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■ ■ FURTHER READING Bhattacharya D et al: Hepatitis C guidance update 2023 update:

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Liver Transplantation Liver transplantation—the replacement of the native, diseased liver by a normal organ (allograft)—has matured from an experimental procedure reserved for desperately ill patients to an accepted, lifesaving operation applied more optimally in the natural history of end-stage liver disease. The preferred and technically most advanced approach is orthotopic transplantation, in which the native organ is removed and the donor organ is inserted in the same anatomic location. Pioneered in the 1960s by Thomas Starzl at the University of Colorado and, later, at the University of Pittsburgh and by Roy Calne in Cambridge, England, liver transplantation is now performed routinely worldwide. Success measured as 1-year survival has improved from ~30% in the 1970s to >90% today. These improved prospects for prolonged survival resulted from refinements in operative technique, improvements in organ procurement and preservation, advances in immunosuppressive therapy, and, perhaps most influentially, more enlightened patient selection and timing. Despite the perioperative morbidity and mortality, the technical and management challenges of the procedure, and its costs, liver transplantation has become the approach of choice for selected patients whose chronic or acute liver disease is progressive, life-

threatening, and unresponsive to medical therapy. Based on the current level of success, the number of liver transplants has continued to grow each year; in 2022, 9528 patients received liver allografts in the United States—8925 deceased donor (94%) and 603 living donor (6%). Still, the demand for new livers continues to outpace availability; as of September 2023, 10,285 patients in the United States were on a waiting list for a donor liver. **INDICATIONS** Potential candidates for liver transplantation are children and adults who, in the absence of contraindications (see below), suffer from severe, irreversible liver disease for which alternative medical or surgical treatments have been exhausted or are unavailable. Timing of the

operation is of critical importance. Indeed, improved timing and better patient selection are felt to have contributed more to the increased success of liver transplantation in the 1980s and beyond than all the impressive technical and immunologic advances combined. Although the disease should be advanced, and although opportunities for spontaneous or medically induced stabilization or recovery should be allowed, the procedure should be done sufficiently early to give the surgical procedure a fair chance for success. Ideally, transplantation should be considered in patients with end-stage liver disease who are experiencing or have experienced a life-threatening complication of hepatic decompensation or whose quality of life has deteriorated to unacceptable levels.

Although patients with well-compensated cirrhosis can survive for many years, many patients with quasi-stable chronic liver disease have much more advanced disease than may be apparent. As discussed below, the better the status of the patient prior to transplantation, the higher will be its anticipated success rate. The decision about when to transplant is complex and requires the combined judgment of an experienced team of hepatologists, transplant surgeons, anesthesiologists, and specialists in support services, not to mention the well-informed consent of the patient and the patient's family. ■ ■

TRANSPLANTATION IN CHILDREN Indications for transplantation in children are listed in Table 356-1. The most common is biliary atresia. Inherited or genetic disorders of metabolism associated with liver failure constitute another major indication for transplantation in children and adolescents. In Crigler-Najjar disease type I and in certain hereditary disorders of the urea cycle and of amino acid or lactate-pyruvate metabolism, transplantation may be the only way to prevent impending deterioration of central nervous system function, despite the fact that the native liver is structurally normal. Combined heart and liver transplantation has yielded dramatic improvement in cardiac function and in cholesterol levels in children with homozygous familial hypercholesterolemia; combined liver and

TABLE 356-1
Indications for Liver Transplantation
CHILDREN Biliary atresia Primary biliary cholangitis Neonatal hepatitis Primary sclerosing cholangitis Congenital hepatic fibrosis Caroli's diseasea Alagille's syndromeb Secondary biliary cirrhosis Byler's diseasec Autoimmune hepatitis Inherited disorders of metabolism Hemochromatosis-associated cirrhosis Wilson's disease α 1 Antitrypsin deficiency Tyrosinemia Metabolic dysfunction-associated steatohepatitis (MASH)d Glycogen storage diseases Alcohol-associated cirrhosis Lysosomal storage diseases Severe alcohol-associated hepatitis Protoporphyria Cryptogenic cirrhosis Crigler-Najjar disease type I Chronic viral hepatitis with cirrhosis Familial hypercholesterolemia Hepatic venous outflow obstruction

(Budd-Chiari syndrome) Primary hyperoxaluria type I Hemophilia Acute liver failure (ALF)

Hepatocellular carcinoma Select cases for the following indications: Hepatic adenomas

Familial amyloidosis Hepatic epithelioid hemangioendothelioma (HEHE) Erythropoietic

protoporphyria (EPP) Metastatic neuroendocrine tumors Polycystic liver disease aMultiple cystic

dilatations of the intrahepatic biliary tree. bArteriohepatic dysplasia, with paucity of bile ducts, and

congenital malformations, including pulmonary stenosis. cIntrahepatic cholestasis, progressive liver failure, and mental and growth retardation. dFormerly nonalcoholic steatohepatitis (NASH).

