The Liver Transplant Patient Part 2: Transplantation and Posttransplant Care

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L iver transplantation is a life-saving therapy for patients with end-stage liver disease. Since the advent of calcineurin inhibitors in the mid-1980s, liver transplantation has moved into the mainstream of medical care. Nearly 75,000 liver transplants were performed in the United States between 1988 and 2005; over 6400 transplants were performed in 2005 alone, and the number of transplants performed each year continues to grow.[1] Physicians in all areas of practice can expect to encounter patients with transplanted livers and should be familiar with essential aspects of their care. This is the second article of a 2-part series on medical care of adults before and after liver transplantation. Part 1, published in the March 2007 issue of *Hospital Physician*,[2] discussed the primary care physician's role of identifying patients with liver disease who may require liver transplantation and optimizing management of liver disease while the patient awaits transplantation. This article reviews transplantation and posttransplant care.

OBTAINING AN ALLOGRAFT

Livers for transplantation can be obtained from either deceased donors or living donors. Most livers for transplantation are from deceased donors who have been declared brain dead (ie, cerebral cortical and brainstem function are completely and irreversibly destroyed) but whose heart continues to beat and whose blood continues to be oxygenated via artificial ventilation.[3] The liver deteriorates rapidly after cessation of blood flow. Occasionally, livers retrieved after cardiac arrest ("non–heart-beating donors") can be used for transplantation provided that they were immediately harvested by skilled surgeons; however, periods of warm ischemia longer than 30 minutes are associated with poor graft function and high posttransplant mortality.[4] In the United States, donation of organs following death generally requires consent, either from an advanced directive or the patient's next of kin, but specific regulations vary from state to state. Costs

TAKE HOME POINTS

- Most livers for transplantation are obtained from deceased (brain dead) donors. Partial liver transplantation from living donors is also possible.
- During the first weeks posttransplant, complications of surgery (eg, bleeding, anastomotic bile leakage, biliary ductal anastomosis) dominate the clinical picture.
- Immunosuppression following liver transplantation can usually prevent graft rejection, but opportunistic infections can occur, especially during the first 6 months posttransplantation. Other potential complications of immunosuppression include hypertension, renal insufficiency, neurotoxicity, hyperlipidemia, and pancytopenia.
- Liver disease may recur in the transplanted liver and can cause graft cirrhosis. Retransplantation is possible, but overall survival is much poorer as compared with primary transplantation.

associated with organ retrieval are considered part of the transplant procedure and are paid by the recipient's health insurance. Costs related to transplantation are never charged to the estate of the donor.

Transplantation of portions of liver from healthy living donors began in the early 1990s and became

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widespread after 2000. Living donor transplantation in adults generally requires resection and transplantation of the entire right hepatic lobe (approximately 60% of the liver mass) from a healthy volunteer. This is feasible because the healthy liver has the capacity for compensatory hypertrophy, restoring near-normal liver mass in both donor and recipient within weeks.[5] Living donor transplantation is attractive to the patient awaiting transplantation because it circumvents the waiting list, permitting earlier transplantation under elective conditions, and it benefits society by increasing the pool of organs available for transplantation. However, living donation involves risks to the healthy donor, including a nontrivial mortality risk (1 in 500 chance of death).[6] Right lobe liver transplantation is associated with increased risk of complications in the recipient, such as bile leakage.[7] If the transplanted portion of liver is too small to meet the needs of the recipient and to accommodate portal blood flow, the graft may fail, a phenomenon known as small-for-size syndrome.[8] Because of these constraints, living donation currently accounts for only approximately 5% of all liver transplants.[1]

The donor liver is perfused immediately with ice-cold preservative solution to rapidly arrest metabolic activity, and it is kept cold until ready for reperfusion. The preservation solutions employed today (eg, University of Wisconsin solution) contain several additives to minimize damage to cells during storage and reperfusion, including impermeant molecules to prevent cell swelling, antioxidants, buffers, and sources of adenosine triphosphate.[9] Cold preservation for up to 10 hours is associated with excellent functional recovery upon reperfusion. However, beyond 12 hours of cold preservation, liver allograft quality progressively deteriorates.

