97 Liver Transplantation

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CHAPTER OUTLINE

Although specific treatments for certain chronic liver diseases may favorably alter their natural history by diminishing, halting, or permitting regression of hepatic fibrosis, once major complications of cirrhosis such as ascites or hepatic encephalopathy develop, treatment options are limited and typically do not extend or significantly improve quality of life. Interventions such as variceal band ligation and placement of a TIPS can effectively control life-threatening bleeding but do not abort progression of underlying cirrhosis (see Chapters 5, 74 and 92). With some notable exceptions, as occur with abstinence from alcohol in decompensated alcohol-associated liver disease and antiviral therapy in advanced liver disease due to HBV or HCV infection, the course of clinically overt cirrhosis is almost invariably progressive. Even a patient with previously well-compensated cirrhosis who experiences an index complication of liver disease can develop precipitous deterioration with "acute-on-chronic liver failure," leading to multiorgan involvement, frequently with sepsis and renal failure (see Chapter 74). The major indications for LT include decompensated cirrhosis, unresectable primary hepatic malignancies, and ALF, which account for the majority of adult cases.[1]

Current post-transplant patient and graft survival rates (91% and 89% after 1 year, respectively, and 76% and 72% after 5 years, respectively) reflect major advances in surgical techniques, postoperative intensive care, and immunosuppression, as well as better selection of potential candidates. Recurrent disease remains an ongoing concern during long-term follow-up of liver transplant recipients and may result in diminished patient and/or graft survival after an otherwise successful procedure. The advent of interferon-free antiviral regimens with DAAs for HCV infection now permits treatment of recurrent infection in liver transplant recipients with efficacy and safety comparable to those for nontransplant populations.[2] Similarly, oral antiviral agents in combination with hepatitis B immunoglobulin permits LT with a low likelihood of recurrent HBV infection post-transplant.[3] Recurrence or development of de novo nonviral liver disease, particularly NAFLD, post-transplantation is also recognized and presents major future challenges. Effective immunosuppression has made graft rejection a less likely threat.[4,5] Recognition that excessive immunosuppression is deleterious and that variable degrees of immune tolerance may develop in selected liver transplant recipients has led to more individualized immunosuppressive regimens.[6]

The greatest challenge in LT remains the shortage of donor organs. Deaths on the transplant waiting list reflect in large part the sizable and ongoing disparity between the number of individuals in need of transplantation and that of available donor organs. Efforts to expand the deceased-donor supply by public education programs have succeeded, although many potential organ donors remain unidentified. Although live-donor LT (LDLT) in adult recipients can potentially increase the available donor organ pool, potential risks to the donor have limited its widespread application.[7] Other innovations such as splitting of a deceased-donor graft to share between 2 recipients and use of "extended-criteria" grafts, including those from older and non–heart-beating donors, have also expanded the organ supply, albeit modestly; however, there is an increased frequency of biliary complications with these allografts. Utilization of HCV-infected grafts for candidates with HCV infection is one of the more recent strategies aimed at increasing the donor organ pool.[8] Prior to licensure of DAAs that permit safe and effective treatment of HCV infection in liver transplant recipients, this strategy was not considered feasible because of the risk of HCV acquisition. A consequence of the ongoing opioid epidemic in young adults has been expansion of the deceased donor pool due to accidental drug overdoses.[9] Although the shortage of donor organs will undoubtedly persist, and recurrence of the original disease remains a threat, the prospects for long-term survival appear to be excellent for most liver transplant recipients who otherwise would succumb to their underlying liver disease. The predicted 1-year survival rate for patients with decompensated cirrhosis is less than 10% without LT; by contrast, survival is 91% at 1 year and 76% at 5 years post-transplant for most indications.[10]

Access to LT has transformed the management of advanced liver disease but has resulted in an expanding cohort of potential recipients with decompensated cirrhosis who require detailed medical attention.[11] The best outcomes following LT are obtained in recipients who have not already experienced multiple complications of liver disease[12]; therefore, referral is appropriate when a patient with cirrhosis has had an index complication, such

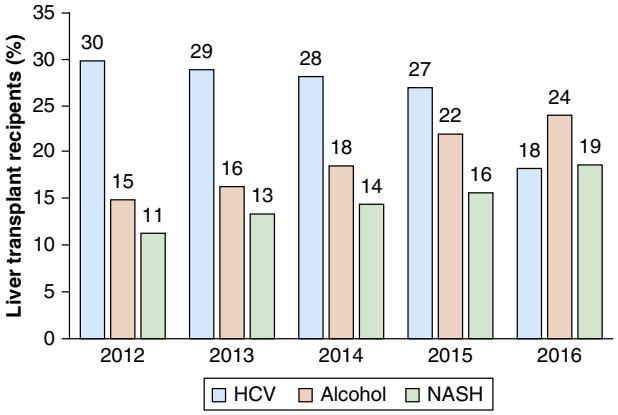

Fig. 97.1 Leading indications for LT in adults in the USA, 2012-2016. (From Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2018;16:1356-8).

as the new onset of ascites. For at least some potential recipients, access to LDLT may avoid a lengthy waiting period attended by potentially life-threatening complications of liver disease.

In parallel with the evolution of LT, the care of transplant candidates with advanced disease and transplant recipients has become an area of special expertise. The transplant hepatologist must combine the skills necessary to practice gastroenterology, multidisciplinary internal medicine, and intensive care. This skill set has been formally recognized by the development of a secondary subspecialty in transplant hepatology by the American Board of Internal Medicine.[13]

INDICATIONS

The major indications for LT in adults reflect the most frequent causes of cirrhosis (see Chapter 74), notably alcohol-associated liver disease, NAFLD, HCV infection, and to a lesser extent, PBC, PSC, autoimmune hepatitis, HBV infection, and hemochromatosis (Fig. 97.1; see Chapters 68, 75, 79, 80, 86, 87, 90, and 91). HCC is the leading indication for LT in the USA, reflecting the high risk for this primary hepatic malignancy in individuals with cirrhosis.[14] Alcohol-associated liver disease remains another major indication for LT in the USA, with temporal trends demonstrating that the frequency of LT for this indication has steadily increased and has become the leading non-neoplastic indication for LT. Many candidates for LT previously described as having "cryptogenic" cirrhosis are now considered to have NAFLD (see Chapter 87), which currently follows alcohol-associated liver disease and is the second leading non-neoplastic indication for LT in the USA.[15,16] The number of patients with HCV-related chronic liver disease listed for LT in the USA has declined steeply following licensure of DAAs.[17,18] An uncommon but important indication is ALF, which has a high mortality rate in the absence of LT (see Chapter 95). Cholangiocarcinoma, the other major primary adult hepatic malignancy after HCC, had been regarded as a contraindication to LT because of its rapid and almost invariable recurrence, leading to dismal recipient survival rates; however, acceptable outcomes have been reported in a subset of patients with perihilar tumors who receive neoadjuvant external beam radiation and chemosensitization (see Chapter 69).[19] The major indication for pediatric LT is biliary atresia following a failed Kasai procedure (portoenterostomy) or delayed recognition of the diagnosis (see Chapter 62). Other major pediatric indications include α_1-antitrypsin deficiency and other metabolic disorders (see Chapter 77).

BOX 97.1 Indications for LT

- ALF
- Complications of cirrhosis
  - Ascites
  - Chronic GI blood loss due to portal hypertensive gastropathy
  - Encephalopathy
  - Liver cancer
  - Refractory variceal hemorrhage
  - Synthetic dysfunction
- Liver-based metabolic conditions with systemic manifestations
  - α_1-Antitrypsin deficiency
  - Familial amyloidosis
  - Glycogen storage disease
  - Primary oxaluria
  - Tyrosinemia
  - Urea cycle enzyme deficiencies
  - Wilson disease
- Systemic complications of chronic liver disease
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension

A diagnosis of cirrhosis per se is not an indication for LT, although a key issue in managing patients with cirrhosis is assessing whether this intervention will be needed in the future and when referral for transplant evaluation is appropriate (Box 97.1). Other important aspects of care are the anticipation of complications such as variceal bleeding (see Chapter 92) and surveillance for HCC (see Chapter 96).[11] LT should normally be recommended only when the limits of medical therapy for complications of cirrhosis have been reached. The risk of surgery must always be weighed against a realistic assessment of the potential recipient's prognosis in the absence of LT. For example, in a patient with decompensated cirrhosis caused by HBV infection, effective antiviral therapy may result in significant clinical improvement, delaying or even obviating the need for LT (see Chapter 79). Similarly, abstinence from alcohol can result in resolution of signs of hepatic decompensation in a patient with alcohol-associated liver disease (see Chapter 86). However, evaluation for LT should not be deferred even when a potentially reversible component of hepatic decompensation is identified, because clinical improvement does not occur invariably and the course of chronic liver disease remains unpredictable. Although recognition of cirrhosis implies a risk for major complications and diminished life expectancy, the natural history of cirrhosis is a dynamic process, and multiple variables such as the treatment of the underlying cause of liver disease or the presence of comorbid conditions may affect the course.

The development of disease-specific predictive models based on the natural history of PBC (see Chapter 91) and PSC (see Chapter 68) can help clinical decision making for patients with these cholestatic disorders, which tend to progress in a fairly stereotypical fashion.[20] Before the introduction of the MELD score (see later), analogous models had not been available for noncholestatic forms of cirrhosis, and the decision to refer a patient for LT was generally based on an estimate of disease severity using objective parameters such as the serum albumin level, as well as more subjective variables such as the presence of hepatic encephalopathy, as in the Child-Turcotte-Pugh score (see Chapter 92).

Important indications for LT remain severe hepatocellular dysfunction, reflected by the presence of coagulopathy and jaundice, complications of portal hypertension such as refractory ascites and recurrent variceal bleeding, or the combination of portosystemic shunting and diminished hepatocellular function, as in hepatic encephalopathy (see Box 97.1). Deterioration of a

patient's quality of life is not reflected adequately in predictive models, including the MELD score. Disabling symptoms and complications, such as intractable pruritus, severe fatigue and incapacitating daytime sleepiness in patients with cholestatic and other forms of cirrhosis, and recurrent bacterial cholangitis in those with PSC, are also important considerations. MELD "exceptions"—the addition of points to the "biological" MELD score—can be requested on a case-by-case basis from the local UNOS Regional Review Board to facilitate LT for individual patients (see later). The awarding of extra points recognizes that although the MELD score has been a major advance in organ allocation, at least some patients may be disadvantaged by the use of purely objective parameters and exclusion of factors that were incorporated into older allocation schemes (e.g., intractable ascites, encephalopathy) or disabling symptoms that are disease specific. Ideally, LT should occur before a protracted period of disability reduces the likelihood that the recipient will return to full employment and normal social functioning.

LISTING CRITERIA AND POLICIES OF THE UNITED NETWORK FOR ORGAN SHARING

Organ allocation within the USA is administered by UNOS, which uses disease severity (not waiting time, as in the past) to assign a graft to a recipient. Prior to 2002, organ allocation was based on the Child-Turcotte-Pugh score (see Chapter 92). The MELD score (available at www.unos.org [https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/]) is a formula that incorporates the serum bilirubin level, creatinine level, and INR. It provides a numerical value (based on a log-transformed equation) that predicts the 3-month mortality rate without LT (e.g., 1.9% with a score <9; 71.3% with a score of 40).[21] The MELD score also overcomes some of the inherent limitations of the Child-Turcotte-Pugh score, including limited discriminatory ability, subjective interpretation of parameters such as the presence or absence of ascites on the basis of the physical examination, and the "ceiling effect" of the Child-Turcotte-Pugh score (i.e., no greater weight is given to a serum bilirubin level of 35 mg/dL than to a level of 3.5 mg/dL, even though a patient with the markedly higher bilirubin level clearly has more advanced liver disease). Inclusion of the serum creatinine level reflects its prognostic importance in patients with advanced liver disease. A modification of the MELD score in 2016 incorporated the serum sodium concentration into the formula (MELD-Na), reflecting the adverse effects of hyponatremia on the prognosis of patients with cirrhosis.

An analogous predictive model has been developed and validated for children younger than 12 years of age with chronic liver disease (Pediatric End-stage Liver Disease [PELD] score). The main difference between the MELD and PELD scores is that the pediatric model does not incorporate serum creatinine but instead uses age, growth failure (≤2 standard deviations below the mean value for that age), and serum albumin level (also available at www.unos.org [https://optn.transplant.hrsa.gov/resources/allocation-calculators/peld-calculator/]).

CONTRAINDICATIONS

Contraindications to LT are continually evolving. Effective oral antiviral therapy now allows LT for HBV-related liver disease with a low likelihood of recurrence.[22] Similarly, antiviral therapy for HCV infection with all-oral DAAs is now well tolerated and highly effective in liver transplant recipients, and retransplantation can be considered for recipients with a failing graft caused by recurrent HCV infection.[23] The introduction of antiretroviral therapy has permitted LT in HIV-infected recipients with decompensated liver disease, typically caused by either HCV or HBV infection.[24] Still, absolute and relative contraindications remain (Box 97.2). An absolute contraindication to LT implies that a successful outcome is so unlikely that transplantation should not be offered. A relative contraindication implies that the likelihood of a good outcome is suboptimal, although LT may still be considered in some patients. The role of LT in the management of HCC has become better defined with recognition that a large tumor burden is associated with a high probability of metastatic spread postoperatively.[25] Despite the sophistication of current imaging techniques, tumor characteristics predictive of a poor outcome, most notably vascular invasion, may only be apparent once the explant is available. Although results of LT for cholangiocarcinoma had been poor because of a high rate of tumor recurrence, a subset of patients with perihilar tumors may benefit from multimodal therapy, including neoadjuvant chemotherapy along with concurrent external beam radiation, followed by LT in selected candidates in whom surgical exploration demonstrates stage I or II disease (see Chapter 69).[19] Outcomes of LT remain poor for angiosarcoma, which is an absolute contraindication. By contrast, at least some patients with epithelioid hemangioendothelioma have been transplanted successfully despite an extensive tumor burden, with documented regression of extrahepatic metastases (see Chapter 96).