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CHAPTER 356 kidney transplantation has been successful in patients with primary hyperoxaluria type I. In hemophiliacs with transfusion-associated hepatitis and liver failure, liver transplantation has been associated with recovery of normal factor VIII synthesis. ■ ■

TRANSPLANTATION IN ADULTS

Liver transplantation is indicated for end-stage cirrhosis of all causes (Table 356-1). In sclerosing cholangitis and Caroli's disease (multiple cystic dilatations of the intrahepatic biliary tree), recurrent infections and sepsis associated with inflammatory and fibrotic obstruction of the biliary tree may be an indication for transplantation. Because prior biliary surgery complicates and is a relative contraindication for liver transplantation, surgical diversion of the biliary tree has been all but abandoned for patients with sclerosing cholangitis. Currently, the most common indication for liver transplantation is steatotic liver disease (SLD), which encompasses alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD). Patients with alcohol-associated cirrhosis can be considered as candidates for transplantation if they meet strict criteria for abstinence and reform; however, these criteria still do not prevent return to alcohol use in up to a quarter of cases. In highly selected cases in a limited but growing number of centers, transplantation for severe acute alcohol-associated hepatitis has been performed with success; however, because patients with acute alcohol-associated hepatitis are still actively using alcohol and because continued alcohol use remains a concern, acute alcohol-associated hepatitis is not a routine indication for liver transplantation. Patients with chronic hepatitis C have early allograft and patient survival comparable to those of other subsets of patients after transplantation; however, they have historically experienced a higher frequency of allograft failure beyond 5 years due to universal reinfection and progressive fibrosis in cases of recurrent hepatitis C is insidiously progressive, with allograft cirrhosis and failure occurring at a higher frequency beyond 5 years. Fortunately, with the introduction of highly effective direct-acting antiviral (DAA) agents targeting hepatitis C virus (HCV), allograft outcomes have improved substantially. In patients with chronic hepatitis B, in the absence of measures to prevent recurrent hepatitis B, survival after transplantation is reduced by ~10–20%; however, prophylactic use of hepatitis B immune globulin (HBIG) during and after transplantation increases the success of transplantation to a level comparable to that seen in patients with nonviral causes of liver decompensation. Specific oral antiviral drugs (e.g., entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide) (Chap. 352) can be used both for prophylaxis against and for treatment of recurrent hepatitis B, facilitating further the management of patients undergoing liver transplantation for endstage hepatitis B; most transplantation centers rely on antiviral drugs with or without HBIG to manage patients with hepatitis B. Issues of disease recurrence are discussed in more detail below. In patients who undergo transplantation for hepatic vein thrombosis (Budd-Chiari syndrome), postoperative anticoagulation is essential, as is the treatment of any myeloproliferative disorder. Patients with acute liver failure are candidates for liver transplantation, provided a donor organ can be located quickly, before life-threatening complications—including cerebral edema—set in. Patients with nonmetastatic primary hepatobiliary tumors—primary hepatocellular carcinoma (HCC), cholangiocarcinoma, hepatoblastoma, angiosarcoma, epithelioid hemangioendothelioma, and multiple or massive hepatic adenomata—have undergone liver transplantation; however, for some hepatobiliary

malignancies, overall survival is significantly lower than that for other categories of liver disease. Most transplantation centers have reported 5-year recurrence-free survival rates in patients with unresectable HCC for single tumors <5 cm in diameter or for three or fewer lesions all <3 cm comparable to those seen in patients undergoing transplantation for nonmalignant indications. Consequently, liver transplantation is currently restricted to patients whose hepatic malignancies meet these criteria. Expanded criteria for patients with HCC continue to be evaluated in exploratory clinical trials. Because the likelihood of recurrent cholangiocarcinoma is very high, only highly selected patients with limited disease are being evaluated for transplantation after intensive chemotherapy and radiation.

CONTRAINDICATIONS Absolute contraindications for transplantation include life-threatening systemic diseases, uncontrolled extrahepatic bacterial or fungal infections, preexisting advanced cardiovascular or pulmonary disease, multiple uncorrectable life-threatening congenital anomalies, metastatic malignancy, and active drug or alcohol use disorders (Table 356-2). Because carefully selected patients in their sixties and even seventies have undergone transplantation successfully, advanced age per se is no longer considered an absolute contraindication; however, in older patients, a more thorough preoperative evaluation should be undertaken to exclude ischemic cardiac disease and other comorbid conditions. Still, advanced age (>70 years) should be considered a relative contraindication—that is, a factor to be considered with other relative contraindications. Other relative contraindications include extensive portal vein thrombosis, preexisting renal disease not associated with liver disease (which may prompt consideration of combined liver and kidney transplantation), intrahepatic or biliary sepsis, severe hypoxemia (PO₂ <50 mmHg) resulting from right-to-left intrapulmonary shunts, portopulmonary hypertension with high mean pulmonary artery pressures (>35 mmHg), uncontrolled psychiatric conditions, and lack of sufficient social supports. Any one of these relative contraindications may be insufficient in and of itself to preclude transplantation. For example, the problem of portal vein thrombosis may be overcome in certain cases by constructing a graft from the donor liver portal vein to the recipient's superior mesenteric vein. Now that combination antiretroviral therapy has dramatically improved the survival of persons with HIV infection (Chap. 208) and because end-stage liver disease caused by chronic hepatitis C and B has emerged as a serious source of morbidity and mortality in the HIV-infected population, liver transplantation has now been performed successfully in selected HIV-positive persons who have excellent control of HIV infection. Selected patients with CD4⁺ T-cell counts >100/μL and with pharmacologic suppression of HIV viremia have undergone transplantation for end-stage liver disease. HIV-infected persons who have received liver allografts for end-stage liver disease resulting from chronic hepatitis B have experienced survival rates comparable to those of HIV-negative persons undergoing transplantation for the same indication. In contrast, until recently, recurrent HCV infection in the allograft has limited long-term success in persons with HCV-related end-stage