At the time the liver is removed from a deceased donor, it is evaluated visually and by biopsy. Livers exhibiting moderate to severe steatosis function poorly after transplantation and are considered of marginal or poor quality.[10] In addition, donor history is reviewed and screening tests are performed to exclude the presence of infections, metastatic cancers, or other processes that might be transmitted to the recipient with the allograft. The donor's blood is tested to exclude the presence of potential pathogens, including hepatitis B and C viruses (HBV and HCV), HIV types 1 and 2, human T-lymphotropic virus types 1 and 2, syphilis, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). Screening for other transmittable pathogens, such rabies virus, severe acute respiratory syndrome, West Nile virus, or Creutzfeldt-Jacob disease involves review of risk factors and clinical history. Although thorough, donor screening is not infallible, and transmission of disease is an unavoidable risk of human-to-human transplantation.[11]

The term "extended criteria donor" (ECD) livers is used to describe donor livers that may carry higher than average risk when transplanted.[12] Reasons for this label may include advanced donor age, moderate hepatic steatosis, a donor history that suggests high risk of recent exposure to bloodborne pathogens, presence of a potential pathogen such as HBV or HCV (for recipients who are already infected with these viruses), severe donor metabolic derangements (eg, hypernatremia, shock), or a period of warm ischemia prior to organ retrieval. In many cases, ECD livers can be transplanted successfully provided that care is taken to match the organ with the needs of the recipient. As the demand for livers continues to overwhelm the supply, ECD livers are increasingly being used for transplantation.[12]

COMPLICATIONS OF TRANSPLANTATION

Liver transplantation is a demanding procedure for both the patient and physician. Technical aspects of liver transplantation have been summarized in a recent review by Eghtesad et al.[13] Initial dissection to isolate the vascular and biliary structures and remove the native liver can lead to severe bleeding, especially in the presence of severe portal hypertension or adhesions from prior surgery. During the period between removal of the native liver and implantation of the allograft (anhepatic phase), obstruction of the portal vein and inferior vena cava may cause hypotension. Hypotension can be minimized by using venovenous bypass or by preserving the retrohepatic vena cava ("piggyback" technique). Upon reperfusion of the graft, the release of cytokines and potassium into the circulation may cause cardiac arrhythmias and pulmonary edema. Patients with compensated cardiovascular disease, cardiomyopathy, or pulmonary hypertension may experience rapid deterioration of cardiac function pre- and postoperatively.

In the first postoperative week, re-exploration may be required for continued bleeding or anastomotic bile leakage. The transplanted liver may fail to function (primary nonfunction), necessitating urgent retransplantation. Thrombosis of the hepatic artery may occur as a result of intimal dissection caused by intraoperative manipulation; this often results in necrosis and stricture of the bile ducts with intractable biliary sepsis and may require urgent retransplantation. Portal vein stricture or thrombosis may lead to massive ascites. Hepatic venous outflow obstruction may occur due to anastomotic stricture or graft rotation, resulting

in ascites, graft dysfunction, and renal impairment. Pneumonia or other infections, respiratory failure, or heart failure may require prolonged intensive care. Patients with hepatorenal syndrome may require perioperative and postoperative dialysis.

The biliary ductal anastomosis is a common source of problems following transplantation. In most cases, the donor and recipient bile ducts are connected with a duct-to-duct anastomosis (choledochocholedochostomy), but in some cases a Roux-en-Y choledochojejunostomy may be employed. Leaks and strictures at the anastomosis are not uncommon, and they usually can be managed successfully with endoscopic stenting and dilatation;[14] however, severe or refractory strictures may require surgical revision. If uncorrected, anastomotic hepatic arterial stenosis may lead to development of intrahepatic biliary strictures. The arterial flow often can be restored via surgical revision or by percutaneous transluminal interventions such as angioplasty and stenting.[15] Despite these many concerns, most transplants go relatively smoothly. The median hospital stay following liver transplantation in most programs is approximately 11 days.[16]