BOX 97.2 Absolute Contraindications to LT

- ALF with a sustained ICP >50 mm Hg or CPP <40 mm Hg
- AIDS
- Active alcoholism or substance abuse
- Advanced cardiac or pulmonary disease
- Anatomic abnormality that precludes LT
- Angiosarcoma
- Cholangiocarcinoma (with few exceptions described in the text)
- Extrahepatic malignancy
- Persistent nonadherence
- Uncontrolled sepsis

ICP, intracranial pressure; *CPP*, cerebral perfusion pressure (CPP = mean arterial pressure minus ICP).

For transplant candidates with a prior extrahepatic malignancy, therapy of the malignancy must have been curative, with the resected specimen indicating a low likelihood of metastatic spread. A 2-year recurrence-free interval prior to LT is adequate for most nonhepatic malignancies, but a longer period following resection may be desirable for breast cancer, colon cancer, and melanoma.[26] Myeloproliferative disorders frequently underlie Budd-Chiari syndrome (see Chapter 85), but fortunately evolution to acute leukemia is not accelerated following LT.[27]

Ongoing alcohol and recreational drug use remain absolute contraindications to LT. If continued abuse is a concern, random toxicology screening tests are appropriate. Although medicinal marijuana may be used legitimately for palliation, most transplant programs discourage its use because of concerns about the adherence of users to other therapies and possible pulmonary complications as well as evidence of accelerated fibrosis in HCV-induced liver disease.[28] Cigarette smoking is prohibited in transplant candidates because of its multiple adverse effects, including an association with hepatic artery thrombosis and malignancy postoperatively.[29] A history of prescription narcotic abuse is also a cause for concern because it may contribute to difficulties with pain management postoperatively. Non-narcotic alternatives should be encouraged for the management of chronic pain. NSAIDs are contraindicated in patients with cirrhosis because of potential renal and GI toxicity. With increasing use of herbal compounds and other complementary and alternative medicines, a discussion of their unproved efficacy and unknown

toxicities—with caution against their use after transplant because of potential for drug interactions—is appropriate (see Chapters 89 and 131).[30]

The pretransplant evaluation frequently uncovers important comorbidities—typically cardiac and pulmonary. Patients with decompensated cirrhosis were previously considered to have a diminished risk of coronary artery disease (CAD) because of low afterload (reflecting peripheral vasodilatation), decreased hepatic synthesis of cholesterol, and increased circulating estrogen levels. However, subsequent studies have shown that the prevalence of CAD in this population is at least equal to that of an age-matched control population.[31] Risk factors for CAD in patients with cirrhosis include diabetes mellitus, which is prevalent among cirrhotic patients. Additional risk factors for CAD in the post-LT period include immunosuppressive drugs that contribute to systemic hypertension, hyperlipidemia, and obesity (see later). Clinical assessment of cardiac risk with exercise stress testing may be difficult in patients with cirrhosis because of poor physical stamina, frailty, volume overload, hepatic encephalopathy, and pulmonary complications. IV administration of dobutamine mimics the physiologic effects of exercise and is used in stress echocardiography to exclude clinically significant CAD in liver transplant candidates. Patients who reach 85% of their maximal predicted heart rate without wall-motion abnormalities on stress echocardiography have a low likelihood of peri- and postoperative ischemic cardiac events.[32] CT coronary angiography (CTCA) can provide noninvasive measurement of coronary calcium scores, which correlate well with obstructive CAD. Studies of CTCA in liver transplant candidates are limited and restricted by small sample size. Although the negative predictive value of CTCA for excluding significant CAD (>50% obstruction) in liver transplant candidates was 100% in one small study, its specificity (44%) and positive predictive value (25%) were poor.[33] Cardiac catheterization and coronary angiography should be performed if CAD cannot be confidently excluded by noninvasive testing; however, this intervention is associated with an increased risk of bleeding and higher transfusion requirements for blood products in patients with coagulopathy and thrombocytopenia due to advanced chronic liver disease.[34] Coronary artery stenoses can be managed by pre-LT angioplasty and stenting; however, antiplatelet therapy prescribed following endovascular interventions may pose an important risk for bleeding. Although coronary artery bypass grafting is usually contraindicated because of a risk of perioperative morbidity and mortality in a patient with decompensated cirrhosis, successful bypass surgery may render a patient an acceptable candidate for LT.[35] The pretransplant evaluation may overestimate cardiac performance, and impaired cardiac function may become apparent only after the protective effect of decreased systemic vascular resistance (typical of cirrhosis) is lost following LT, when afterload increases, because of the hypertensive effects of the primary immunosuppressive agents or excessive volume repletion.[36] Specific causes of cirrhosis may be associated with additional cardiovascular events that diminish long-term survival. A large study using the Organ Procurement and Transplantation Network database showed that liver transplant recipients with NAFLD have the highest frequency of CAD (7.4%), compared with those with alcohol-associated liver disease (2.9%), HCV infection (2.7%), HBV infection (2.3%), and PBC (1.7%).[37] Fatal cardiac arrhythmias may result in poorer survival in patients with hemochromatosis or amyloidosis who undergo LT.[38]

Pulmonary evaluation in the liver transplant candidate may reveal abnormal arterial oxygenation (see Chapter 94). Although severe chronic obstructive pulmonary disease or pulmonary fibrosis precludes LT, respiratory restriction because of ascites or diminished mass and strength of respiratory muscles caused by chronic illness is reversible and is not a contraindication to LT. Even patients who undergo LT for α_1-antitrypsin deficiency may show improvement in pulmonary function tests postoperatively.[39]

Pulmonary artery hypertension (hemodynamically defined as mean pulmonary artery pressure [MPAP] ≥25 mm Hg and pulmonary vascular resistance ≥240 dynes • s • cm^{-5} by right heart catheterization) in a patient with established portal hypertension is known as *portopulmonary hypertension*. Importantly, moderate and severe portopulmonary hypertension (MPAP ≥35 mm Hg and MPAP ≥45 mm Hg, respectively) increases the mortality rate beyond that predicted by the MELD score and, if not improved by medical therapy, is a contraindication to LT (see Chapter 94).[40,41]

The *hepatopulmonary syndrome* (HPS) is characterized by the triad of chronic liver disease, pulmonary vascular dilatations (with right-to-left shunting), and hypoxemia.[42] The diagnosis is suggested by an arterial oxygen tension (PaO_2) less than 80 mm Hg on arterial blood gas obtained with the patient sitting upright or an alveolar-arterial (A-a) oxygen gradient of 15 mm Hg or greater when breathing ambient air; in patients older than 65 years of age, a PaO_2 of 70 mm Hg or less and an A-a gradient of 20 mm Hg or greater are commonly used thresholds (see Chapter 94). Liver transplant candidates should be screened for HPS with pulse oximetry, using a threshold saturation of peripheral oxygen (SpO_2) value less than 96% at sea level (corresponding to a PaO_2 <70 mm Hg). The sensitivity and specificity of pulse oximetry for diagnosing HPS are 100% and 88%, respectively; therefore, confirmatory evaluation should be performed in patients with a low SpO_2.[43] Definitive diagnosis is made by the demonstration of intrapulmonary vascular dilatations by contrast-enhanced echocardiography (which is the most sensitive technique), perfusion lung scanning with ^{99m}Tc-labeled macroaggregated albumin, or right heart catheterization with pulmonary arteriography. Contrast-enhanced echocardiography is the imaging test of choice for the diagnosis of HPS. Detection of contrast in the left side of the heart within 3 to 8 beats after its appearance in the right atrium indicates intrapulmonary shunting. Predictors of potential reversibility of HPS after LT include younger age, a lesser degree of preoperative hypoxemia, and adequate correction of hypoxemia with inspiration of 100% oxygen.[44] In the majority of patients with HPS, hypoxemia resolves within several months after LT, although protracted ventilatory support may be required. Because of the potential for improvement with LT, extra MELD points may be allocated to a patient with HPS.

HPS must be distinguished from portopulmonary hypertension because the latter is associated with high perioperative mortality and frequently unchanged pulmonary hemodynamics despite LT. Specifically, a MPAP greater than 35 mm Hg, pulmonary vascular resistance greater than 300 dynes • s • cm^{-5}, and cardiac output less than 8 L/minute are indicative of a high perioperative risk because the patient will be unable to increase cardiac output appropriately in response to altered intra- and postoperative hemodynamics. Vasodilator therapy may reduce pulmonary arterial pressure and permit LT (see Chapter 94).[45]

Hepatic hydrothorax is accumulation of transudative fluid in the pleural cavity, usually on the right side and often with relatively little ascites remaining in the abdominal cavity, as a result of portal hypertension (see Chapter 93). It can be difficult to manage, often requiring repeated thoracentesis or placement of a TIPS prior to LT.[46] Insertion of an indwelling pleural drainage catheter is usually discouraged, because it can lead to infection in the pleural cavity. Similarly, interventions such as pleurodesis or pleural decortication should be avoided.

Active uncontrolled extrahepatic infection is an absolute contraindication to LT. In patients with decompensated cirrhosis, unexplained clinical deterioration, such as the onset of altered mental status or systemic hypotension in the absence of GI bleeding, must be presumed to reflect sepsis and is an indication to start antibiotics empirically. LT, however, may be the only option for patients with recurrent bacterial cholangitis complicating PSC (see Chapter 68). Repeated bouts of SBP need to be controlled by antibiotic therapy prior to LT (see Chapter 93). A particularly

ominous finding is fungemia, which is typically impossible to eradicate in a debilitated patient with decompensated cirrhosis and precludes LT. HIV infection is not a contraindication to LT per se; however, the HIV viral load must be undetectable at the time of transplantation, and the CD4+ T-cell count should be greater than 100/μL in candidates who have never had an opportunistic infection and greater than 200/μL in those who have had an opportunistic infection.[47] Overall survival rates for HIV-infected liver transplant recipients are similar to those for non–HIV-infected recipients but have historically been worsened by HCV coinfection, inability of the patient to tolerate antiretroviral medications, and low CD4+ T-cell counts.[48] However, recurrent allograft HCV infection is decreasing dramatically with the availability of highly effective DAAs.

An important consideration in the liver transplant candidate is the presence of vascular abnormalities that may increase the complexity of surgery. With increased surgical experience, such abnormalities, most notably portal vein thrombosis, are less likely to be an obstacle to LT. More extensive vascular thrombosis with involvement of the superior mesenteric vein may require extensive vascular reconstruction.[49] The presence of a prior portosystemic shunt, particularly a nonselective (side-to-side or end-to-side) portacaval shunt, increases the technical complexity of LT (because the shunts need to be taken down during the surgery) but is not a contraindication. A TIPS placed to control complications of portal hypertension, including variceal hemorrhage, intractable ascites, and hydrothorax, is now the most frequently encountered shunt and does not usually present an operative challenge unless the stent extends into the inferior vena cava or the superior mesenteric vein.[50]

Age restrictions have been relaxed for liver transplant candidates, although close attention must be paid to comorbid conditions in older patients. The presence of comorbidities not only increases perioperative mortality but may also diminish the likelihood that the recipient will be able to return to an active lifestyle, particularly because severe liver disease may cause more debility in older than in younger patients.[51] Because a subset of robust older recipients have good outcomes, candidates in their late 60s or even older who are otherwise in good health should not be precluded a priori from LT.

The differential diagnosis of renal insufficiency in patients with advanced liver disease includes hepatorenal syndrome, which is potentially reversible (see Chapter 94). Renal insufficiency has a detrimental effect on survival in cirrhotic patients and remains an important predictor of poor outcomes after LT.[52] Typically, renal dysfunction in patients with decompensated cirrhosis reflects a variety of insults, including sepsis, hypotension, and use of nephrotoxic medications. Assessment of the potential for renal function to improve following LT is critical. According to UNOS policy (UNOS policy 9.7, available at www.unos.org), approval for simultaneous liver-kidney transplants (SLK) transplantation should be granted to patients with any of the following criteria: (1) chronic kidney disease (CKD), (2) sustained acute kidney injury, or (3) metabolic disease. CKD is defined by an estimated glomerular filtration rate (eGFR) of 60 mL/min or less for greater than 90 consecutive days before listing; to qualify for SLK transplantation, patients should also meet at least one of the following criteria: (1) hemodialysis has been started as standard treatment for end-stage renal disease or (2) an eGFR equal to or less than 30 mL/min at the time of listing and during the time the patient is on the kidney transplant waiting list. Sustained acute kidney injury is defined as the requirement for hemodialysis and an eGFR less than 25 mL/min for at least 6 consecutive weeks, and candidates for SLK transplantation must also meet at least one of the following criteria: (1) the candidate has been on dialysis at least once every 7 days or (2) an eGFR equal to or less than 25 mL/min at least once every 7 days. Metabolic diseases that are indications for SLK transplantation include hyperoxaluria, atypical hemolytic-uremic syndrome from mutations in complement factor H or factor I, familial nonneuropathic systemic amyloidosis, and methylmalonic aciduria.