TABLE 356-2 Contraindications to Liver Transplantation

ABSOLUTE	RELATIVE
Uncontrolled extrahepatic infection	Advanced age
Active, untreated sepsis	Prior extensive hepatobiliary surgery
Life-limiting congenital anomalies	Extensive portal vein thrombosis
Cholangiocarcinoma (except those tumors that fit into protocols)	Renal failure not attributable to liver disease (consider dual organ transplantation)
Advanced cardiopulmonary disease	Extrahepatic malignancy
Severe obesity	Severe malnutrition/wasting
Medical noncompliance	AIDS
HIV seropositivity with failure to control HIV viremia or CD4 <100/μL	Life-threatening systemic diseases
Severe hypoxemia secondary to right-to-left intrapulmonary shunts (PO ₂ <50 mmHg)	Severe pulmonary hypertension (mean pulmonary artery pressure >35 mmHg)
Active substance use disorder	Uncontrolled psychiatric disorder

aFor patients 70 years and older, comprehensive assessment to exclude concurrent comorbidities, in

particular cardiovascular compromise, is indicated.

liver disease. Again, the availability of DAA agents targeting HCV (see below and Chap. 352) has improved allograft outcomes substantially.

TECHNICAL CONSIDERATIONS ■ ■ DECEASED-DONOR SELECTION Deceased-donor livers for transplantation are procured primarily from victims of head trauma, termed donation after brain death (DBD). Cardiovascular and respiratory functions in these donors are maintained artificially until the liver can be removed. Organs from brain-dead donors up to age 60 are acceptable if the following criteria are met: hemodynamic stability, adequate oxygenation, absence of bacterial or fungal infection, absence of abdominal trauma, and absence of hepatic dysfunction. Historically serologic exclusion of infections with hepatitis B virus (HBV), HCV, and HIV was required, but organs from donors infected with HBV, HCV, and HIV are now used in select cases when matched appropriately with the recipient after thorough informed consent and antiviral medication planning. Transplantation of organs procured from deceased donors who have succumbed to cardiac death, termed donation after circulatory death (DCD), can be performed successfully under selected circumstances, when ischemic time is minimized and liver histology preserved. Encouraging improvements in normothermic ex vivo liver perfusion techniques may make broader use of these organs possible. Compatibility in ABO blood group and organ size between donor and recipient are important considerations in donor selection; however, ABO-incompatible, split-liver, or reduced-donor organ allografts can be performed in emergencies or marked donor scarcity. Tissue typing for human leukocyte antigen (HLA) matching is not required, and preformed cytotoxic HLA antibodies do not preclude liver transplantation. Following perfusion with cold electrolyte solution, the donor liver is removed and packed in ice. The use of University of Wisconsin (UW) solution, rich in lactobionate and raffinose, has permitted the extension of cold ischemic time up to 20 h; however, 12 h

may be a more reasonable limit. Improved techniques for harvesting multiple organs from the same donor have increased the availability of donor livers, but the availability of donor livers is far outstripped by the demand. Currently in the United States, all donor livers are distributed through a nationwide organ-sharing network (United Network for Organ Sharing [UNOS]) designed to allocate available organs based on regional considerations and recipient acuity. Recipients who have the highest disease severity generally have the highest priority, but allocation strategies that balance highest urgency against best outcomes continue to evolve to distribute deceased-donor organs most effectively. Allocation based on the Child-Turcotte-Pugh (CTP) score, which uses five clinical variables (encephalopathy stage, ascites, bilirubin, albumin, and prothrombin time) and waiting time, has been replaced by allocation based on urgency alone, calculated using the Model for End-Stage Liver Disease (MELD) score. The MELD score is based on a mathematical model that includes serum bilirubin, albumin, sodium, creatinine, and prothrombin time expressed as international normalized ratio (INR); gender assigned at birth is included in the MELD calculation for females (Table 356-3). The MELD scale is continuous with scores ranging between 6 and 40; higher values correlate with increased illness severity. On the lower end of this scale, the value of proceeding to transplantation is limited, because liver recipients with MELD scores <15 experience higher posttransplantation mortality rates than similarly classified patients who remain on the waiting list. The MELD score has undergone modifications over time, including the development of MELD-Na in 2016 and MELD-3.0 in 2023 to improve model accuracy in predicting short-term

survival and prioritizing allocation. Neither waiting time (except as a tie breaker between two potential recipients with the same MELD scores) nor posttransplantation outcome is taken into account, but use of the MELD score has been shown to reduce waiting list mortality, to reduce waiting time prior to transplantation, to be the best predictor of pretransplantation mortality, to satisfy the prevailing view that medical need should be the decisive determinant, and to eliminate both the subjectivity inherent in the CTP scoring system (presence and degree of ascites and hepatic encephalopathy) and the differences in waiting times among different regions of the country.