IMMUNOSUPPRESSIVE MEDICATIONS AFTER TRANSPLANTATION

The medications commonly used to prevent rejection following liver transplantation and their side effects are listed in **Table 1**. Although the transplant center is generally responsible for regulating the immunosuppressive regimen, every physician should be familiar with some features of these drugs.[17,18] Calcineurin inhibitors, specifically cyclosporine and tacrolimus, are the backbone of solid organ transplant immunosuppression and work by inhibiting cytokine production required for clonal expansion of T lymphocytes. Side effects of these medications include hypertension, diabetes, renal insufficiency, hyperkalemia, and neurotoxicity (eg, confusion, tremor, seizures). Sirolimus (rapamycin), a second-generation immunosuppressive agent, is sometimes used in combination with low doses of tacrolimus. Sirolimus acts at a later step in the immune response, blocking lymphocyte proliferation in response to cytokines. The major advantage of sirolimus as compared with tacrolimus and cyclosporine is that it does not cause nephrotoxicity or neurotoxicity. The principal side effects of sirolimus are pancytopenia, hyperlipidemia, and impaired wound healing. Use of sirolimus in liver transplantation has been limited because 1 major study showed an increased risk of hepatic artery thrombosis.[19]

Tacrolimus, cyclosporine, and sirolimus are all ad-

Table 1. Medications Used to Prevent Allograft Rejection After Liver Transplantation and Respective Side Effects

Medication	Side Effects	Typical Therapeutic Trough Blood Level
Cyclosporine	Hypertension, acute and chronic nephrotoxicity, neurotoxicity, alopecia	Early: 200–300 ng/mL Late: 100–150 ng/mL
Tacrolimus (FK 506)	Hypertension, hyperkalemia, acute and chronic nephrotoxicity, neurotoxicity (tremor, headache, seizures), diabetes mellitus, hirsutism	Early: 8–12 ng/mL Late: 5–8 ng/mL
Sirolimus (rapamycin)	Hyperlipidemia, pancytopenia, impaired wound healing, hypersensitivity	Early: 10–20 ng/mL Late: 5–10 ng/mL
Mycophenolate mofetil	Pancytopenia, nausea, anorexia, diarrhea	—
Azathioprine	Pancytopenia, pancreatitis	—
Prednisone	Cushingoid habitus, emotional lability, glucose intolerance, hypertension, impaired wound healing, osteoporosis, aseptic femoral necrosis	—

NOTE: The choice of immunosuppressant medications and target therapeutic drug levels for the individual patient are determined by the transplant physician and may vary depending on past history of rejection, renal function, concurrent use of other immunosuppressants, and other considerations.

ministered orally, typically once daily (sirolimus) or twice daily at 9 AM and 9 PM (tacrolimus, cyclosporine). Absorption, distribution, excretion, and metabolism vary widely from patient to patient, and dosage must be individualized. Predose morning trough levels of these agents are monitored, with dose adjustments to achieve the target level (Table 1). Major drug interactions involving these 3 primary immunosuppressants are very common. All are eliminated by hepatic metabolism via cytochrome P450 3A4. Inhibitors of hepatic drug metabolism, such as ketoconazole, erythromycin, or antiretroviral drugs (nonnucleoside reverse transcriptase inhibitors and protease inhibitors), can cause immunosuppressive drugs to accumulate to toxic levels. Medications that induce drug metabolizing enzymes (eg, rifampin, phenytoin) can cause immunosuppressant levels to fall below the therapeutic range, which leads to organ rejection.[18] After any significant changes in the medical regimen of a transplant patient, the fasting blood level of the immunosuppressant drug should be rechecked within a few days. When major drug interactions are expected (eg, when a transplant

Table 2. Routine Outpatient Prophylaxis of Infections After Liver Transplantation*

Drug	Dose	Duration	Indication	Effective Against
Acyclovir	800 mg 4 times daily	100 days	All patients not receiving valganciclovir	Herpes simplex 1 and 2; varicella
Valganciclovir	900 mg daily	100 days	CMV-negative donor with CMV-positive recipient	CMV, herpes simplex, varicella, other herpesviruses
Trimethoprim-sulfamethoxazole	400 mg twice weekly	12 months	All patients except those with sulfon-amide intolerance	*Pneumocystis*, *Nocardia*, *Toxoplasma*, and *Listeria*
Pentamidine	300 mg monthly by nebulizer	12 months	Patients intolerant of sulfonamides	*Pneumocystis*
Nystatin	5 mL 4 times daily	14 days	All patients	Oral *Candida*
Fluconazole	200 mg daily by mouth	14 days	All patients	*Candida*, other invasive fungi
Ciprofloxacin	500 mg daily by mouth	While biliary drain in place	Patients with postoperative external biliary drain (T tube)	Enteric gram-negative bacteria

CMV = cytomegalovirus.