An important reflection of impaired free water handling in patients with decompensated cirrhosis is dilutional hyponatremia. Consequences of marked hyponatremia include altered mental status and an increased risk of calcineurin inhibitor–induced neurotoxicity after LT (see later). Incorporation of the serum sodium level into the MELD formula (MELD-Na) increases the prognostic accuracy of the MELD score, particularly in patients with relatively low MELD scores, and is now used for organ allocation.[53,54]

Another consequence of decompensated cirrhosis is malnutrition. Loss of muscle mass increases the likelihood of perioperative morbidity, with the need for more protracted ventilatory support and poorer patient survival. Peripheral edema and ascites result in changes in body weight or anthropometric measurements such as the BMI, making them unreliable for assessing nutritional status in patients with advanced cirrhosis. More profound nutritional deficiencies may reflect the specific cause of cirrhosis, as with deficiency of multiple vitamins and electrolytes in a malnourished individual with alcohol use disorder or depletion of fat-soluble vitamins in a person with cholestatic liver disease due to malabsorption. Evaluation by a dietitian is an integral part of the pretransplant evaluation. Attempts to improve the nutritional status of liver transplant candidates have included enteral and parenteral nutritional support, which may result in improvement of clinical outcomes, albeit modest.[55] An increasingly growing pool of obese liver transplant candidates is raising concerns about the role of obesity in the pathogenesis of NAFLD and in postoperative mortality resulting from cardiovascular events, as well as postoperative complications such as wound infections.[56] Frailty is increasingly recognized in cirrhosis, particularly in patients listed for LT (17%). Importantly, frailty has been identified as a strong predictor of wait-list mortality in liver transplant candidates, even after adjusting for severity of liver disease and other important variables.[57]

TRANSPLANT EVALUATION AND LISTING

Although details of the evaluation process vary by center, key elements include confirmation that LT is indicated for the management of the potential recipient's liver disease, exclusion of comorbidities severe enough to preclude transplantation, and identification of adequate emotional and social resources for the patient to undergo a major surgical procedure and continue on long-term immunosuppression thereafter (Table 97.1). Approval for liver transplant evaluation is sought from the patient's insurance carrier before the necessary extensive testing is undertaken. The patient is typically seen during the pretransplant evaluation by a transplant surgeon, hepatologist, psychiatrist, dietitian, and social worker, with additional consultations as clinically indicated. As increasingly frailer and older candidates are evaluated, identifying potential causes of perioperative morbidity, such as sarcopenia or carotid artery stenosis, is imperative. Detailed abdominal imaging is performed not only to screen for HCC but also to uncover vascular abnormalities such as portal vein thrombosis that may make surgery technically challenging. Disease-specific issues need to be addressed, such as the likelihood of recidivism in a patient with alcohol use disorder or management of a large tumor burden in a patient with HCC. The appropriateness of LT is then discussed formally at a meeting of the patient selection committee. If the patient's candidacy is deemed to be appropriate, formal listing is undertaken with UNOS, followed by matching of recipients by blood type and weight with potential deceased donors. Once listed, a patient's priority for organ allocation is determined by the MELD score, either the "biological" score or with additional points awarded in specific circumstances such

TABLE 97.1 Transplantation Evaluation Process

Step	Comment
Financial screening	Secure approval for the evaluation
Medical evaluation	As discussed in the text
Hepatology evaluation	Confirm the diagnosis and optimize management
Laboratory testing	Assess hepatic synthetic function, serum electrolytes, renal function, viral serologies, markers of other causes of liver disease, tumor markers, ABO-Rh blood typing; 24-hr urine for creatinine clearance; urinalysis and urine drug screen
Cardiac evaluation	Electrocardiography and 2-dimensional echocardiography; stress testing and cardiology consult if risk factors are present and/or the patient is ≥40 years of age
Hepatic imaging	US with Doppler to document portal vein patency, triple-phase CT or MRI with gadolinium for tumor screening
General health assessment	Chest x-ray, colonoscopy if the patient is ≥50 years of age or has PSC, Pap smear and mammogram (women), consider prostate-specific antigen level (men)
Transplantation surgery evaluation	Assess technical issues and discuss the risks of the procedure
Anesthesia evaluation	Required if operative risk is unusually high (i.e., the patient has portopulmonary hypertension, hypertrophic obstructive cardiomyopathy, previous anesthesia complications)
Psychiatry or psychology consultation	If there is a history of substance use disorder, psychiatric illness, or adjustment difficulties
Social work evaluation	Address potential psychosocial issues and the possible effect of transplantation on the patient's personal and social supports
Financial and insurance counseling	Itemize the costs of transplantation and post-transplantation care; help develop a financial management plan
Nutritional evaluation	Assess the patient's nutritional status and provide patient education

Adapted from O'Leary JG, Lepe R, Davis GL. Indications for liver transplantation. Gastroenterology 2008;134:1764-76, with permission.

as HCC. With the seemingly intractable shortage of deceased-donor organs, the challenge has been to develop an equitable system of organ allocation and to ensure that hepatic allografts are not allocated to recipients whose prognosis without LT remains good. Patients with a MELD score of less than 15 appear to have better survival without rather than with transplantation.[58] As shown in Fig. 97.2, the MELD score has been found to correlate with the 3-month survival rate. Patients with a MELD score of less than 10 are ineligible for active listing with UNOS unless they receive extra points for additional complications of liver disease, such as HCC or HPS (UNOS policies 3.6.4.4 and 3.5.5.1, available at www.unos.org).

Once the evaluation process is complete and the patient is accepted for LT, financial clearance is sought from the patient's insurer. Unfortunately, criteria for LT coverage vary among insurers; however, in the USA, if Medicare, the major federal payor, funds a particular indication, other insurance carriers generally follow suit.

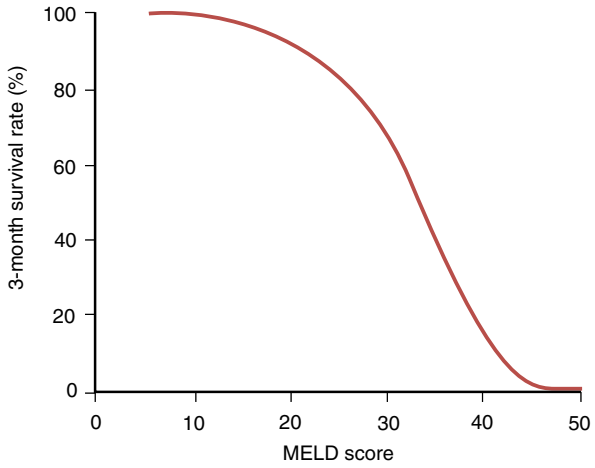

Fig. 97.2 Relationship between the 3-month survival rate and the MELD score in patients with cirrhosis.

DISEASE-SPECIFIC INDICATIONS

Hepatic Malignancy

HCC is the most common primary hepatic malignancy in adults and is currently the leading indication for LT in the USA.[14] This neoplasm typically occurs in the setting of cirrhosis; a notable exception is chronic HBV infection, in which HCC can arise in the absence of cirrhosis (see Chapters 79 and 96). The likelihood of tumor recurrence increases markedly with greater tumor burden, vascular invasion, the presence of multiple lesions, alpha-fetoprotein levels greater than 1000 ng/mL, and certain histologic features such as high nuclear grade, microsatellitosis, and presence of giant or bizarre cells.[59,60] LT remains the definitive treatment of choice for HCC in patients with cirrhosis; indeed, it accounts for approximately 20% to 40% of adult LT performed at most centers worldwide, reflecting the frequency of HCC in patients with cirrhosis and the awarding of extra MELD points for this neoplasm.[61]

Improvements in outcome of LT for HCC are attributable to better patient selection rather than post-transplant adjuvant therapies.[62] The preoperative workup includes a bone scan and chest CT, in addition to abdominal imaging. Portal vein occlusion in a patient with HCC is typically considered evidence of metastatic spread, which precludes LT. PET-based imaging is not accurate for staging early HCC. Generally accepted criteria for LT in patients with HCC include a tumor diameter of less than 5 cm, if the tumor is solitary, or no more than 3 lesions, with the diameter of the largest lesion measuring no greater than 3 cm—the so-called Milan criteria, based on an initial experience from that city. Patients who meet the Milan criteria have a post-transplant survival rate comparable to that for patients undergoing LDLT for decompensated cirrhosis in the absence of complicating HCC: 75% at 4 years.[63] Whether the Milan criteria are excessively restrictive, excluding potential recipients who might have done well with a low risk of tumor recurrence, remains controversial.[62] Expanded criteria have been proposed from multiple groups including the University of California, San Francisco (UCSF) to increase the limits of tumor size and number while preserving patient survival rates: specifically, a solitary tumor measuring 6.5 cm or less in diameter or no more than 3 lesions, with the largest lesion measuring 4.5 cm or less and a total tumor diameter of 8 cm or less.[64,65] A meta-analysis, however, supports restriction of LT for HCC to patients who meet the Milan criteria rather than exceed them, although significant heterogeneity among included studies limits the strength of this conclusion.[66] With LDLT, recipients with HCC beyond Milan

criteria had comparable survival to those meeting the criteria.[66] The comparable survival between patients undergoing LDLT for HCC under the Milan criteria and those undergoing LT under the expanded criteria reflects a reduction in waiting time for LDLT. An international consensus statement, however, concluded that the Milan criteria remain the benchmark for selection of potential LT candidates with HCC.[67]

Adoption of the MELD score and awarding of exception points resulted in proportionally more patients with HCC undergoing LT.[68] In the most recent modification of the MELD score, patients with a solitary HCC measuring less than 2 cm do not receive additional MELD points, and patients with a solitary HCC measuring 2 to 5 cm or 3 nodules each measuring less than 3 cm are initially listed for LT with their "biological" MELD score but automatically accrue 28 points after 6 months, and continue to accrue 10% increments every 3 months until attaining a score of 34, at which point the exception points are capped.[69] Importantly, when expanded criteria for LT (i.e., UCSF criteria) are used in patients with HCC, no additional MELD points are given to these patients.

Strategies to expand criteria for LT in HCC include downstaging the tumor with the use of locoregional therapies so that the Milan criteria are met; whether this approach will ultimately improve patient survival remains to be determined (see Chapter 96).[65] For example, transarterial chemoembolization is commonly used to reduce tumor burden during the often protracted wait for LT. This intervention, however, can be hazardous in patients with decompensated cirrhosis. Radiofrequency ablation has also been used increasingly to manage HCC in transplant candidates.

Confounding the management of LT candidates with HCC is the frequent observation that the tumor burden in the explant is significantly underestimated by preoperative imaging studies. The use of locoregional therapies for HCC reduces waiting list dropout rates. A Markov model has suggested that these interventions could be cost effective when the time on the waiting list exceeds 6 months.[70,71]

One class of immunosuppressive agents, the mammalian target of rapamycin (mTOR) inhibitors (i.e., sirolimus and everolimus), has antineoplastic properties, and uncontrolled pilot studies had suggested lower tumor recurrence rates and improved survival in liver transplant recipients with HCC treated with sirolimus.[72,73] These results, however, have not been confirmed in randomized controlled trials, and therefore, current recommendations do not endorse the routine use of mTOR inhibitors to reduce the risk of HCC recurrence after LT.[67] Systemic chemotherapy for HCC with sorafenib in combination with sirolimus has been evaluated for treatment of recurrent HCC following LT, albeit only in small and uncontrolled preliminary studies. Conclusions about the efficacy of sorafenib in the treatment of post-LT recurrent HCC cannot be established at this time; however, there appear to be frequent side effects with sorafenib use in this setting.[74,75]A retrospective study showed that preemptive treatment with sorafenib in LT recipients with high-risk features for post-transplant recurrence noted in the explant (1 viable tumor exceeding Milan criteria, micro- or macrovascular invasion, lymph node or hepatic capsule invasion, or satellite nodules) was not associated with increased recurrence-free survival.[76] There are currently no data about the efficacy or safety of regorafenib for prevention of recurrent HCC post-LT. Nivolumab has been licensed for treatment of HCC in nontransplant populations, and scant data from a small series suggest an increased risk for irreversible acute graft rejection when this agent is used in LT recipients.[77]

Patients with the fibrolamellar variant of HCC, which is more common in younger adults without underlying cirrhosis, often present when the tumor burden is already large (see Chapter 96). Extensive resection can be tolerated because cirrhosis is absent, and LT may be performed in patients who have recurrent tumor after resection. Tumor recurrence after LT may be relatively indolent, and although not as infrequent as was once thought, survival rates are acceptable.[78]

Hepatoblastoma is a rare pediatric tumor that also occurs in the absence of underlying parenchymal liver disease. Initial management consists of surgical resection. Adjuvant chemotherapy is indicated for metastatic disease, and LT is an option when the tumor cannot be resected (see Chapter 96).

Cholangiocarcinoma remains the only major primary hepatic tumor for which a definitive role for LT has been difficult to establish. Outcomes following LT for cholangiocarcinoma diagnosed preoperatively had been so poor that its presence has been regarded as a contraindication to LT, and even tumors discovered only incidentally in the explant have a high recurrence rate. A subset of patients with a perihilar tumor and absence of nodal involvement have acceptable 5-year survival rates. The tumor burden, however, is frequently more extensive than suspected on imaging. The addition of en bloc pancreaticoduodenectomy to LT has not improved survival. Newer approaches to treatment include preoperative irradiation and chemotherapy, with careful intraoperative tumor staging followed by LT (see Chapter 69). A retrospective report evaluating the efficacy of neoadjuvant chemoradiation followed by LT for treatment of perihilar cholangiocarcinoma showed a 65% recurrence-free survival rate at 5 years, with the size of the tumor being an important determinant of recurrent disease (32% and 69% recurrence-free survival rates for patients with tumors measuring 3 cm or less and greater than 3 cm, respectively).[79]

Alcohol-Associated Liver Disease

Alcohol-associated liver disease remains the most frequent cause of decompensated chronic liver disease (see Chapter 86).[80] Decompensated alcohol-associated cirrhosis is now firmly established as an appropriate indication for LT, despite some lingering controversy, and has become the leading non-neoplastic indication for LT in adults in the USA.[81] Concerns had included recidivism following LT, as well as potentially poor patient adherence; however, these fears have not been confirmed.[82] Excellent graft and patient survival rates are the norm following LT for alcohol-associated liver disease.