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TABLE 356-3 United Network for Organ Sharing (UNOS) Liver Transplantation Waiting List Criteria
Status 1 Acute liver failure (including primary graft nonfunction and hepatic artery thrombosis)^a
The Model for End-Stage Liver Disease (MELD) score, on a continuous scale, determines allocation of the remainder of donor organs^b. Candidates who are at least 18 years old at the time of registration receive an initial MELD score equal to:

$1.33 \text{ (if female)} + [4.56 \times \log_e(\text{bilirubin})] + [0.82 \times (137 - \text{sodium})] - [0.24 \times (137 - \text{sodium}) \times \log_e(\text{bilirubin})] + [9.09 \times \log_e(\text{INR})] + [11.14 \times \log_e(\text{creatinine})] + [1.85 \times (3.5 - \text{albumin})] - [1.83 \times (3.5 - \text{albumin}) \times \log_e(\text{creatinine})] + 6$

Candidates who are currently at least 12 years old and were less than 18 years old at the time of registration receive a MELD score equal to:

$[4.56 \times \log_e(\text{bilirubin})] + [0.82 \times (137 - \text{sodium})] - [0.24 \times 137 - \text{sodium}) \times \log_e(\text{bilirubin})] + [9.09 \times \log_e(\text{INR})] + 11.14 \times \log_e(\text{creatinine}) +$

$[1.85 \times (3.5 - \text{albumin})] - [1.83 \times (3.5 - \text{albumin}) \times \log_e(\text{creatinine})] + 7.33$

The PELD calculator is for candidates under the age of 12. Online calculators to determine MELD scores are available, such as the following:

<https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/> ^aFor children <18 years of age, status 1 includes acute or chronic liver failure plus hospitalization in an intensive care unit or inborn errors of metabolism. Status 1 is retained for those persons with acute liver failure and supersedes the MELD score. MELD scale is continuous, with 34 levels ranging between 6 and 40 (scores above 40 are categorized as 40). ^bIn certain cases, the natural MELD score may not represent the severity of illness or need for transplantation; in such cases, an exception MELD score may be granted if select criteria are met upon review by the National Liver Review Board (NLRB): <https://optn.transplant.hrsa.gov/professionals/by-topic/guidance/liver-review-board-guidance/>. The highest priority (status 1) continues to be reserved for patients with acute liver failure (ALF) or complications following transplantation such as primary graft nonfunction and hepatic artery thrombosis. Because candidates for liver transplantation who have HCC may not be sufficiently decompensated to compete for donor organs based on urgency criteria alone, and because protracted waiting for deceased-donor organs often results in tumor growth beyond acceptable limits for transplantation, such patients are assigned disease-specific MELD exception points. In addition to HCC, other disease-specific MELD exceptions are evaluated on a regular basis and updated by the National Liver Review Board (NLRB) (Table 356-3). ■ ■

LIVING-DONOR TRANSPLANTATION Occasionally, especially for liver transplantation in children, one deceased-donor organ can be split between two recipients (one adult and one child). A more viable alternative, transplantation of the right lobe of the liver from a healthy adult donor into an adult recipient, has gained increased popularity. Living-donor transplantation of the left lobe (left lateral segment), introduced in the early 1990s to alleviate the extreme shortage of donor organs for small children, accounts currently for approximately one-third of all liver transplantation procedures in children. Driven by the shortage of deceased-donor organs, living-donor transplantation

involving the more sizable right lobe is being considered with increasing frequency in adults; however, livingdonor liver transplantation cannot be expected to solve the donor organ shortage; 603 such procedures were done in 2023, representing only ~6% of all liver transplant operations done in the United States. Living-donor transplantation can reduce waiting time and cold ischemia time; is done under elective, rather than emergency, circumstances; and is lifesaving in recipients who cannot afford to wait for a deceased donor. The downside, of course, is the risk to the healthy donor (a mean of 10 weeks of medical disability; biliary complications in ~5%; postoperative complications such as wound infection, smallbowel obstruction, and incisional hernias in 9–19%; and death in 0.2–0.4%) as well as the increased frequency of biliary (15–32%) and vascular (10%) complications in the recipient. Potential donors must participate voluntarily without coercion, and transplantation teams should go to great lengths to exclude subtle coercive or inappropriate psychological factors as well as outline carefully to both donor and

recipient the potential benefits and risks of the procedure. Donors for the procedure should be 18–65 years old; have a compatible blood type with the recipient; have no serious chronic medical problems or history of major abdominal surgery; and pass an exhaustive series of clinical, biochemical, and serologic evaluations to unearth disqualifying medical disorders. The recipient should meet the same UNOS criteria for liver transplantation as recipients of a deceased donor allograft. ■ ■ **SURGICAL TECHNIQUE** Removal of the recipient's native liver is technically difficult, particularly in the presence of portal hypertension with its associated collateral circulation and extensive varices and especially in the presence of scarring from previous abdominal operations. The combination of portal hypertension and coagulopathy (elevated prothrombin time and thrombocytopenia) may translate into large blood-product transfusion requirements. After the portal vein and infrahepatic and suprahepatic inferior vena cava are dissected, the hepatic artery and common bile duct are dissected. Then the native liver is removed and the donor organ inserted. During the anhepatic phase, coagulopathy, hypoglycemia, hypocalcemia, and hypothermia are encountered and must be managed by the anesthesiology team. Caval, portal vein, hepatic artery, and bile duct anastomoses are performed in succession, the last by end-to-end suturing of the donor and recipient common bile ducts (Fig. 356-1) or by choledochojejunostomy to a Roux-en-Y loop if the recipient common bile duct cannot be used for reconstruction (e.g., in sclerosing cholangitis). A typical transplant operation lasts 8 h, with a range of 6–18 h. Because of excessive bleeding, large volumes of blood, blood products, and volume expanders may be required during surgery; however, blood requirements have fallen sharply with improvements in surgical technique, blood-salvage interventions, and experience. As noted above, emerging alternatives to orthotopic liver transplantation include split-liver grafts, in which one donor organ is divided and inserted into two recipients, and living-donor procedures, in which part of the left (for children), the left (for children or small adults), or the right (for adults) lobe of the liver is harvested from a living donor for transplantation into the recipient. In the adult procedure, once the right lobe is removed from the donor, the donor right hepatic vein is anastomosed to the recipient right hepatic vein remnant, followed by donor-to-recipient anastomoses of the portal vein and then the hepatic artery. Finally, the biliary anastomosis is performed, duct-to-duct if practical or via Roux-en-Y anastomosis. Heterotopic liver