*Standard regimen employed at the Virginia Commonwealth University liver transplant program, 2006. Specific algorithms used by other transplant programs may vary. Dosages of some medications may require adjustment in patients with renal failure.

patient is started on antituberculous or anticonvulsant medications or when an HIV-positive transplant patient requires modification of antiretroviral drugs), more frequent (even daily) testing of drug levels and adjustment of immunosuppressant dosage may be required.

Other immunosuppressive medications employed after liver transplantation include antimetabolites such as azathioprine and mycophenolate mofetil. These drugs prevent lymphocyte proliferation by inhibiting purine synthesis. The major side effect of these agents is pancytopenia. Mycophenolate is more predictable in its dosing and more effective than azathioprine and has less idiosyncratic toxicity, but dosing may be limited by nausea, anorexia, and diarrhea. Allopurinol inhibits metabolism of azathioprine, and therefore azathioprine should be avoided in patients taking allopurinol. Glucocorticosteroids usually are employed in the early posttransplant period, but they are tapered and discontinued within weeks to months after transplantation in most patients. However, in patients with autoimmune hepatitis, chronic maintenance glucocorticoids usually are required to prevent disease recurrence. The side effects of glucocorticoids are well known to most clinicians and are not enumerated here.

POSTTRANSPLANT INFECTIONS
General Principles

The risk of infection after transplantation is related to 3 factors: the surgical procedure, the immunosuppression employed, and environmental exposure to potential pathogens.[20] Certain infections tend to occur at specific time points following transplantation. During the first month, most infections consist of postoperative pneumonias and other bacterial and fungal infections related to the surgical procedure, the wound, and the accompanying catheters, intravenous lines, and other hardware. In this period, preexisting infections dormant in the host or donor prior to the transplant may emerge. Between 1 and 6 months posttransplantation, opportunistic infection with viruses (CMV, EBV, human herpesvirus 6), bacteria (*Listeria monocytogenes*, mycobacteria, *Nocardia* species), and fungi and protozoans (*Candida, Aspergillus, Pneumocystis*, and *Toxoplasma* species) are most likely to manifest. This is also the time when recurrence of HBV or HCV infection is seen. More than 6 months posttransplantation, community-acquired respiratory viruses and other common pathogens dominate, although *Cryptococcus, Listeria, Nocardia*, tuberculosis, and other late opportunistic infections also may be seen, especially in individuals with chronic posttransplant liver disease or excessive immunosuppression.[20]

Anti-infective agents after transplantation may be administered prophylactically (to prevent infection at high-risk time points), preemptively (to abort infection before it becomes clinically apparent), or therapeutically (to eradicate established infection). Specific regimens for routine prophylaxis vary between programs but may include cotrimoxazole, dapsone, or pentamidine (to prevent *Pneumocystis* pneumonia), fluconazole or itraconazole (for *Candida* and other fungal infections), acyclovir (for herpes simplex and zoster), and valganciclovir (for herpesviruses and CMV).[21] The standard medications used for prophylaxis after transplantation at Virginia Commonwealth University are outlined in **Table 2**.

Infection in the posttransplant patient warrants special considerations by the primary care physician. Prolonged or repeated antibiotic therapy before and after transplantation often results in emergence of resistant organisms, such as multiresistant gram-negative organisms, methicillin-resistant *Staphylococcus aureus,* or vancomycin-resistant enterococci,[22,23] or may cause superinfection with fungal pathogens. Antibiotic use predisposes to *Clostridium difficile* colitis, which should be suspected if a transplant patient on antibiotics develops diarrhea, fever, or abdominal pain.[24] Patients with prior positive tuberculin skin tests may experience reactivation of tuberculosis after transplantation; this risk is reduced if the patient completes a course of antituberculous prophylaxis prior to the transplant. Overwhelming systemic posttransplant infections may occur without dramatic physical findings, fever, or leukocytosis. Manifestations of opportunistic infections often are puzzling, and routine diagnostic tests such as blood cultures may be unrevealing. When infection is suspected, early consultation with an infectious disease specialist is strongly recommended. Severe, even fatal, drug hypersensitivity reactions can occur after transplantation and may mimic infection. For more information on management of a wide spectrum of posttransplant infections, refer to guidelines developed by the American Society for Transplantation (www. blackwell-synergy.com/toc/ajt/4/s10).

