic (50). Furthermore, peripheral monocytes harbor HCV and may act as a source of virus, which reinfects the donor liver (51). The outcome of patients transplanted for HCV is variable. Recent analysis of the UNOS database showed diminished survival rates for HCV-positive patients compared to HCV-negative transplant recipients at 5 years (65.6% vs. 56.7%) (52). Evidence is accumulating that the post-transplant course of HCV infection is accelerated compared to the pretransplant setting. A report from King's College found that protocol biopsies done 5 years after transplant showed that 20% of patients transplanted for HCV already had evidence of allograft cirrhosis (53, 54). There is no consensus on the role of prophylactic antiviral therapy to prevent HCV recurrence after OLT (55). A recent study using combination ribavirin and pegylated interferon for managing recurrent HCV is promising (56). However, there is no consensus on the optimal strategies for administering therapy. Because of the side-effect profile of these drugs, many patients are not eligible for treatment or they withdraw during therapy. Most transplant centers attempt to reduce immunosuppression and treat rejection cautiously. Until more is known about host and viral factors that may predispose transplant patients to aggressive recurrent disease, the treatment and timing of the initiation of therapy remain undefined.

HCV recurrence may ultimately lead to the need for retransplantation. Unfortunately, the prognosis for such patients is generally poor (57–61).

Recurrence of hepatocellular carcinoma (HCC) can be minimized by exclusion of high-risk candidates with features predictive of tumor recurrence: tumor size and number and evidence of vascular invasion (62). Based on a large European experience reported by Mazzaferro and colleagues, generally accepted criteria for OLT in patients with HCC have included a tumor diameter of less than 5 cm if the tumor is solitary or, if multiple, two or three lesions with the diameter of the largest lesion being no greater than 3 cm (4). Survival rates comparable to those for transplantation for decompensated cirrhosis in the absence of complicating HCC (75% at 4 years) have been reported. Cholangiocarcinoma has historically been a contraindication

to transplant due to rapid tumor recurrence. Recent protocols with adjuvant external beam radiation and chemotherapy have shown early promise and may permit carefully selected patients with primary sclerosing cholangitis (PSC) and cholangiocarcinoma to be transplanted (63).

Graft failure secondary to recurrence of PSC, primary biliary cirrhosis (PBC), and autoimmune hepatitis has been observed in a subset of patients, although less frequently or rapidly than for viral hepatitis. A report from the Mayo Clinic described PSC recurrence in 20% of OLT recipients using cholangiographic and hepatic histologic criteria. For a majority of individuals recurrent disease was mild, but 8% required retransplantation (64). It is now generally accepted that PBC can recur following LT, although there was much initial debate. A precise estimate of the recurrence rate is uncertain, since not all studies have used uniform criteria for defining recurrent PBC, and studies have had variable follow-up. In a series of 400 patients from Birmingham, England, recurrence was observed in 18% at five years and 30% at 10 years (65). Recurrent autoimmune hepatitis, as defined by histologic chronic hepatitis, positive autoantibodies >1:40 and the need for steroid increase, was noted in 13/47 patients in one series (66). Risk of recurrence increased with prednisone withdrawal or lower immunosuppression. Hence, individuals transplanted for autoimmune liver disease may not tolerate complete prednisone withdrawal.

Retransplantation for recurrent disease is a difficult ethical issue faced by transplant teams in an era of intractable organ shortage. Perioperative risk, survival, quality of life, as well as the presence of comorbidities such as renal failure related to immunosuppression toxicity all need to be weighed in the decision to retransplant.

Novel Strategies

In order to maximize donor organ access for adult and pediatric recipients, novel surgical and liver replacement procedures have evolved. Newer surgical techniques include split cadaveric liver and living donor transplantation (67).

Cadaveric split liver transplantation creates two functioning allografts: the left lateral segment for a child and a right trisegment for an adult. The advantage of split liver transplantation is that it increases the total number of transplants performed from a static cadaveric donor organ supply. Disadvantages include greater technical complexity, longer procurement times, and feasibility only in a subset of donor organs.

Live donor liver transplantation (LDLT) provides one means to expand organ availability (68). Ethical concerns regarding LDLT are related to the potential for donor morbidity and mortality (68, 69). Opponents argue that it is unacceptable to place a healthy donor at risk of long-term debility or death. Despite these risks, proponents of LDLT suggest that it is unethical to deny an informed and willing adult the opportunity to participate in the donation process.

LDLT was initially performed for pediatric recipients. Access to LDLT had a dramatic impact on reducing mortality on the pediatric waiting list, with excellent recipient and graft survival rates reported. LDLT in adults is an even more technically challenging endeavor (70). A potential live donor is extensively evaluated for candidacy, as is shown in Table 9 (71). Every effort should be made to confirm that consent is informed and to ensure that the prospective donor has adequate time to contemplate the risks of the procedure and to decline participation, if desired. Advantages of living donor transplantation include expansion of the donor pool, ability to assess graft quality prior to transplant, and elective transplantation before significant debilitation of the potential recipient. Disadvantages are that living donor transplants require greater surgical technical skill and that donor morbidity and mortality from major abdominal surgery can occur. Donor morbidity is estimated at 10–20%, with major complications being biliary leaks, gastrointestinal complications, and vascular injury. Donor mortality is estimated at 0.2–1% (72, 73).

Conclusion

Liver transplantation has revolutionized the management of acute and chronic liver diseases. The scarcity of donor organs is still the factor limiting its use. In parallel to the evolution of liver

transplantation, the care of both transplant candidates with severe liver disease and post-OLT patients has become a major clinical challenge, with the transplant team combining the skills necessary to practice multidisciplinary medicine.

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TABLE 9

Evaluation of Prospective Living Liver Donors

Blood group compatibility
Comprehensive history and physical examination
Routine laboratory studies including viral serologies, HIV
Anatomic imaging: liver volume, vascular anatomy, biliary anatomy
Pulmonary function tests
Cardiac clearance
Psychosocial evaluation: life circumstances, motivation, understanding
Independent advocate opinion
Review of candidacy with prospective donor
Presentation to selection committee

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