Suprahepatic vena cava Donor liver Hepatic artery Portal vein
Common bile duct Infrahepatic vena cava

FIGURE 356-1 The anastomoses in orthotopic liver transplantation. The anastomoses are performed in the following sequence: (1) suprahepatic and infrahepatic vena cava, (2) portal vein, (3) hepatic artery, and (4) common bile duct-to-duct anastomosis. (Reproduced with permission from S Vilarinho, RP Lifton: Liver transplantation: From

inception to clinical practice. 150:1096, 2012.)

transplantation, in which the donor liver is inserted without removal of the native liver, has met with very limited success and acceptance, except in a very small number of centers. Areas of research with the potential to overcome the shortage of donor organs include hepatocyte transplantation and xenotransplantation with genetically modified organs of nonhuman origin (e.g., swine).

POSTOPERATIVE COURSE AND MANAGEMENT ■ ■ IMMUNOSUPPRESSIVE THERAPY The introduction in 1980 of cyclosporine as an immunosuppressive agent contributed substantially to the improvement in survival after liver transplantation. Cyclosporine, a calcineurin inhibitor, blocks early activation of T cells and is specific for T-cell functions that result from the interaction of the T cell with its receptor and that involve the calcium-dependent signal transduction pathway. As a result, the activity of cyclosporine leads to inhibition of lymphokine gene activation, blocking interleukins 2, 3, and 4, tumor necrosis factor α , and other lymphokines. Cyclosporine also inhibits B-cell functions. This process occurs without affecting rapidly dividing cells in the bone marrow, which may account for the reduced frequency of posttransplantation systemic infections. The most common and important side effect of cyclosporine therapy is nephrotoxicity. Cyclosporine causes dose-dependent renal tubular injury and direct renal artery vasospasm. Following renal function is therefore important in monitoring cyclosporine therapy and is perhaps even a more reliable indicator than blood levels of the drug. Nephrotoxicity is reversible and can be managed by dose reduction. Other adverse effects of cyclosporine therapy include hypertension, hyperkalemia, tremor, hirsutism, glucose intolerance, and gingival hyperplasia.

CHAPTER 356 Tacrolimus, a macrolide lactone antibiotic isolated from a Japanese soil fungus, *Streptomyces tsukubaensis*, has the same mechanism of action as cyclosporine but is 10–100 times more potent. Initially applied as “rescue” therapy for patients in whom rejection occurred despite the use of cyclosporine, tacrolimus was shown to be associated with a reduced frequency of acute, refractory, and chronic rejection. Although patient and graft survival are the same with these two drugs, the advantage of tacrolimus in minimizing episodes of rejection, reducing the need for additional glucocorticoid doses, and lowering the likelihood of bacterial and cytomegalovirus (CMV) infection has simplified the management of patients undergoing liver transplantation. In addition, the oral absorption of tacrolimus is more predictable than that of cyclosporine. As a result, tacrolimus has now supplanted cyclosporine for primary immunosuppression, and most centers rely on oral rather than IV administration from the outset. Liver Transplantation Although more potent than cyclosporine, tacrolimus is also more toxic and more likely to be discontinued for adverse events. The toxicity of tacrolimus is similar to that of cyclosporine; nephrotoxicity and neurotoxicity are the most commonly encountered adverse effects, and neurotoxicity (tremor, seizures, hallucinations, psychoses, coma) is more likely and more severe in tacrolimus-treated patients. Both drugs can cause diabetes mellitus, but tacrolimus does not cause hirsutism or gingival hyperplasia. Because of overlapping toxicity between cyclosporine and tacrolimus, especially nephrotoxicity, and because tacrolimus reduces cyclosporine clearance, these two drugs should not be used together. Because 99% of tacrolimus is metabolized by the liver, hepatic dysfunction reduces its clearance; in primary graft nonfunction (when, for technical reasons or because of ischemic damage prior to its insertion, the allograft is defective and does not function normally from the outset), tacrolimus doses have to be reduced substantially, especially in children. Both cyclosporine and tacrolimus are metabolized by the cytochrome P450 IIIA system, and therefore, drugs that induce cytochrome

P450 (e.g., phenytoin, phenobarbital, carbamazepine, rifampin) reduce available levels of cyclosporine and tacrolimus, and drugs that inhibit cytochrome P450 (e.g., erythromycin, fluconazole, ketoconazole, clotrimazole, itraconazole, verapamil, diltiazem, danazol, metoclopramide, the HIV protease inhibitor ritonavir, and the HCV protease inhibitors glecaprevir [cyclosporine only] and

sofosbuvir) increase cyclosporine and tacrolimus blood levels. Indeed, itraconazole is used occasionally to help boost tacrolimus levels. Like azathioprine, cyclosporine and tacrolimus appear to be associated with a risk of lymphoproliferative malignancies (see below), which may occur earlier after cyclosporine or tacrolimus than after azathioprine therapy. Because of these side effects, combinations of cyclosporine or tacrolimus with prednisone and an antimetabolite (azathioprine or mycophenolic acid, see below)—all at reduced doses—are preferable regimens for immunosuppressive therapy.