Cytomegalovirus

CMV is a herpesvirus that chronically colonizes a majority of adults in the United States. In immunocompetent individuals, CMV remains dormant in cells, under constraint of the cell-mediated immune system. With transplant immunosuppression, CMV can proliferate to produce systemic illness characterized by a combination of fever, hepatitis, rash, pneumonia, pancytopenia, diarrhea with gastrointestinal ulceration, retinitis, and cerebritis.[25] Risk of CMV disease is greatest if a patient who is seronegative for CMV receives an organ from a CMV-positive donor. Clinical illness occurs most commonly between 1 and 3 months after transplantation, but in patients receiving prophylactic antiviral therapy, the onset of CMV disease may occur after prophylaxis is stopped. CMV also may emerge late in the postoperative phase if the patient receives intensified immunosuppression for treatment of rejection. The physician should suspect CMV disease in the patient with unexplained fever, cytopenia, abnormal results on liver testing, diarrhea, or pulmonary infiltrates. Diagnosis is supported by elevated levels of CMV viral antigen on laboratory testing or CMV DNA in plasma. In the past, systemic CMV infection was often fatal, but now it can be managed with a 2- to 4-week course of antiviral therapy (ganciclovir, valganciclovir, foscarnet). CMV disease may trigger allograft rejection,[26] and immunosuppression must be maintained during antiviral therapy.

LONG-TERM CARE AFTER LIVER TRANSPLANTATION

Following liver transplantation, patients continue to receive care at the transplant center for weeks to months. Initial management includes identification and correction of surgical complications, primary immunosuppression, prophylaxis for potential infections, and physical rehabilitation. By the time the patient returns to the referring physician, he/she is usually fully ambulatory and on a stable maintenance medical regimen. Over time, the primary care physician increasingly assumes responsibility for managing the care of these patients.

After transplantation, patients can return to most normal activities, but certain precautions are prudent.[27] Patients are advised to wash hands thoroughly and frequently and to wear gloves when coming in contact with heavily contaminated items such as soil. Patients should also avoid contact with individuals with respiratory infections and avoid exposure to airborne mold, such as in construction sites and gardens. When such exposure is unavoidable, use of a dust-filtering mask may be appropriate. Patients should avoid consuming raw meat and seafood and unpasteurized milk or cheese. Raw vegetables should be washed thoroughly. Contact with animals and birds should be avoided; if there are pets in the home (especially cats), measures should be taken to assure the pet's health and to minimize direct or indirect contact with animal feces.

REJECTION

Liver enzymes and liver function must be monitored regularly after liver transplantation, especially during the first year. Abnormal liver tests may be an indication of acute cellular rejection and should be reported immediately to the transplant physicians. Episodes of acute cellular rejection occur in about half of liver transplants.[18] Urgent liver biopsy is often necessary to guide therapy when rejection is suspected. Biopsy findings suggestive of acute cellular rejection include lymphocytic infiltration of portal tracts, inflammatory destruction of bile ducts, and venous endothelial inflammation. These findings are expressed semiquantitiatively using the Banff score on a scale from 0 to 9 (the higher the score, the greater the severity of rejection).[28] Biopsy often can distinguish rejection

from other possible causes of liver injury, including opportunistic infections, recurrence of the primary liver disease in the transplanted liver (especially HCV), hepatic artery thrombosis, biliary tract strictures, steatosis, and drug toxicity (especially antibiotics or medications for hypolipidemia). Acute cellular rejection usually subsides following a short course of intensified immunosuppression using high-dose glucocorticosteroids or, in severe cases, an antilymphocyte antibody (eg, anti-thymocyte globulin [rabbit]). However, rejection may progress despite treatment, leading to chronic ductopenic rejection, severe cholestasis, and progressive fibrosis with graft failure. Treatment for acute cellular rejection increases risk of opportunistic infection and may increase the aggressiveness of recurrent viral hepatitis. For these reasons, patients experiencing episodes of rejection have a poorer prognosis.