Key factors in determining candidacy for LT include recognition by the patient of the key role alcohol has played in the genesis of the liver disease, participation in some form of alcohol rehabilitation such as attendance at Alcoholics Anonymous, stable social support, and a defined period of abstinence prior to LT. Conventionally this period of abstinence has been 6 months, although rigorous studies have failed to confirm that this duration of abstinence confers a high likelihood of continued sobriety but have emphasized the importance of adverse factors such as social isolation or depression. Up to 25% of patients with alcohol-associated liver disease listed for LT deemed to be abstinent continue to use alcohol; therefore, monitoring for continued abstinence is prudent.[83] Nevertheless, despite these strategies, as many as 40% of transplant recipients resume alcohol use during long-term follow-up.[84] Surprisingly, graft loss or early death attributable to post-transplant alcohol abuse has been uncommon. A higher rate of return to alcohol use is elicited by use of anonymous questionnaires or toxicology screening than by direct questioning of patients.

Particularly difficult dilemmas arise in individuals with severely decompensated liver disease and recent alcohol use, in whom the likelihood of surviving without prompt LT is low, and in those with severe alcohol-associated hepatitis (defined by a Maddrey's discriminant function score ≥32) that is nonresponsive to medical therapy with glucocorticoids (Lille score ≥0.45 after 7 days of medical therapy or continuous rise in the MELD score; see Chapter 86). To offer or not to offer LT to individuals with severe acute alcohol-associated hepatitis not responding to medical therapy represents a growing quandary, as data from clinical

trials have demonstrated a higher rate of survival 6 months after LT compared with those who continue medical therapy (77% and 23%, respectively).[82] In addition, post-transplant outcomes are similar in patients with alcohol-associated hepatitis and those with alcohol-associated cirrhosis.[85]

Clearly enunciated criteria, including a contractual commitment by the patient to sobriety and active involvement in alcohol rehabilitation, ensure that selection is equitable. Patients who return to pathologic drinking after LT have more medical problems, including pneumonia, cellulitis, and pancreatitis, that can lead to graft loss and death.[86] In addition, recipients with alcohol use disorder are prone to develop de novo oropharyngeal and lung tumors, likely reflecting other aspects of their lifestyle—most notably cigarette smoking.[87]

NAFLD

NAFLD is an increasingly frequent cause of cirrhosis and HCC (see Chapter 87). In fact, a report published in 2018 listed NAFLD as the second leading non-neoplastic indication for LT in adults in the USA, following alcohol-associated liver disease.[16] Obesity (BMI ≥30 kg/m^2) and type 2 diabetes mellitus are commonly encountered in patients with NAFLD; these 2 diseases have been recognized as risk factors for HCC, irrespective of the presence or etiology of cirrhosis.[88] Although BMI is not necessarily a reliable indicator of adiposity in patients with end-stage liver disease, particularly in those with fluid retention and ascites, it is commonly used by many LT centers during the patient selection process. Morbid obesity (BMI ≥40 kg/m^2 without significant obesity-related comorbidities or BMI ≥35 kg/m^2 associated with obesity-related comorbidities) is commonly regarded as a relative contraindication to LT; however, data from the Organ Procurement and Transplantation Network demonstrate that 16.5% and 5% of patients who underwent LT in 2016 had a BMI greater than or equal to 35 kg/m^2 and greater than or equal to 40 kg/m^2, respectively.[81]

Analysis of data from the UNOS registry has suggested that the risk of primary graft nonfunction is increased and short- and long-term survival is poorer in morbidly obese liver transplant recipients with various causes of end-stage liver disease.[89] However, when analyzed as an entire cohort and not stratified by BMI, patients with NAFLD have patient and graft survival rates that are comparable to those for other indications for LT.[90,91] Many of the key precipitants of NAFLD (obesity, hyperlipidemia, and insulin resistance) are exacerbated by immunosuppression.[92] Recurrence of NAFLD after LT causes graft injury, although graft loss does not typically occur. De novo NAFLD after LT has also been described. In the absence of specific therapy for NAFLD, therapeutic efforts after LT should center on weight control, optimal diabetic management, and use of a lipid-lowering agent, if indicated. Intensive noninvasive weight loss interventions pre-LT appear to be successful (reduction of BMI to <35 kg/m^2) in a large proportion of patients (84%) enrolled in carefully monitored multidisciplinary protocols; however, 60% of patients regained weight to a BMI ≥35 kg/m^2 post-LT.[93] Although bariatric surgery is feasible in selected patients with NAFLD, this intervention is typically reserved for patients with early stages of liver disease and, as is the case for many other abdominal surgical procedures, is contraindicated in those with decompensated cirrhosis because of high morbidity and mortality. A strategy of combining LT with sleeve gastrectomy during the same operation has only been evaluated in small prospective series.[93,94] The mean surgical time was not significantly different between LT and combined LT/sleeve gastrectomy, and the mean BMI reduction with the combined surgical approach was 20 kg/m^2. Metabolic complications, such as post-transplant diabetes mellitus, as well as steatosis of the graft noted by US were significantly less frequent in patients undergoing LT/sleeve gastrectomy compared with patients who lost weight noninvasively pre-LT.[93] The safety and efficacy of this combined surgical approach and other combinations of less invasive weight loss interventions, such as endoscopic techniques, pre-LT must be confirmed by large prospective studies before they can be recommended. Bariatric interventions are still an option post-LT; however, the procedure should be performed by an experienced surgeon, and the role of less invasive endoscopic techniques post-LT is still under investigation.[95]

Hepatitis C

HCV infection was previously the most frequent indication for LT in the USA and many other Western countries; however, data following licensure of DAAs demonstrated a marked decline in the yearly number of wait-listed and transplanted patients for HCV-related liver disease.[17,18] HCV has become the third commonest non-neoplastic indication for LT in adults in the USA, after alcohol-associated liver disease and NAFLD. Recurrent HCV infection post-LT had been a major concern, because, if left untreated, it leads to accelerated fibrosis and progression to cirrhosis, resulting in inferior graft and patient outcomes compared with LT for other major causes of cirrhosis. Treatment of recurrent HCV infection in LT recipients changed dramatically with the availability of DAAs that permit use of interferon-free regimens that are highly effective, safe, and associated with a low rate of drug-drug interactions.

Biopsy of the graft helps identify recipients with recurrent HCV infection at increased risk of rapidly progressive disease. Less than 10% of patients with histologically mild recurrent HCV infection at 1 year after LT progress to cirrhosis of the graft within 5 years, whereas two thirds of those with at least moderately severe HCV infection at one year after LT develop cirrhosis.[96] Concern has been raised, however, that with longer follow-up, some patients with initially mild recurrent HCV infection will also progress. A prospective study using serial protocol liver biopsy specimens to assess the histologic outcomes of 57 HCV genotype 1b–infected liver transplant recipients with an initially mild histologic recurrence, defined as no or minimal hepatic fibrosis (fibrosis stage F0 or F1) during the first 3 years after LT (see Chapter 80), found that some degree of fibrosis at baseline appears to predict accelerated recurrent HCV infection.[97] With effective antiviral therapy with DAAs resulting in sustained virological response, however, this progression will be avoided.

A particularly ominous manifestation of recurrent HCV infection had been fibrosing cholestatic hepatitis (FCH). The frequency of FCH in some series had been as frequent as 5% to 10%. Infection with HCV genotype 1, and recipient interleukin-28B (interferon lambda-3) genotypes CT or TT (see Chapter 80) were implicated in the development of FCH, as was excessive immunosuppression.[98,99] Histologically, FCH is characterized by extensive dense portal fibrosis with immature fibrous bands extending into sinusoidal spaces, ductal proliferation with hypercellularity, marked canalicular and cellular cholestasis, and moderate inflammation with mononuclear cells.[100] These histologic features, however, lack specificity and may also be observed in acute cellular rejection and chronic graft rejection. Recognition of FCH should prompt a reduction in immunosuppression and initiation of antiviral therapy.[100a]

Reported predictors of severe recurrent HCV infection have included a number of viral and nonviral factors (Box 97.3). Higher serum levels of HCV RNA before and immediately after LT, as well as the possibility of more rapid evolution of HCV quasispecies, have been implicated in aggressive recurrent HCV infection (see Chapter 80).[97] Older deceased-donor age is also an important risk factor. Episodes of acute cellular rejection, particularly if multiple, increase the severity of recurrent HCV infection.

BOX 97.3 Factors Associated with Severe HCV Recurrence Following LT

VIRAL FACTORS

Absence of pretransplantation HBV coinfection
CMV coinfection
HCV genotype 1b
High serum HCV RNA levels before transplantation and within 2 wk after transplantation

IMMUNOSUPPRESSION

Multiple episodes of rejection (indicating a high cumulative prednisone dose)
Use of OKT3 to treat rejection

OTHER FACTORS

High TNF-α production in the graft
Impaired HCV-specific $CD4^+$ T-cell responses
Ischemic-preservation injury
Non-white recipient

A major challenge is to distinguish recurrent HCV infection from graft rejection, because many of the histologic hallmarks of acute rejection, including bile duct injury, are also consistent with recurrent HCV infection. Examination of serial liver biopsy specimens may help clarify this issue and help avoid inappropriate additional immunosuppression in the recipient with recurrent HCV infection, rather than graft rejection. Nevertheless, the replacement of interferon-based regimens with DAAs now allows early initiation of antiviral therapy even if rejection remains in the differential for graft injury.

Once recurrent HCV infection of the graft progresses to cirrhosis, hepatic decompensation, had been frequent until DAAs, which permit treatment of HCV infection even in patients with decompensated cirrhosis prior to LT, became available.[4] Strategies for the treatment of HCV infection in individuals being considered for LT generally fall into 2 broad categories: (1) pre-LT antiviral therapy, with some restrictions of specific antiviral agents in individuals with decompensated cirrhosis, and (2) post-LT antiviral therapy, generally with initiation of antiviral therapy within 6 months after LT. Results of a simulated model have shown that treating HCV infection pre-LT in candidates with a high MELD score (≥27) may not offer a meaningful benefit and, in fact, may be associated with decreased life expectancy in some cases.[101] Importantly, the decision to treat HCV pre- versus post-LT should be made in conjunction with the transplant center, because many centers now consider transplanting HCV-positive grafts into individuals with HCV infection with administration of antiviral therapy following transplantation. This approach is supported by the International Liver Transplantation Society, which has endorsed antiviral treatment pre-LT for liver transplant candidates with a MELD score less than 20 (in the absence of refractory portal hypertension or other condition requiring more immediate LT) or with HCC who are not expected to undergo LT within 3 to 6 months.[2]

Hepatic function commonly improves during and after successful antiviral therapy with DAAs, even in individuals with severe hepatic decompensation, as reflected mainly by reductions in the serum bilirubin level and the prothrombin time, thereby resulting in lower MELD scores.[102,103] Nevertheless, despite reductions in the MELD score, some patients may continue to experience a poor quality of life and severe complications of cirrhosis. This scenario has been termed "MELD limbo" or "MELD purgatory" and should be considered before antiviral therapy is started in a patient with decompensated cirrhosis and a MELD score approaching the range in which LT is a realistic option,[104] particularly if manifestations of hepatic decompensation, such as intractable ascites, which is not captured by the MELD score, are present. DAAs are highly effective and now commonly used to treat recurrent HCV infection post-LT with excellent safety profiles and high virologic efficacy. Drug-drug interactions must be anticipated, and appropriate dose adjustments and close monitoring of immunosuppression during and after antiviral therapy are mandatory (see also Chapter 80).