Mycophenolic acid, a nonnucleoside purine metabolism inhibitor derived as a fermentation product from several *Penicillium* species, is another immunosuppressive drug being used for patients undergoing liver transplantation. Mycophenolate has been shown to be better than azathioprine, when used with other standard immunosuppressive drugs, in preventing rejection after renal transplantation and has been adopted widely as well for use in liver transplantation. The most common adverse effects of mycophenolate are bone marrow suppression and gastrointestinal complaints. In patients with pretransplantation renal dysfunction or renal deterioration that occurs intraoperatively or immediately postoperatively, tacrolimus or cyclosporine therapy may not be practical; under these circumstances, induction or maintenance of immunosuppression with antithymocyte globulin (ATG; thymoglobulin) or monoclonal antibodies to T cells (basiliximab, daclizumab) may be appropriate. Therapy with some of these agents (ATG) has also been effective in reversing acute rejection in the posttransplantation period and is the standard treatment for acute rejection that fails to respond to methyl prednisolone boluses. Available data support the use of thymoglobulin induction to delay calcineurin inhibitor use and its attendant nephrotoxicity. IV infusions of thymoglobulin may be complicated by fever and chills, which can be ameliorated by premedication with antipyretics and a low dose of glucocorticoids.

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Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), blocks later events in T-cell activation and is another agent approved for use in solid-organ transplantation. Sirolimus, however, is not used early in the posttransplantation course, because it impairs wound healing and is associated with an increased frequency of hepatic artery thrombosis in the first 30 days after transplantation. In patients with calcineurin inhibitor-related nephrotoxicity, conversion to sirolimus has been demonstrated to be effective in preventing rejection with accompanying improvements in renal function. Because of its profound antiproliferative effects, sirolimus has also been suggested to be a useful immunosuppressive agent in patients with a prior or current history of malignancy, such as HCC. Side effects include hyperlipidemia, peripheral edema, oral ulcers, and interstitial pneumonitis. Everolimus is a hydroxyethyl derivative of sirolimus that, when used in conjunction with low-dose tacrolimus, also provides successful protection against acute rejection, with decreased renal impairment compared to that associated with standard tacrolimus dosing. Everolimus and sirolimus share a similar adverse event profile. The most important principle of immunosuppression is that the ideal approach strikes a balance between immunosuppression and immunologic competence. In general, given sufficient immunosuppression, acute liver allograft rejection is nearly always reversible. On one hand, incompletely treated acute rejection predisposes to the development of chronic

rejection, which can threaten graft survival. On the other hand, if the cumulative dose of immunosuppressive therapy is too large, the patient may succumb to opportunistic infection. Data show a benefit to minimizing the use of glucocorticoids, a mainstay of immunosuppressive regimens, as cases allow. In select conditions, such as hepatitis C, early steroid withdrawal and initiation of DAAs can avert recurrent allograft hepatitis successfully. Patients who undergo liver transplantation for autoimmune diseases such as autoimmune hepatitis are less likely to achieve freedom from glucocorticoids, although, in many cases, immunosuppression can be narrowed to a dual-agent regimen of a calcineurin inhibitor and an antimetabolite. ■ ■ POSTOPERATIVE COMPLICATIONS Complications of liver transplantation can be divided into nonhepatic and hepatic categories (Tables 356-4 and 356-5). In addition, both

TABLE 356-4 Nonhepatic Complications of Liver Transplantation	CATEGORY	COMPLICATION
Cardiovascular instability	Arrhythmias	Congestive heart failure
Cardiomyopathy	Pulmonary compromise	Pneumonia
Pulmonary capillary vascular permeability	Fluid overload	Renal dysfunction
Prerenal azotemia	Hypoperfusion injury (acute tubular necrosis)	Drug nephrotoxicity
↓ Renal blood flow secondary to ↑ intraabdominal pressure	Hematologic	Anemia secondary to gastrointestinal and/or intraabdominal bleeding
Hemolytic anemia, aplastic anemia	Thrombocytopenia	Infection
Bacterial: early, common postoperative infections	Fungal/parasitic: late, opportunistic infections	Viral: late, opportunistic infections, recurrent hepatitis
Neuropsychiatric	Seizures	Metabolic encephalopathy
Depression	Difficult psychosocial adjustment	Diseases of donor
Infectious	Malignant	Malignancy
B-cell lymphoma (posttransplantation lymphoproliferative disorders)	De novo neoplasms (particularly squamous cell skin carcinoma)	Immediate postoperative and late complications are encountered. As a rule, patients who undergo liver transplantation have been chronically ill for protracted periods and may be malnourished and wasted. The impact of such chronic illness and the multisystem failure that
TABLE 356-5 Hepatic Complications of Liver Transplantation	Hepatic Dysfunction	Common after Major Surgery
Prehepatic	Pigment load	Hemolysis
Blood collections (hematomas, abdominal collections)	Intrahepatic	Early
Hepatotoxic drugs and anesthesia	Hypoperfusion (hypotension, shock, sepsis)	Benign postoperative cholestasis
Late	Transfusion-associated hepatitis	Exacerbation of primary hepatic disease
Posthepatic	Biliary obstruction	↓ Renal clearance of conjugated bilirubin (renal dysfunction)
Hepatic Dysfunction Unique to Liver Transplantation	Primary graft nonfunction	Vascular compromise
Portal vein obstruction	Hepatic artery thrombosis	Anastomotic leak with intraabdominal bleeding
Bile duct disorder	Stenosis, obstruction, leak	Rejection
Recurrent primary hepatic disease		