Chronic ductopenic liver rejection is uncommon provided that the patient adheres to the posttransplant medical regimen and episodes of acute rejection are identified and treated early. However, in patients who stop immunosuppression after transplantation, severe rejection usually occurs within weeks to months. Cessation of immunosuppressive therapy is sometimes seen in patients with uncontrolled psychiatric problems (eg, depression) or in those who relapse into drug or alcohol abuse. It also may be precipitated by financial reverses (eg, loss of health insurance), leading to inability to purchase drugs. Once severe chronic rejection is established, it often cannot be reversed and progresses to chronic cholestasis, cirrhosis, and liver failure. Chronic ductopenic liver rejection leading to graft loss occurs in fewer than 5% of liver transplants.

RECURRENCE OF LIVER DISEASE

In patients with cirrhosis caused by HBV, recurrence of HBV infection in the transplanted liver leading to rapidly progressive fibrosing cholestatic hepatitis and eventual liver failure had been a major concern in the past. However, long-term administration of hepatitis B immune globulin starting at the time of transplantation, along with availability of effective antiviral agents (eg, lamivudine, adefovir, entecavir) has largely eliminated this complication in compliant patients.[29,30]

Unfortunately, recurrent HCV infection remains an unresolved problem that adversely affects posttransplant survival.[31] Although the presence of decompensated cirrhosis in the pretransplant setting adds to the risk of major side effects, serious cytopenias, and potentially lethal infections as well as to difficulty in managing HCV infection with antiviral therapy, treatment in some cases can be successful using a low-accelerating dose regimen. Cirrhotic patients who achieve a sustained virologic response have a low risk of posttransplant HCV recurrence.[32] In patients who have persistent HCV infection at the time of transplant, HCV recurrence in the allograft is almost universal. After transplantation, HCV often follows an indolent course; however, HCV may rapidly progress in some cases, leading to cirrhosis and hepatic decompensation within a few years. In approximately 3% to 5% of HCV-infected patients who receive a liver transplant, recurrence takes the form of fibrosing cholestatic hepatitis C, which is associated with intense cholestasis and results in liver failure and death within a few months.[33] After transplantation, antiviral therapy with pegylated interferon and ribavirin may be effective in some patients in controlling or eradicating HCV, but concurrent treatment with hemopoietic factors is often necessary to permit administration of effective doses of antiviral drugs. Both acute and chronic rejection occasionally may be triggered by interferon therapy after transplantation.[34]

Other conditions that have been shown to recur following liver transplantation include autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, sarcoidosis, and nonalcoholic steatohepatitis. In most cases, progression is gradual and may be delayed or prevented using the same treatment measures employed in these conditions prior to transplantation.

RETRANSPLANTATION

Patients who develop recurrent liver failure after transplantation can be offered retransplantation.[35] Early liver retransplantation (within days to weeks after the initial transplant) may be required because of primary nonfunction of the transplanted liver or hepatic arterial thrombosis. Later retransplantation (months to years after the initial transplant) may be indicated for liver failure caused by chronic ductopenic rejection, recurrence of primary liver disease in the allograft, or surgically incorrectable occlusions of bile ducts or blood vessels.

The decision to retransplant can be difficult. Liver diseases that recur after a primary transplant may recur again, even more aggressively, following a second transplant; however, some patients respond well to retransplantation, and the course following the initial transplant is not a reliable predictor of disease severity following retransplantation. As shown the **Figure**, overall survival after retransplantation is much poorer than after primary transplantation,[1,35] especially if jaundice and renal insufficiency are present. With the growing

expertise of transplant programs and improved models for identifying patients likely to have a poor outcome,[35] retransplantation has become less common, decreasing from 27% of all liver transplants in 1989 to 8% in 2005.[1]

LONG-TERM PROGNOSIS AFTER LIVER TRANSPLANTATION

Much of the risk of death after liver transplantation occurs within the first 6 to 12 months. For the average-risk patient, posttransplant mortality is approximately 7% at 3 months and 14% at 1 year. Additional mortality of 3% to 4% per year is noted through 5 years, after which survival of patients who have undergone transplantation approaches that of age-matched controls.[1,36,37] Worse outcomes can be expected in high-risk patients, including patients who are older or morbidly obese and those with diabetes, hepatitis C, or hepatocellular carcinoma. Outcomes are also worse if patients are critically ill, actively infected, or severely debilitated at the time of transplantation. Retransplantation carries substantially higher mortality risk than primary transplantation (Figure).