Hepatitis B

The availability of the HBV vaccine and public health interventions to promote universal immunization of newborns and high-risk individuals, along with access to potent oral antiviral agents with low rates of resistance, have resulted in a steady decline in the need for LT in patients with decompensated cirrhosis due to HBV infection in the USA and many other countries.[105,106] In addition, suppression of HBV prior to LT leads to a lower rate of recurrent HBV infection of the graft and improved survival after LT.[107] Effective prevention of graft reinfection in HBV-infected candidates has been a major triumph in LT. HBV recurrence was frequent and resulted in reduced patient and graft survival rates during the 1980s. Long-term administration of high-dose hepatitis B immune globulin (HBIG) was the initial step in improving post-transplant outcomes. Subsequently, HBIG administered in combination with the nucleoside analog lamivudine further decreased the rate of HBV recurrence. Lamivudine monotherapy for prevention of recurrent post-LT HBV infection was limited by frequent mutations in the HBV polymerase gene, with resulting resistance and graft reinfection (see Chapter 79).[108] Some groups have titrated HBIG doses according to trough serum levels of antibody to hepatitis B surface antigen (anti-HBs). Intramuscular administration of HBIG has been confirmed as an efficacious and less expensive alternative to intravenous HBIG regimens when used in combination with lamivudine. In addition, novel formulations of HBIG for subcutaneous administration are being evaluated.[109,110] Use of HBIG, however, is being replaced by newer oral antiviral agents with a low risk of HBV resistance and a further decrease in post-LT HBV recurrence rates.[111] Emerging data support the efficacy of entecavir and tenofovir in preventing recurrence of hepatitis B after LT, and the use of these potent antiviral agents may obviate the need for HBIG.[112,113] The results of prospective studies evaluating the efficacy of entecavir, tenofovir, or a combination of emtricitabine and tenofovir in preventing post-LT recurrence of HBV after discontinuation of HBIG have supported this approach.[114,115]

Cholestatic Liver Disease

PBC and PSC are less common indications for LT. Despite a steady increase in the incidence and prevalence of PBC, there has been a decline in the absolute number of patients requiring LT due to end-stage liver disease, primarily because of earlier diagnosis and the efficacy of pharmacotherapy in delaying disease progression.[116] PBC and PSC played a key role in the development of prognostic models, and PBC is a benchmark for patient and graft survival. The Mayo disease models to predict the course of cholestatic disorders (Table 97.2) have aided in determining the optimal timing of referral for LT (see Chapters 68 and 91). A patient with PBC or PSC should be referred for LT evaluation if his or her Mayo risk score predicts a one-year survival rate of less than 95%. The models, however, do not take into account prominent and frequently disabling complications of cholestatic liver diseases, such as pruritus, fatigue, osteopenia, or, in PSC, recurrent bouts of bacterial cholangitis, and have now been superseded by the MELD score. Indications for LT in patients with cholestatic liver diseases are similar to those for patients with other chronic liver diseases. Additional MELD points may be granted to patients with PSC with either (1) 2 or more episodes

TABLE 97.2 Components of the Mayo Predictive Models for Survival in PBC and PSC

PBC	PSC
Serum bilirubin level	Serum bilirubin level
Serum albumin level	Serum albumin level
Patient's age	Patient's age
Prothrombin time	Serum AST level
Peripheral edema	History of variceal bleeding

Adapted from Murtaugh PA, Dickson ER, Van Dam GM, et al. Primary biliary cirrhosis: prediction of short-term survival based on repeated patient visits. Hepatology 1994;20:126-34; and Kim WR, Therneau TM, Wiesner RH, et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clin Proc 2000;75:688-94.

of culture-proved bacteremia within a 6-month period or (2) noniatrogenic septic complications of cholangitis, no identifiable correctable structural lesion, and absence of a biliary stent.[117] Despite generally excellent outcomes of LT for cholestatic disorders, PBC and PSC recur in approximately 25% of recipients at 10 years post-transplantation.[118,119]

The type of reconstructive biliary anastomosis for patients with PSC undergoing LT has been a matter of debate: Roux-en-Y hepatico- or choledochojejunostomy versus a duct-to-duct anastomosis. Roux-en-Y hepatico- or choledochojejunostomy has been the preferred reconstructive technique by many surgeons because of concern about the development of nonanastomotic biliary strictures post-LT and risk of cholangiocarcinoma in the remnant recipient bile duct. However, data suggest that a duct-to-duct anastomosis is safe, technically feasible in most cases, and associated with lower frequencies of post-LT cholangitis and nonanastomotic strictures compared with Roux-en-Y hepatico- or choledochojejunostomy. Published series have shown no difference in recurrence of PSC or survival between these 2 biliary reconstructive techniques.[120,121] From a therapeutic perspective, one of the main advantages of a duct-to-duct anastomosis is that it permits easier endoscopic access for treatment of anastomotic strictures or other post-transplant biliary complications (see Chapter 70).

Biliary stricturing can be identified in a minority of recipients following LT for PSC. Differentiation of recurrent disease from other causes of graft injury, such as chronic rejection or ischemia, may be difficult. Recurrent PSC results in nonanastomotic stricturing of the intrahepatic biliary tract. Although some improvement in symptoms can be obtained by balloon dilation and stent placement, long-term graft viability is reduced. Graft loss caused by recurrent PBC appears to be less frequent than that for PSC. A controversial issue is whether colectomy reduces the risk of recurrent PSC in liver transplant recipients with PSC and IBD (see Chapter 68).[122]

Management of recurrent PBC entails exclusion of other causes of hepatic dysfunction. Primary immunosuppression with tacrolimus has been implicated in the recurrence of PBC by some but not all investigators. Data from a retrospective study have suggested that preemptive administration of UDCA to individuals who have undergone LT for PBC may diminish the risk of recurrent PBC post-transplantation; however, these results need to be corroborated by prospective studies before this intervention can be widely recommended.[123] There are as yet no data about the role of obeticholic acid for prevention of recurrent PBC post-transplantation (see Chapter 91).

Autoimmune Hepatitis

Failure of immunosuppression to arrest progression of autoimmune hepatitis and subsequent overt hepatic decompensation is an indication for LT (see Chapter 90).[124] In addition, the initial presentation of autoimmune hepatitis can be fulminant, requiring prompt LT, and a trial of glucocorticoid therapy may not be prudent because of the patient's decompensated state. Excellent long-term survival is usual after LT for autoimmune hepatitis, although acute cellular rejection may occur more frequently than in recipients with other causes of cirrhosis. In addition, recurrent autoimmune hepatitis has been recognized increasingly and may require higher maintenance doses of immunosuppression. Recurrent disease mimics the features of the disease in the native liver, with associated hypergammaglobulinemia and autoantibodies, and is generally responsive to glucocorticoids. Graft survival is generally not reduced by recurrent autoimmune hepatitis.[125]

BOX 97.4 Criteria for LT in ALF

CRITERIA OF KING'S COLLEGE, LONDON

Acetaminophen Cases

Arterial pH <7.30 more than 24 hr after drug ingestion*
All of the following:
- Prothrombin time >100 sec or INR >6.5
- Serum creatinine level >3.4 mg/dL (300 μmol/L) or anuria
- Grade 3 to 4 encephalopathy

Nonacetaminophen Cases

Prothrombin time >100 sec or INR >6.7
Any 3 of the following:
- Unfavorable etiology (seronegative hepatitis or drug reaction)
- Age <10 or >40 yr
- Acute or subacute category (duration of jaundice >7 days)
- Serum bilirubin level >17.5 mg/dL (300 μmol/L)
- Prothrombin time >50 sec or INR >3.5

CRITERIA OF HÔPITAL PAUL-BROUSSE, VILLEJUIF

Hepatic encephalopathy *and*
Factor V level <20% in patients age <30 yr OR
Factor V level <30% in patients age ≥30 yr

*Subsequent modification: arterial pH <7.30 or serum lactate >3.0 mmol/L after adequate fluid resuscitation.
From Keeffe EB. Liver transplantation: current status and novel approaches to liver replacement. Gastroenterology 2001;120:749-62, with permission.

ALF

ALF is an uncommon but important indication for LT, owing to a low likelihood of spontaneous recovery. ALF is defined by the onset of hepatic encephalopathy within 26 weeks of the initial recognition of acute liver disease (see Chapter 95). Despite an abrupt onset, antecedent chronic liver disease is absent, and hepatic recovery is possible. In the past, LT for ALF resulted in poorer patient survival rates than those for benchmark indications such as PBC. Subsequent experience, however, has shown that excellent patient survival rates are possible if ALF is identified early in its course and transplantation occurs before irreversible complications, especially neurologic, supervene.[126] The absence of papilledema on funduscopy and of typical findings on CT do not preclude the presence of cerebral edema complicating worsening encephalopathy; therefore, direct intracranial pressure monitoring may be useful to detect and manage this frequently lethal complication of ALF. Direct intracranial pressure monitoring can only be recommended, however, if local neurosurgical expertise and interest are available, because a high rate of complications has tempered enthusiasm for its use. Patients with ALF, regardless of etiology, should be referred promptly for urgent LT evaluation. Specific criteria to identify patients with ALF who are unlikely to recover spontaneously are shown in Box 97.4. The challenge in

managing patients with ALF is to avoid unnecessary LT in those who will recover spontaneously or who will not recover with LT, while not delaying it in patients in whom it is their only option for survival. The role of liver assist devices in managing ALF, either as definitive therapy or as a "bridge to transplantation," remains an area of active investigation (see Chapter 95).

Metabolic Disorders

Metabolic disorders amenable to LT (see Chapters 75 to 77) fall into 2 broad categories: diseases dominated clinically by obvious hepatocellular disease (e.g., Wilson disease, hemochromatosis, α^1-antitrypsin deficiency) and those without clinical evidence of liver disease (e.g., primary hyperoxaluria, familial hypercholesterolemia). Metabolic disorders in general are more prominent in pediatric patients. Adult indications for LT include Wilson disease and hemochromatosis. Substantial improvement can occur following LT for Wilson disease in patients who present with neurologic involvement. A Wilsonian crisis with severe hemolysis is an indication for urgent LT because chelation therapy is ineffective. Compared with other forms of cirrhosis, hemochromatosis was previously associated with poorer survival following LT; however, a more recent study analyzing outcomes for transplants performed between 1997 and 2006 demonstrated survival comparable with that for other indications for LT.[127] Iron reaccumulation in the graft of patients transplanted for hemochromatosis is a theoretical concern, but iron depletion is not typically required.[128] LT has also been performed as a curative procedure in combination with renal transplantation for primary hyperoxaluria, in which end-organ damage is confined to the kidney but the metabolic defect is hepatic. LT may be indicated in cases of multiple hepatic adenomas associated with glycogen storage disease and not only eliminates the risk of progression to HCC but also corrects the underlying metabolic disorder (see Chapter 77).

Vascular Disorders

Budd-Chiari syndrome, characterized by hepatic venous outflow obstruction, often mimics decompensated cirrhosis (see Chapter 85).[129] Good long-term results have been described in patients who undergo prompt TIPS or portosystemic shunt surgery, although LT is typically required if advanced fibrosis is present on a liver biopsy specimen. Despite the frequency of an underlying myeloproliferative disorder, accelerated progression to leukemia or bone marrow failure does not seem to occur after LT. Long-term anticoagulation is indicated in transplant recipients with Budd-Chiari syndrome.

Sinusoidal obstruction syndrome (SOS) is a vascular disorder manifested by necrosis of zone 3 hepatocytes and fibrous obliteration of the lumen of central venules. Most commonly seen after hematopoietic stem cell transplantation (HSCT), SOS may lead to hepatic failure and death in up to 25% of patients, despite an otherwise successful procedure. Although experience with LT for hepatic complications of HSCT is limited, LT appears to be the only intervention that consistently alters the course of advanced SOS.[130] Similarly, LT has been shown to be effective in the management of severe post-HSCT graft-versus-host disease with predominantly hepatic involvement (see Chapter 36). Patients with hypocoagulable (e.g., hemophilia A and B) as well as hypercoagulable (e.g., protein C and S deficiencies) hematologic disorders who undergo LT for other indications have been cured of these disorders owing to production of normal clotting factors by the graft and its vascular tissue.

Others

Several other diagnoses are potential indications for LT (see Box 97.1). Adult polycystic disease with marked abdominal distention resulting from multiple hepatic cysts that are not amenable to resection has been treated successfully by LT (see Chapter 96). If CKD is present, combined liver-kidney transplantation is indicated. Cerebral imaging is indicated to exclude intracranial aneurysms, which are a feature of this disease.[131] Diseases with multiorgan involvement for which LT has been performed include Alagille syndrome, sarcoidosis, and amyloidosis (see Chapters 37 and 62). LT successfully arrests systemic manifestations of familial amyloid polyneuropathy. In addition, the explant, which is the source of the abnormal protein, is available for use in a "domino" fashion in an older recipient who will not live long enough for neurologic injury to develop.[132] Biliary cirrhosis associated with CF also has been managed successfully with LT, although patients remain at risk for infectious and other complications of this systemic disorder (see Chapters 57 and 77).

SURGICAL ASPECTS

Once a potential organ donor is identified, the local organ procurement organization coordinates harvesting and supplies pertinent donor medical information to centers with suitable potential recipients listed with UNOS. In contrast to other types of organ transplantation, including kidney transplantation and HSCT, absence of HLA compatibility does not appear to affect liver graft survival. Donor-recipient matching is based primarily on ABO blood compatibility and recipient weight. In critically ill recipients, an ABO-incompatible organ may be implanted, with the recognition that graft survival may be diminished.[133] In addition to screening serologic studies and routine liver biochemical testing, particular attention is paid to the donor's medical history, including cardiovascular instability and the need for vasopressor support before determination of brain death.

The typical deceased donor has had a catastrophic head injury or an intracerebral bleed, with brain death but without multisystem organ failure. Electrolyte imbalance and hepatic steatosis in the donor are predictors of graft nonfunction. A "donor risk index" has been derived to assess the likelihood of good graft function.[134] Key adverse factors include older donor age (especially >60 years of age), use of a split or partial graft, and a non–heart-beating donor, from which the organs are harvested after the donor's cardiac output ceases, in contrast to the more typical deceased donation in which the organs are harvested prior to cardiovascular collapse. Use of non–heart-beating donors is associated with reduced rates of long-term graft survival and increased risk of biliary complications, which correlate with the duration of "warm ischemia" after cardiovascular collapse and before retrieval of the organ.[134a] With the critical shortage of deceased organ donors, expansion of the donor pool has included acceptance of donors 70 years of age and older for selected recipients.

Prior to hepatectomy, the harvesting team makes a visual and, if necessary, histologic assessment of the donor organ. Particular attention is paid to anatomic variants in the hepatic artery that may complicate the graft arterial anastomosis in the recipient. Once donor circulation is interrupted, the organ is rapidly infused with a cold preservation solution (e.g., University of Wisconsin, histidine-tryptophan-ketoglutarate, or Institut Georges Lopez solution). Donor iliac arteries and veins are also retrieved in case vascular grafting is required. After its arrival at the recipient institution, further vascular dissection, with arterial reconstruction if necessary, is performed before implantation.