accompanies liver failure continue to require attention in the post operative period. Because of the massive fluid losses and fluid shifts that occur during the operation, patients may remain fluid overloaded during the immediate postoperative period, straining cardiovascular reserve; this effect can be amplified in the face of transient renal dysfunction and pulmonary capillary vascular permeability. Continuous monitoring of cardiovascular and pulmonary function, measures to maintain the integrity of the intravascular compartment and to treat extravascular volume overload, and scrupulous attention to potential sources and sites of infection are of paramount importance. Cardiovascular instability may also result from the electrolyte imbalance that may accompany reperfusion of the donor liver as well as from restoration of systemic vascular resistance following implantation. Pulmonary function may be compromised further by paralysis of the right hemidiaphragm associated with phrenic nerve injury. The hyperdynamic state with

increased cardiac output that is characteristic of patients with liver failure reverses rapidly after successful liver transplantation. Other immediate management issues include renal dysfunction. Prerenal azotemia, acute kidney injury associated with hypoperfusion (acute tubular necrosis), and renal toxicity caused by antibiotics, tacrolimus, or cyclosporine are encountered frequently in the postoperative period, sometimes necessitating dialysis. Hemolytic-uremic syndrome can be associated with cyclosporine and tacrolimus. Occasionally, postoperative intraperitoneal bleeding may be sufficient to increase intraabdominal pressure, which, in turn, may reduce renal blood flow; this effect is rapidly reversible when abdominal distention is relieved by exploratory laparotomy to identify and ligate the bleeding site and to remove intraperitoneal clot. Anemia may also result from acute upper gastrointestinal bleeding or from transient hemolytic anemia, which may be autoimmune, especially when blood group O livers are transplanted into blood group A or B recipients. This autoimmune hemolytic anemia is mediated by donor intrahepatic lymphocytes that recognize red blood cell A or B antigens on recipient erythrocytes. Transient in nature, this process resolves once the donor liver is repopulated by recipient bone marrow-derived lymphocytes; the hemolysis can be treated by transfusing blood group O red blood cells and/or by administering higher doses of glucocorticoids. Transient thrombocytopenia is also encountered commonly. Aplastic anemia, a late occurrence, is rare but has been reported in almost 30% of patients who underwent liver transplantation for acute, severe hepatitis of unknown cause. Bacterial, fungal, or viral infections are common and may be lifethreatening postoperatively. Early after transplant surgery, common postoperative infections predominate—pneumonia, wound infections, infected intraabdominal collections, urinary tract infections, and IV line infections—rather than opportunistic infections; these infections may involve the biliary tree and liver as well. Beyond the first postoperative month, the toll of immunosuppression becomes evident, and opportunistic infections—CMV, herpes viruses, fungal infections (*Aspergillus*, *Candida*, cryptococcal disease), mycobacterial infections, parasitic infections (*Pneumocystis*, *Toxoplasma*), and bacterial infections (*Nocardia*, *Legionella*, *Listeria*)—predominate. Rarely, early infections represent those transmitted with the donor liver, either infections present in the donor or infections acquired during procurement processing. De novo viral hepatitis infections acquired from the donor organ or, almost unheard of now, from transfused blood products occur after typical incubation periods for these agents (well beyond the first month). Obviously, infections in an immunosuppressed host demand early recognition and prompt management; prophylactic antibiotic therapy is administered routinely in the immediate postoperative period. Use of sulfamethoxazole with trimethoprim reduces the incidence of postoperative *Pneumocystis jirovecii* pneumonia. Antiviral prophylaxis for CMV with ganciclovir should be administered in patients at high risk (e.g., when a CMV-seropositive donor organ is implanted into a CMV-seronegative recipient). Neuropsychiatric complications include seizures (commonly associated with cyclosporine and tacrolimus toxicity), metabolic encephalopathy, depression, and difficult psychosocial adjustment. Rarely, diseases are transmitted by the allograft from the donor to the recipient. In

addition to viral and bacterial infections, malignancies of donor origin have occurred. Posttransplantation lymphoproliferative disorders, especially B-cell lymphoma, are a recognized complication associated with immunosuppressive drugs such as azathioprine, tacrolimus, and cyclosporine (see above). Epstein-Barr virus has been shown to play a contributory role in some of these tumors, which may regress when immunosuppressive therapy is reduced. De novo neoplasms appear at increased frequency after liver transplantation, particularly squamous cell carcinomas of the skin. Routine screening should be performed.

Long-term complications after liver transplantation attributable primarily to immunosuppressive medications include diabetes mellitus and osteoporosis (associated with glucocorticoids and calcineurin inhibitors) as well as hypertension, hyperlipidemia, and chronic renal insufficiency (associated with cyclosporine and tacrolimus). Monitoring and treating these disorders are routine components of posttransplantation care; in some cases, they respond to changes in immunosuppressive regimen, while in others, specific treatment of the disorder is introduced. Data from a large U.S. database showed that the prevalence of renal failure was 18% at year 5 and 25% at year 10 after liver transplantation. Similarly, the high frequency of diabetes, hypertension, hyperlipidemia, obesity, and the metabolic syndrome renders patients susceptible to cardiovascular disease after liver transplantation; although hepatic complications account for most of the mortality after liver transplantation, renal failure and cardiovascular disease are the other leading causes of late mortality after liver transplantation. ■ ■