Mortality that occurs early after transplantation is often related to poor allograft function, complications of surgery, and opportunistic infections. In contrast, mortality that occurs in the late posttransplant period usually is related to general medical problems, such as cardiovascular disease, cancer, or recurrent liver disease. Posttransplant hypertension and nephrotoxicity (related to treatment with tacrolimus and cyclosporine), diabetes mellitus (due to tacrolimus and glucocorticoids), and hyperlipidemia (seen with treatment with sirolimus or secondary to diabetes) can lead to accelerated atherosclerosis, cerebrovascular accidents, myocardial infarction, heart failure, and renal failure. Measures used to manage these problems after transplantation are similar to those used in the general patient population with a few caveats.[38,39] In managing hypertension, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and spironolactone should be used with caution, as they can cause serious hyperkalemia in patients receiving calcineurin antagonists. Instead, calcium channel antagonists, clonidine, and β-blockers are generally preferred. Thiazides are relatively ineffective in this setting. Several agents used to treat diabetes and hyperlipidemia have the potential to cause elevations in transaminase levels. While this rarely leads to significant hepatotoxicity, liver biopsy may be required to exclude rejection.

De novo malignancies are an important cause of late deaths after liver transplantation.[40] Transplant immunosuppression is associated with an increased risk
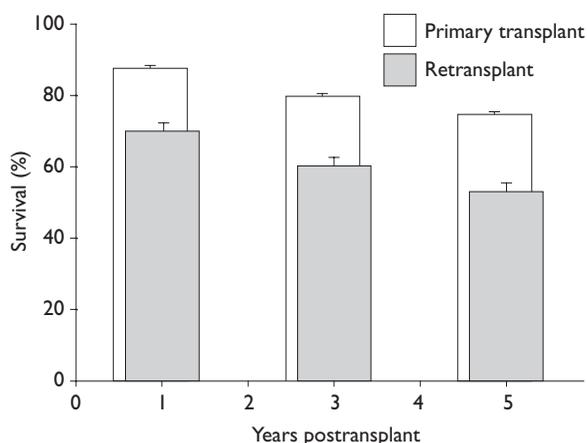
Figure. Survival following liver transplantation. US national data for 1997–2004. (Data from the Organ Procurement and Transplantation Network. Available at www.optn.org. Accessed 23 Feb 2007.)

of skin cancers (basal or squamous cell), and regular dermatologic evaluation should be a routine part of posttransplant care. Because many patients who have undergone transplantation have a history of alcohol and tobacco use, bronchogenic carcinoma and squamous cancers of the head, neck, and esophagus are also frequently encountered. Routine cancer surveillance such as prostate-specific antigen testing and prostate examination in men, mammography and breast examination in women, and colonoscopy in all patients aged older than 50 years should be continued. Posttransplant lymphoproliferative disease[41] is a form of lymphoma associated with EBV infection in immunosuppressed patients. Early onset posttransplant lymphoproliferative disease often resembles infectious mononucleosis and may respond dramatically to reduction of immunosuppression. Late-onset disease is typically diffuse B-cell lymphoma, which can be treated with systemic chemotherapy and/or immunotherapy.[42]

CONCLUSION

For many patients with end-stage liver disease, liver transplantation is the only option for survival. However, not all patients with liver disease are candidates for transplantation. Comprehensive management of cirrhosis[43] can prolong pretransplant survival and can delay or eliminate the need for transplantation. Timely evaluation and referral to a specialist when prognosis begins to deteriorate is key to getting patients listed in the United Network for Organ Sharing and eventual transplantation.[44] Early posttransplant deaths are largely the result of surgical complications and opportunistic infections.

Death several months to years after transplantation may be caused by recurrent liver disease, malignancies, and cardiovascular problems. Long-term survival after transplantation is largely influenced by patient compliance, comprehensive care by the primary care physician, and maintenance of a healthy lifestyle.   **HP**

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