Splitting deceased donor livers either in situ during harvesting or ex vivo on return to the transplant center allows 2 recipients to receive portions of the organ if graft volume and quality are sufficient. An adult deceased donor liver can be divided into 2 functioning grafts; the left lateral segment (segments II and III) is used for a pediatric recipient, and segments IV to VIII (the so-called right trisegment) are used for an adult recipient. Acceptable graft and patient survival rates can be obtained with split grafts, although

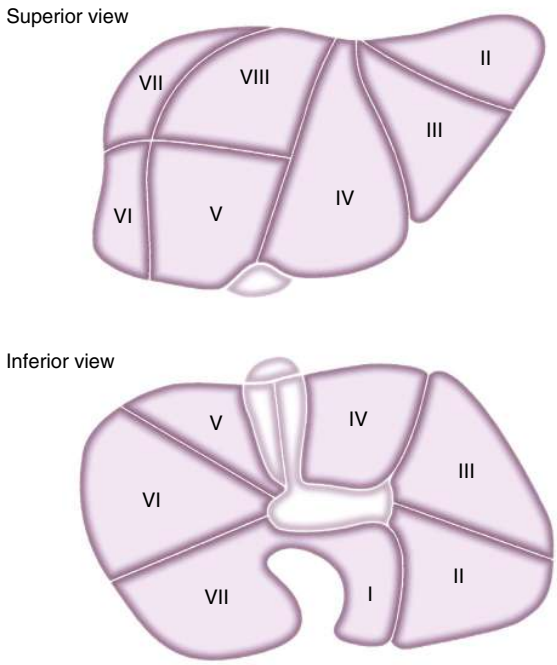

Fig. 97.3 Superior and inferior views of the segmental anatomy of the liver. Segment VIII is visible only on the superior view, and segment I (caudate lobe) is visible only on the inferior view. (From Keeffe EB. Liver transplantation: Current status and novel approaches to liver replacement. Gastroenterology 2001;120:749-62, with permission.)

high-risk unstable recipients may have poorer outcomes. Fig. 97.3 shows the segmental anatomy of the liver, which is the basis of dissection for both split and LDLT.

Native Hepatectomy

Removal of the native liver is the most technically challenging aspect of deceased-donor LT. Previous abdominal surgery and severe portal hypertension add to the complexity of hepatectomy, which is technically easier after placement of a TIPS than after a surgical portosystemic shunt. Hilar dissection is performed to access the major hepatic vessels and devascularize the liver. Clamping of the portal vein during hepatectomy and liver implantation results in increased bleeding during dissection, mesenteric congestion, and production of lactate, whereas clamping of the inferior vena cava aggravates venous stasis and causes renal hypertension, with diminished venous return to the heart. To circumvent these problems, venovenous bypass is achieved by cannulation of the portal vein and inferior vena cava via the femoral vein and return of blood via the axillary vein to the right side of the heart. This technique can be performed in adults and older pediatric recipients. In some recipients, only a suprahepatic anastomosis to the vena cava is performed, the "piggyback" technique, in contrast to the more usual circumstance in which anastomosis to the vena cava is performed above and below the graft. The piggyback technique may be applicable if uninterrupted caval flow during LT is particularly beneficial, as in a recipient with cardiac instability; a prior portosystemic shunt obviates the need for portal bypass; or the recipient is a pediatric patient in whom venovenous bypass may not be possible. The portal venous anastomosis is performed after portal bypass is terminated and is followed by the hepatic arterial anastomosis. Bile duct continuity is generally fashioned directly as a "duct-to-duct" anastomosis between the graft and recipient. Hepatico- or choledochojejunostomy has been the preferred anastomosis if there is intrinsic bile duct disease, such as PSC, or a major discrepancy in donor and recipient bile duct diameters; however, as previously mentioned, studies have demonstrated that duct-to-duct anastomosis is technically feasible and safe in PSC.[121] Microscopic surgical techniques facilitate the donor-recipient biliary and vascular anastomoses. Vascular anatomic anomalies increase the complexity of surgery further. In the past, a direct duct-to-duct anastomosis was typically stented by placement of a T-tube, with the added advantage of easy assessment of bile flow and its quality, as well as potential access for cholangiography postoperatively. The risk of a bile leak during subsequent removal of the T-tube, however, has led to its abandonment.

The use of a living donor involves implantation of only a portion of the donor graft and is technically more challenging than using a whole cadaveric organ (see later). In contrast to orthotopic LT, in which the native liver is removed, auxiliary cadaveric LT is the placement of a graft without removal of the native liver. This technique has usually been performed in critically ill patients such as those with ALF who are too unstable to tolerate native hepatectomy.

Irrespective of the type of graft used, after the anastomoses are complete, the newly implanted graft is reperfused, with restoration of normal blood flow. The resulting release of vasoactive agents from pooled blood in the lower half of the body, however, can lead to lethal cardiovascular instability and tachyarrhythmias. Prompt bile production should occur if graft function is adequate. Hyperacute rejection is rare but devastating after LT and leads to rapid graft necrosis within hours and the need for urgent retransplantation.

Live-Donor LT

Extension of LDLT from pediatric recipients to adult recipients has remained controversial because of the risk to the donor in light of the large volume of donor liver required. Data from UNOS demonstrate that LDLT accounted for only 4.5% of all liver transplants performed in the USA in 2017. By contrast, LDLT accounts for 76.5% of transplants in Korea and more than 96% of all liver transplants in Japan because of minimal deceased donation due to cultural considerations in these countries.[135] The potential donor is a healthy adult, typically a family member or close friend of the recipient, who volunteers to be evaluated. A series of checks and balances is necessary to ensure that the potential donor undergoes an adequate medical assessment and is not proceeding under duress. The potential recipient cannot be privy to details of the potential donor's evaluation. In most centers, a hepatologist not involved in the care of the recipient performs an assessment of the donor. Often an independent advocate is also appointed to safeguard the donor's interests. At each stage of the process, the potential donor is given the opportunity to withdraw from consideration.[136] Preoperative evaluation of the donor is best performed in 4 stages over a period of 1 to 3 months, with more invasive testing such as liver biopsy undertaken later in the evaluation (Box 97.5). After undergoing complete evaluation, only a relatively small proportion of potential donors are acceptable. One consequence of the evaluation of many potential donors has been the recognition that anatomic aberrations of the biliary and vascular system and unsuspected abnormalities on liver biopsy specimens are common in apparently healthy persons.

Right lobes (segments V to VIII), extended right grafts (segments IV to VIII), or left hepatic grafts (segments II to IV) have been used successfully in adult-to-adult LDLT. Adult LDLT allows a reduction in waiting time and potentially mortality for recipients. An expected reduction in the risk of graft rejection because of receipt of a graft from a relative has not been confirmed, and a meta-analysis comparing recipients of deceased- and live-donor grafts has shown similar patient and graft survival.[137]

The overriding concern about LDLT are the consequences to the donor, including immediate perioperative morbidity and mortality, time lost from work, possible uninsurability in the future, and a lack of long-term follow-up data to ensure that hepatic resection and subsequent regeneration do not result in biliary or other abnormalities. The estimated mortality for live liver donors is different during the early post-donation period and long-term follow-up. For example, the risk of death for live liver donors within the first 90 days after donation has been estimated to be 1.7 per 1000, which is higher than the risk of death for healthy age-matched persons but not significantly different from the risk of death in live kidney donors. Cumulative long-term mortality estimates, however, are not different between live liver donors, live kidney donors, and healthy matched persons up to 11 years after donation.[138] Up to 38% of donors experience complications related to hepatic donation during the first 2 years that follow, including bile leaks, bacterial infections, incisional hernias, pleural effusions, neurapraxia, surgical site infections, and intra-abdominal abscesses.[139]

BOX 97.5 Protocol for the Evaluation of Potential Living-Related Donors

STAGE 1

Complete history and physical examination
Liver biochemical test levels, blood chemistries, CBC, coagulation profile, urinalysis, AFP, CEA, and serologic tests for HAV, HBV, HCV, CMV, EBV, and HIV
Abdominal US examination, chest x-ray

STAGE 2

Complete psychiatric and social evaluation
CT of the abdomen and pelvis
Pulmonary function tests, echocardiography

STAGE 3

Liver biopsy
Celiac and superior mesenteric CTA with portal phase

STAGE 4

MR cholangiography
Informed consent

Adapted from Ghobrial RM, Amersi F, Busuttil RW. Surgical advances in liver transplantation. Living related and split donors. Clin Liver Dis 2000; 4:553-65, with permission.

IMMUNOSUPPRESSION

Immunosuppression is divided into induction (initial) and maintenance (long-term) phases. The goal of immunosuppression is to prevent graft rejection while avoiding morbidity due to its side effects.[140] Episodes of acute cellular and chronic ductopenic rejection require additional immunosuppression (see Chapter 36).[141]

The principal immunosuppressive agents, with route of administration, monitoring, and common adverse effects, are shown in Table 97.3, and drug-drug interactions are shown in Box 97.6. The calcineurin inhibitors cyclosporine and tacrolimus form the basis for common induction and maintenance immunosuppressive regimens but have significant side effects. Patients may be converted from a cyclosporine- to a tacrolimus-based regimen for glucocorticoid- or OKT3-refractory rejection (see later), late rejection (occurring >6 months post-LT), chronic ductopenic rejection, severe cholestasis, intestinal malabsorption of cyclosporine, or cyclosporine toxicity (hirsutism, gingivitis, severe hypertension). In chronic rejection, tacrolimus is less effective once the serum bilirubin levels rise above 10 mg/dL, underscoring the importance of early recognition. The antimetabolite mycophenolate mofetil, and its active metabolite mycophenolic acid, are licensed for prophylaxis of rejection in LT recipients. Either agent, along with a calcineurin inhibitor (typically tacrolimus), is the most common maintenance immunosuppressive regimen used post-LT. Although implicated in hepatic artery thrombosis as well as delayed wound healing and infections, sirolimus has been used as a calcineurin-sparing strategy in liver

TABLE 97.3 Immunosuppressive Agents Used in LT

Agent	Mode of Action	Monitoring	Side Effects
Cyclosporine	Calcineurin inhibitor: suppresses IL-2–dependent T-cell proliferation	Blood level	Renal, neurologic, hyperlipidemia, hypertension, hirsutism
Tacrolimus	Same as cyclosporine	Blood level	Renal, neurologic, diabetes mellitus
Prednisone	Cytokine inhibitor (IL-1, IL-2, IL-6, TNF, and IFN-γ)	None	Hypertension, diabetes mellitus, obesity, osteoporosis, infection, depression, psychosis
Azathioprine	Inhibition of T- and B-cell proliferation by interference with purine synthesis	WBC count	Bone marrow suppression, hepatotoxicity
Mycophenolate mofetil	Selective inhibition of T- and B-cell proliferation by interference with purine synthesis	WBC count	Diarrhea, bone marrow suppression
Sirolimus	Inhibition of late T-cell functions	Blood level	Neutropenia, thrombocytopenia, edema, pleural and pericardial effusions, delayed wound healing, hyperlipidemia
Everolimus	Inhibition of T- and B-cell activation and proliferation via mTOR inhibition	Blood level	Edema, pleural and pericardial effusions, pneumonitis, delayed wound healing, hyperlipidemia
OKT3 (Muromonab-CD3)	Blockade of the T-cell CD3 receptor, preventing stimulation by antigen	CD3 count	Cytokine release syndrome, pulmonary edema, increased risk of infections
Basiliximab	Competitive inhibition of the IL-2 receptor on activated lymphocytes	None	Hypersensitivity reactions

IFN, interferon; *IL,* interleukin; *mTOR,* mammalian (or mechanistic) target of rapamycin.
Adapted from Everson GT, Karn I. Immediate post-operative care. In: Maddrey WC, Schiff ER, Sorrell MF, editors. Transplantation of the liver. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001, p 131.

BOX 97.6 Clinically Relevant Drug Interactions with Immunosuppressive Drugs

Drugs that increase blood levels of cyclosporine and tacrolimus:
- Antifungals: fluconazole, ketoconazole, itraconazole
- Antibiotics: clarithromycin, erythromycin
- Calcium channel blockers: diltiazem, verapamil
- Others: allopurinol, bromocriptine, metoclopramide

Drugs that decrease blood levels of cyclosporine and tacrolimus:
- Anticonvulsants: phenobarbital, phenytoin
- Antibiotics: nafcillin, rifampin

Drugs that increase nephrotoxicity of cyclosporine and tacrolimus:
- Gentamicin, ketoconazole, NSAIDs

Drugs that interact with mycophenolate mofetil:
- Acyclovir, ganciclovir (increase blood levels)
- Antacids (inhibit absorption)
- Bile salt sequestrants: cholestyramine, colestipol, colesevelam (inhibit absorption)

Drugs that interact with azathioprine:
- Allopurinol, angiotensin-converting enzyme (ACE) inhibitors (increase hematologic toxicity)
- Warfarin (decreased anticoagulant effect)

transplant recipients.[142] Similar to sirolimus, everolimus is also an mTOR inhibitor licensed for immunosuppression in liver transplant recipients. Several clinical trials have demonstrated that the use of everolimus permits important dose reductions of tacrolimus with consequent clinically relevant benefits in renal function.[143-145] Basiliximab is a monoclonal antibody directed against the alpha subunit of the interleukin-2 (IL-2) receptor (CD25) and is licensed for rejection prophylaxis in kidney transplant recipients, but it can be used selectively (off label) as an alternative to glucocorticoids as an induction agent in LT.[146] Preliminary data support the efficacy of alemtuzumab (an anti-CD52 monoclonal antibody) as a glucocorticoid-sparing induction agent; however, an increase in the frequency of infectious complications has been reported with its use.[147] Glucocorticoids are also commonly used during the induction phase of immunosuppression, tapered slowly, and discontinued in most cases to avoid toxicity, except for some center-specific protocols for autoimmune hepatitis in which liver transplant recipients may continue on low doses during the maintenance phase.[141]

POSTOPERATIVE COURSE

Initial Phase to Discharge from the Hospital

Because of the complexity of LT and the often markedly decompensated state of recipients, invasive monitoring (with arterial and occasionally pulmonary venous lines) is necessary in the first few postoperative days. If a T-tube is in place, dark copious bile provides evidence of satisfactory graft function. The patient's overall status, including neurologic recovery from anesthesia, urinary output, and cardiovascular stability, also reflects graft function. Routine antimicrobial prophylaxis includes bowel decontamination with oral nonabsorbable antibiotics, perioperative systemic broad-spectrum antibiotics, antifungal agents, and ganciclovir to prevent CMV infection. Markedly abnormal liver biochemical test levels are typical during the initial 48 to 72 postoperative hours and reflect several insults to the graft, including ischemia following harvesting and during preservation and subsequent reperfusion injury. The overall trend in serum aminotransferase levels should be downward, with a corresponding improvement in coagulopathy and a falling serum bilirubin level. Thrombocytopenia in the immediate postoperative period reflects a variety of processes, including residual splenomegaly, the effects of medications, and (importantly) reduced graft function.

Worrisome clinical features include scanty, pale bile if a T-tube has been used, metabolic acidosis, depressed mentation, and the need for continued vasopressor support with worsening liver biochemical test levels. Hepatic artery thrombosis needs to be excluded promptly by Doppler US because it is an indication for urgent retransplantation. Hepatic artery thrombosis is more common in pediatric recipients because of the smaller size of the vessels. Antiplatelet therapy is administered to prevent hepatic artery thrombosis.[148] Primary nonfunction of the graft is also an indication for urgent retransplantation and is suggested by sluggish mentation, diminished urine output, cardiovascular instability, and coagulopathy. Donor characteristics associated with an increased likelihood of primary nonfunction include marked hepatic steatosis and profound hyponatremia. If graft function is adequate, however, vasopressor support can be tapered and extubation attempted, although the recipient who is markedly debilitated from advanced cirrhosis may require several days of ventilatory support. Poor graft function and renal insufficiency can also impede weaning.

During the first postoperative week, liver biochemical and coagulation test levels should steadily improve as ischemia and reperfusion injury resolve. Acute cellular rejection with graft dysfunction occurs at one week and beyond, with a rise in serum aminotransferase, alkaline phosphatase, and bilirubin levels. Because the biochemical features are nonspecific, liver biopsy is indicated to evaluate other diagnostic possibilities such as slowly resolving reperfusion injury, biliary tract obstruction, and cholestasis related to sepsis. Histologic findings characteristic of acute cellular rejection are bile duct injury, portal inflammation with eosinophils, and, with more severe injury, endotheliitis (Fig. 97.4). High doses of glucocorticoids (500 to 1000 mg of IV methylprednisolone or its equivalent daily for 3 doses) followed by a taper (most commonly with oral prednisone or prednisolone) extending over several days constitute first-line therapy. A response is suggested by a return of liver biochemical test levels toward normal.

For the occasional patient with presumed acute cellular rejection who fails to respond to glucocorticoids, additional immunosuppression with the monoclonal antibody OKT3 (muromonab-CD3) may be necessary. Liver biopsy should be repeated before initiating more intensive therapy to confirm the lack of a histologic response and to exclude other important causes of graft dysfunction, such as ischemia. The ability of recurrent HCV infection to mimic the histologic features of acute cellular rejection has led to reevaluation of the need to treat apparent acute cellular rejection aggressively under all circumstances. Routine (protocol) liver biopsies have also fallen out of favor because histologic evidence of acute cellular rejection can be noted in the absence of worsening graft function, with no apparent clinical significance.

In the first 3 to 4 weeks after LT, infections are typically bacterial and related to surgical complications such as intra-abdominal bleeding, bile leak, or wound infection. A meta-analysis has suggested that administration of probiotics before, or on the day of, LT reduces the rate of postsurgical infectious complications such as urinary tract infections and intra-abdominal infections (from 35% to 7%) but does not affect mortality rates.[149] The timing of various infectious complications following LT is shown in Fig. 97.5.

Other issues encountered during the first weeks following LT are listed in Box 97.7. Neurologic dysfunction can present as an acute confusional state or seizures, with a differential diagnosis that includes lingering effects of hepatic encephalopathy, electrolyte imbalance, poor graft function, sepsis, uremia, and side effects of medications. Of particular concern is the development of neurologic toxicity caused by the major immunosuppressive agents.

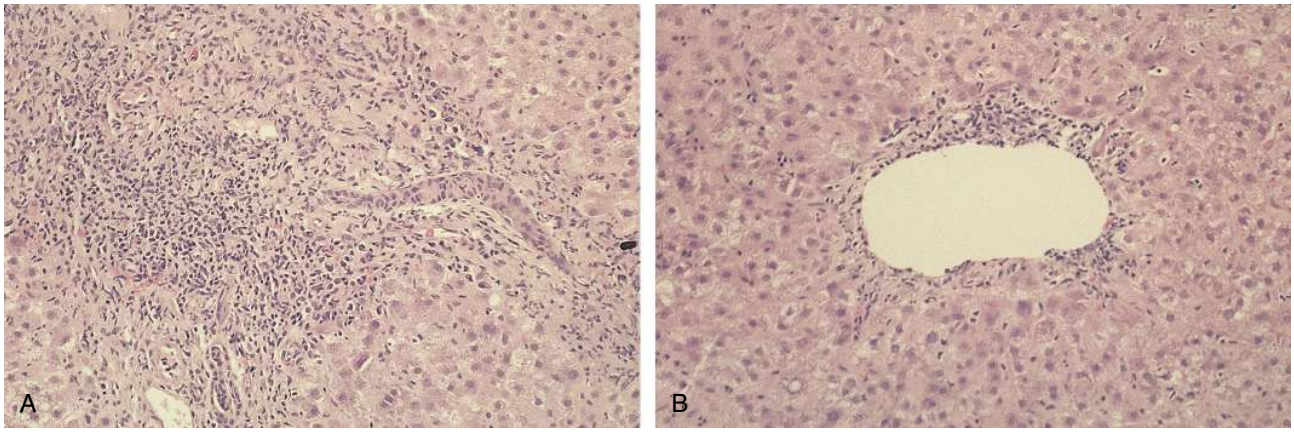

Fig. 97.4 Histopathology of acute cellular rejection of a liver graft. *A,* The portal tract shows a lymphocytic and plasma cell infiltrate that spills over into the periportal hepatocytes and bile duct. *B,* The central vein shows attachment of lymphocytes to the endothelium (endotheliitis). (From Cotran RS, Kumar V, Collins T, editors. Robbins' pathologic basis of disease. 6th ed. CD-ROM. Philadelphia: WB Saunders; 1999, with permission.)

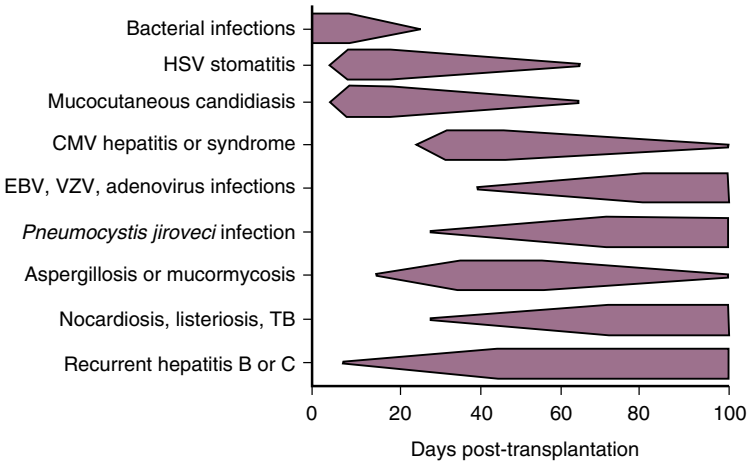

Fig. 97.5 Time course of various infectious complications in liver transplant recipients. *VZV,* varicella-zoster virus. (Adapted from Everson GT, Kam I. Immediate post-operative care. In: Maddrey WC, Schiff ER, Sorrell MF, editors. Transplantation of the liver. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 131.)

Management includes correcting electrolyte imbalances and reducing the dose of calcineurin inhibitors, which can be facilitated by the use of mycophenolate mofetil.[150] Overly rapid correction of hyponatremia perioperatively has been implicated in the genesis of central pontine myelinolysis, with evidence of osmotic demyelination on MRI. Diabetes mellitus can present for the first time postoperatively, and HCV infection increases the risk of diabetes mellitus in liver transplant recipients.[151,152] Post-transplant renal impairment can reflect a number of insults, including slowly resolving pre-LT hepatorenal syndrome or renal failure due to other causes, intraoperative hypotension resulting in acute tubular necrosis, and (importantly) the nephrotoxic effects of cyclosporine and tacrolimus, which cause renal afferent arteriolar vasoconstriction with a reduction in glomerular filtration. Adjunctive therapy with mycophenolate mofetil or mycophenolic acid allows a reduction in the doses of cyclosporine and tacrolimus while providing adequate immunosuppression. Short-term hemodialysis may be necessary until renal function improves.

Following Discharge from the Hospital

If the initial postoperative course has been smooth, planning for discharge is possible by the end of the first or second week after LT. Recovery is often more protracted, particularly in debilitated recipients. Once discharged, patients are seen at frequent intervals during the first postoperative month. Liver biochemical test levels should normalize within a few weeks. Graft dysfunction is an indication for prompt liver biopsy to exclude acute cellular rejection. CMV becomes an important infectious consideration 3 or more weeks post-transplant.[153] Histologic features suggestive of CMV hepatitis include "owl's eye" inclusion bodies in the hepatocytes, as well as neutrophilic abscesses with focal necrosis of the parenchyma (see Chapter 83). Recipients who are CMV naïve are at increased risk of CMV infection, particularly if they receive a graft from a CMV-seropositive donor. These patients are candidates for more intensive antiviral prophylaxis. Oral valacyclovir or valganciclovir for 3 to 6 months following LT is recommended for CMV prophylaxis.[154]

A distinction is made between asymptomatic CMV viremia, which may not require additional antiviral therapy, and CMV disease with systemic complaints such as fever, graft hepatitis, and diarrhea. CMV viremia is detected by PCR-based quantitative nucleic acid testing and by identification of CMV pp65 antigenemia.[154] Reactivation of CMV in a previously infected recipient tends to be less clinically severe than de novo infection. The diagnosis of tissue-invasive CMV disease requires confirmation by immunohistochemistry or in

BOX 97.7 Medical Complications in the Immediate Post-transplantation Period

- Infections
  - Bacterial
  - Viral
    - CMV
    - EBV
  - Fungal
    - Aspergillosis, mucormycosis
    - Candidiasis, torulopsosis
    - *Pneumocystis jiroveci* pneumonia
- Respiratory Complications
  - Acute respiratory distress syndrome
  - Hepatopulmonary syndrome
  - Pneumonia
  - Portopulmonary hypertension
  - Pulmonary edema
- Acute Kidney Injury
- Cardiovascular Diseases
  - Cardiomyopathy
  - Hemochromatosis
  - Hypertrophic cardiomyopathy
  - Hypertension
  - Myocardial ischemia
  - Valvular heart disease
- Neurologic Complications
  - CNS hemorrhage
  - Central pontine myelinolysis
  - Ischemic events
  - Seizures
- Coagulopathies
  - DIC
  - Thrombocytopenia
- Diabetes Mellitus

From Everson GT, Karn I. Immediate post-operative care. In: Maddrey WC, Schiff ER, Sorrell MF, editors. Transplantation of the liver. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001, with permission.

situ DNA hybridization techniques, because CMV viremia is not a reliable diagnostic finding in these cases.[154] High-dose IV ganciclovir is effective for treating CMV infection; however, viral resistance has been described. Oral valganciclovir is also a therapeutic option for milder CMV disease. Intravenous ganciclovir is the preferred antiviral agent for patients with severe CMV infection or GI involvement (which may limit the bioavailability of oral antiviral agents). Treatment of CMV infection should be continued for at least 2 weeks and until complete resolution of symptoms with viral eradication is achieved.[154] Not only is CMV infection an important cause of morbidity and mortality in liver transplant recipients, but it also has been implicated in other complications—notably chronic graft rejection and severe recurrent HCV infection. Following an episode of CMV infection, secondary prophylaxis with antiviral agents is not routinely recommended and is not associated with fewer relapses.[154]

Trimethoprim/sulfamethoxazole is prescribed to prevent *Pneumocystis jiroveci* infection. In patients intolerant of sulfa drugs, options include atovaquone, dapsone tablets, or inhaled pentamidine, although these agents are less effective than trimethoprim/sulfamethoxazole and have a narrower spectrum of protection against other opportunistic pathogens.[155] Prophylaxis needs to be continued for at least one year following LT.

Fungal infections pose a major threat to liver transplant recipients, particularly in the presence of marked debilitation, intensive immunosuppression for rejection, or retransplantation. For high-risk recipients with 2 or more risk factors (prolonged or repeat operation, retransplantation, renal failure, high transfusion requirement, choledochojejunostomy, Candida colonization in the preoperative period), antifungal prophylaxis against invasive candidiasis with fluconazole for up to 4 weeks after LT is recommended; alternatives include liposomal amphotericin B or caspofungin.[156,157] Sites of infection are mucocutaneous (oral and esophageal), pulmonary, and intracerebral. Despite prolonged therapy with amphotericin, voriconazole, or itraconazole, a fatal outcome is usual with invasive fungal infection. A diagnosis of brain abscess due to *Aspergillus* spp. implies a dismal prognosis. Superficial skin infections and simple colonization must be distinguished from invasive fungal infections, because topical antifungal agents such as nystatin or clotrimazole can eradicate the former. Similarly, bladder irrigation with amphotericin can cure candidal cystitis without the need for systemic antifungal therapy.

Although opportunistic infections are always a concern in liver transplant recipients, nonopportunistic infections also occur. Standard antibiotic therapy is appropriate for community-acquired respiratory infections, but a more extensive workup is indicated when symptoms are unusually severe or fail to resolve rapidly with treatment. Invasive diagnostic testing such as bronchoscopy or lumbar puncture with cultures may be necessary if clinically indicated. Enteric bacteremia may be an initial clue to hepatic artery thrombosis in an otherwise stable recipient. Reactivation of TB may present in an atypical fashion after LT.

Early recurrence of HCV infection may also become apparent during initial follow-up. As noted earlier, it is crucial to recognize that recurrent HCV infection may mimic several histologic features of acute cellular rejection, such as bile duct inflammation and endotheliitis (Table 97.4).

If a liver biopsy specimen shows features suggestive of biliary obstruction or if graft dysfunction is associated with clinical features of cholangitis such as fever and abdominal pain, MRCP is necessary because of its noninvasive nature and high degree of accuracy, irrespective of the type of biliary anastomosis.[158] An anastomotic stricture in a choledochocholedochostomy is usually easily managed by endoscopic balloon dilation and temporary internal stenting (see Chapter 70). Surgical intervention is reserved for patients who do not respond to this approach, in which case conversion to a choledocho- or hepaticojejunostomy is usual.

A critical issue is distinguishing anastomotic from nonanastomotic biliary strictures caused by ischemia or other insult to the graft. The bile duct in the transplant recipient is prone to ischemia because of its relatively tenuous arterial blood supply, and the development of a biliary stricture (unless it is obviously anastomotic) may reflect hepatic artery thrombosis. Ischemic stricturing is generally diffuse but can be predominantly hilar. Although temporizing measures such as balloon dilation and stenting may be attempted, such efforts are generally futile if hepatic artery thrombosis is present or stricturing is widespread, and retransplantation will be required. Other causes of nonanastomotic stricturing include the use of an ABO-incompatible graft and protracted cold ischemia after harvesting. Biliary strictures can also be a feature of recurrent PSC.

LONG-TERM MANAGEMENT

General Preventive Measures

Long-term survival after LT is dependent on good general medical care of common disorders, including hypertension, hyperlipidemia, and diabetes mellitus.[159] Once a recipient has stable graft and renal function, serial blood work including blood cell counts

TABLE 97.4 Histologic Features of Recurrent HCV Infection Compared with Acute Cellular Rejection

Feature	Recurrent HCV Infection	Rejection
Time of onset after LT	Any time; onset usually within the first year	Usually within the first 2 months
Portal inflammation	Most cases	Always
Lymphocytes	Bland, uniform	Activated
Lymphoid aggregates	Usually	Occasionally
Lymphoid follicles	50% of cases	Rarely
Eosinophils	Inconspicuous	Almost always
Steatosis	Often	Never
Acidophilic bodies	Common	Uncommon
Bile ductule damage	About 50% of cases	Common
Atypical features	Cholestasis, ballooning degeneration without significant inflammation, marked ductular proliferation mimicking obstruction, granulomas	Prominent periportal and lobular necroinflammatory activity without subendothelial venular inflammation

From Rosen HR, Martin P. Liver transplantation. In: Schiff ER, Sorrell MF, Maddrey WC, editors. Schiff's diseases of the liver. 8th ed. Philadelphia: Lippincott-Raven; 1999, p. 1589.

and serum liver biochemical tests, creatinine, and calcineurin inhibitor levels are obtained every few months for review by the transplant center.

Systemic hypertension is a frequent problem encountered in liver transplant recipients and is related to calcineurin inhibitor–induced renal vasoconstriction, as well as to the effects of other drugs such as glucocorticoids. Unfortunately, a reduction in immunosuppression is generally ineffective in ameliorating hypertension. Another contributing factor is mild renal insufficiency, which is frequent after LT. Initial antihypertensive therapy usually consists of a calcium channel blocker. Angiotensin-converting enzyme inhibitors and potassium-sparing diuretics are relatively contraindicated because of their propensity to accentuate hyperkalemia, which is frequent in liver transplant recipients, who often have renal tubular acidosis caused by the calcineurin inhibitor. Because cyclosporine and tacrolimus levels are increased by verapamil and diltiazem, nifedipine is the agent of choice. β-Adrenergic blocking agents are second-line antihypertensive agents; thiazide and loop diuretics are generally avoided because of concern about exacerbating renal insufficiency and electrolyte imbalance in the liver transplant recipient. Furosemide, however, is the diuretic of choice if fluid overload is present. In the minority of patients in whom hypertension is not controlled, a centrally acting agent such as clonidine may be introduced. For the occasional patient with intractable hypertension on cyclosporine-based immunosuppression, substitution of tacrolimus for cyclosporine may improve blood pressure control. Both cyclosporine and tacrolimus are nephrotoxic and accentuate impairment of renal function that may have existed perioperatively. Although acute nephrotoxicity may respond to interruption of or a reduction in the dose of these drugs, chronic renal impairment is usually irreversible. Drastic dose reductions of a calcineurin inhibitor may precipitate graft rejection and should be avoided. Cofactors implicated in advanced CKD after LT include recurrent HCV infection with associated glomerulonephritis, diabetes mellitus, and systemic hypertension.[160] Renal transplantation may be considered in liver transplant recipients who become dialysis dependent after an otherwise successful LT.

Hyperlipidemia is observed in up to half of liver transplant recipients and reflects a number of factors including diabetes mellitus, obesity, renal dysfunction, and immunosuppressive agents, especially cyclosporine.[161] Pharmacologic therapy is indicated if hypercholesterolemia fails to improve with weight reduction and tight glycemic control. Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme-A-reductase inhibitor (statin), is well tolerated and efficacious in liver transplant recipients.[162] Diabetes mellitus is common in liver transplant recipients and occurs in approximately one third of patients for the first time after LT. The pathogenesis is multifactorial; immunosuppressive therapy is a major factor because of the hyperglycemic effects of prednisone, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil. HCV infection is also implicated. In most diabetic recipients, therapy with insulin is required. The high frequency of diabetes mellitus following LT has prompted the development of glucocorticoid-sparing immunosuppressive regimens (see earlier).

A related problem is *obesity*, which is frequent even in LT recipients who were profoundly malnourished preoperatively. Risk factors include glucocorticoid use, increased caloric intake, and decreased physical activity during recuperation from surgery. Immunosuppression with tacrolimus has been reported to result in less weight gain than occurs with cyclosporine; to a large extent, this difference may reflect the lower glucocorticoid doses used with tacrolimus. Management of obesity in this population includes a reduction in glucocorticoid doses and even complete withdrawal if possible. Use of mycophenolate mofetil may permit maintenance immunosuppression without glucocorticoids.

Excessive alcohol consumption (>20 g/day for women and >30 g/day for men) is associated with poorer long-term survival after LT, regardless of the primary indication for transplantation.[163] Given the lack of data about the safety of more moderate alcohol consumption in liver transplant recipients, complete abstinence should be encouraged as a conservative approach.

Osteopenia is a frequent cause of morbidity in liver transplant recipients.[164] Although hepatic osteodystrophy is typically associated with cholestatic liver diseases, it is also common in patients with cirrhosis of other etiologies. Factors implicated in the pathogenesis of hepatic osteodystrophy include poor nutritional status, immobility, the calciuric effect of many diuretics, hypogonadism, and glucocorticoid use in patients with autoimmune hepatitis. In the initial several months after LT, osteopenia is accelerated further by high-dose glucocorticoid therapy as well as the other major immunosuppressive agents. Atraumatic fractures may occur in trabecular bone such as vertebrae or ribs. Bone mass increases after doses of immunosuppressive agents are reduced as mobility increases. Supplemental calcium and vitamin D are prescribed to patients with osteopenia, as is a bisphosphonate in patients with osteoporosis.

De novo malignancies are increased in frequency following LT.[165] Recipients need ongoing age-appropriate surveillance for common tumors such as breast, cervical, and colon cancer.[166] In the absence of specific recommendations, screening for prostatic carcinoma by yearly digital rectal examination and/or prostate-specific antigen testing in male liver transplant recipients older than age 40 should be individualized. The incidence of prostate cancer in liver transplant

recipients appears to be slightly higher to that in nontransplanted men.[167] Screening for colorectal cancer by colonoscopy should also be performed every 5 years after age 50 in asymptomatic recipients; in patients with a history of PSC and UC, yearly colonoscopy with surveillance mucosal biopsies is recommended (see Chapters 68 and 116). Adherence to cervical cancer screening guidelines for the general population and screening female recipients older than age 40 for breast cancer by yearly mammography seem appropriate.[166] Other malignancies that are increased in frequency in organ transplant recipients include those of the skin, lung, liver, female genital tract, and GI tract. Patients with alcohol use disorder may be particularly prone to malignancies of the oropharynx (see Chapter 86).[168] Patients should be encouraged to use sunscreen regularly and have periodic examinations by a dermatologist.

Post-transplantation lymphoproliferative disorder (PTLD) varies from a low-grade indolent process to an aggressive neoplasm.[169] Uncontrolled proliferation of B cells after LT, typically in response to primary EBV infection, can be polyclonal or monoclonal. Pediatric recipients are at particular risk because of the absence of prior EBV infection. Intensive immunosuppression with OKT3 for severe rejection increases the risk of PTLD, which can present as a mononucleosis-like syndrome, lymphoproliferation, or malignant lymphoma.

Clinical features suggestive of PTLD include lymphadenopathy, unexplained fever, and systemic symptoms such as weight loss. The majority of patients with PTLD present with extranodal masses, primarily involving the GI tract (stomach or intestine), lungs, skin, central nervous system, or hepatic allograft.[168] The WHO classifies PTLD into 4 main categories based on clinical, morphologic, immunophenotypic, and genetic features: benign polyclonal lymphoproliferation (early lesions), polymorphic PTLD, monomorphic PTLD, and classic Hodgkin's lymphoma–like PTLD. Management includes a reduction in immunosuppression and antiviral therapy directed against EBV, if present, with ganciclovir. Systemic chemotherapy, including the anti-CD20 monoclonal antibody rituximab, may be required in patients with malignant lymphoma.[168] The higher frequency of PTLD in pediatric recipients has led to surveillance by PCR methodology for EBV viremia and reduction in the level of immunosuppression in patients with a positive result before clinical features of PTLD occur. In addition, antiviral prophylaxis is prescribed for high-risk recipients, including those who are seronegative for EBV and received a graft from a seropositive donor. Chronic graft rejection is increased in frequency in survivors of PTLD because of the reduction in the level of immunosuppression, which may be increased cautiously after PTLD is contained.

Immunizations and Antibiotic Prophylaxis

Immunization against HAV and HBV, influenza, pneumococcus, tetanus, and diphtheria is part of the standard pre-LT management. A substantial proportion of patients may be unable to mount adequate antibody responses because of the immunosuppression associated with end-stage liver disease. Vaccines based on live or attenuated microorganisms (i.e., measles, mumps, rubella, oral polio, bacille Calmette-Guerin, vaccinia, and varicella-zoster) are contraindicated because of the risk of reactivation. Prophylactic antibiotics are usually recommended for any dental procedure, although this recommendation is not evidence-based.[170]

Hepatic Retransplantation

Although improved immunosuppressive regimens have led to a lower rate of graft loss from chronic rejection, recurrence of the underlying liver disease has been recognized increasingly as a cause of graft failure, as illustrated most strikingly in HCV-infected recipients prior to the availability of DAAs that permit curative antiviral therapy in liver transplant recipients.[171] Understanding the full effect of recurrent disease, especially nonviral disease, on patient and graft survival will require studies with long-term follow-up. For example, although the rate of histologic recurrence of viral hepatitis is greatest in the first year following LT, recurrent PBC or PSC develops in less than 5% of patients by the first year, whereas more than 20% demonstrate histologic recurrence 10 years after LT.[172,173] As patients enter their second and third decades following LT, the number of patients who require retransplantation may deplete the donor pool further. This issue is compounded by the observation that patients who undergo re-transplantation experience an approximate 20% overall reduction in the rate of survival but consume an increased amount of resources when compared with primary liver transplant recipients.

Major challenges remain in LT, including the shortage of donor organs, threat of recurrent disease, and morbidity associated with lifelong therapeutic immunosuppression. Nevertheless, the availability of LT has transformed the lives of patients with advancing liver disease and their health care providers from an ultimately futile effort to manage the complications of cirrhosis into a life-prolonging and life-enhancing intervention.

Full references for this chapter can be found on www.expertconsult.com.

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