HEPATIC COMPLICATIONS Hepatic dysfunction after liver transplantation is similar to the hepatic complications encountered after major abdominal and cardiothoracic surgery; however, in addition, hepatic complications include primary graft failure, vascular compromise, failure or stricture of the biliary anastomoses, and rejection. As in nontransplantation surgery, postoperative jaundice may result from prehepatic, intrahepatic, and posthepatic sources. Prehepatic sources represent the massive hemoglobin pigment load from transfusions, hemolysis, hematomas, ecchymoses, and other collections of blood. Early intrahepatic liver injury includes effects of hepatotoxic drugs and anesthesia; hypoperfusion injury associated with hypotension, sepsis, and shock; and benign postoperative cholestasis. Late intrahepatic sources of liver injury include exacerbation of primary disease. Posthepatic sources of hepatic dysfunction include biliary obstruction and reduced renal clearance of conjugated bilirubin. Hepatic complications unique to liver transplantation include primary graft failure associated with ischemic injury to the organ during harvesting; vascular compromise associated with thrombosis or stenosis of the portal vein or hepatic artery anastomoses; vascular anastomotic leak; stenosis, obstruction, or leakage of the anastomosed common bile duct; recurrence of primary hepatic disorder (see below); and rejection. CHAPTER 356 Liver

Transplantation ■ ■ **ALLOGRAFT REJECTION** Despite the use of immunosuppressive drugs, rejection of the transplanted liver still occurs in a proportion of patients, beginning 1–2 weeks after surgery. Clinical signs suggesting rejection may include fever, right upper quadrant pain, and reduced bile pigment and volume. Leukocytosis may occur, but the most reliable indicators are increases in serum bilirubin and aminotransferase levels. Because these tests lack specificity, and because patients can be asymptomatic, distinguishing among rejection, biliary obstruction, primary graft nonfunction, vascular compromise, viral hepatitis, CMV infection, drug hepatotoxicity, and recurrent primary disease may prove difficult. Radiographic visualization of the biliary tree and/or percutaneous liver biopsy often help to establish the correct diagnosis. Morphologic features of acute rejection include a mixed portal cellular infiltrate, bile duct injury, and/or endothelial inflammation (“endothelialitis”); some of these findings are reminiscent of graft-versus-host disease, primary biliary cholangitis, or recurrent allograft hepatitis C. As soon as allograft rejection is suspected, treatment consists of increased immunosuppression, most commonly IV methylprednisolone in repeated boluses; if this fails to abort rejection, consideration is given to thymoglobulin. Caution

should be exercised when managing acute rejection with pulse glucocorticoids in patients with HCV infection, because of the high risk of triggering recurrent allograft hepatitis C; however, the availability of DAAs for HCV can obviate this concern effectively.

Chronic rejection is a relatively rare outcome that can follow repeated bouts of acute rejection or that occurs unrelated to preceding rejection episodes. Morphologically, chronic rejection is characterized by progressive cholestasis, focal parenchymal necrosis, mononuclear infiltration, vascular lesions (intimal fibrosis, subintimal foam cells, fibrinoid necrosis), and fibrosis. This process may be reflected as ductopenia—the vanishing bile duct syndrome, which is more common in patients undergoing liver transplantation for autoimmune liver disease. Reversibility of chronic rejection is limited; in patients with therapy-resistant chronic rejection, retransplantation has yielded encouraging results.

OUTCOME ■ ■ SURVIVAL The survival rate for patients undergoing liver transplantation has improved steadily since 1983. One-year survival rates have increased from ~70% in the early 1980s to 85–90% from 2003 to the present time. Currently, the 5-year survival rate exceeds 60%. An important observation is the relationship between clinical status before transplantation and outcome. For patients who undergo liver transplantation when their level of compensation is high (e.g., still working or only partially disabled), a 1-year survival rate of >85% is common. For those whose level of decompensation mandates continuous in-hospital care prior to transplantation, the 1-year survival rate is ~70%, whereas for those who are so decompensated that they require life support in an intensive care unit, the 1-year survival rate is ~50%. Since the adoption by UNOS in 2002 of the MELD system for organ allocation, posttransplantation survival has been found to be affected adversely for candidates with MELD scores >25, considered high disease severity. Thus, irrespective of allocation scheme, high disease severity before transplantation corresponds to diminished posttransplantation survival. Another important distinction in survival has been drawn between high- and low-risk patient categories. For patients who do not fit any “high-risk” designations, 1- and 5-year survival rates of 85% and 80%, respectively, have been recorded. In contrast, among patients in high-risk categories—cancer, fulminant hepatitis, age >65, concurrent renal failure, respiratory dependence, portal vein thrombosis, and history of a portacaval shunt or multiple right upper quadrant operations—survival statistics fall into the range of 60% at 1 year and 35% at 5 years. Survival after retransplantation for primary graft nonfunction is ~50%. Causes of failure of liver transplantation vary with time. Failures within the first 3 months result primarily from technical complications, postoperative infections, and hemorrhage. Transplant failures after the first 3 months are more likely to result from infection, rejection, or recurrent disease (such as malignancy, viral hepatitis, or return to alcohol use).

PART 10 Disorders of the Gastrointestinal System ■ ■ RECURRENCE OF PRIMARY DISEASE Features of autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis overlap with those of rejection or posttransplantation bile duct injury. Autoimmune hepatitis and sclerosing cholangitis can recur after liver transplantation. Similarly, reports of recurrent primary biliary cholangitis after liver transplantation have appeared; however, the histologic features of primary biliary cholangitis and chronic rejection are virtually indistinguishable and occur as frequently in patients with primary biliary cholangitis as in patients undergoing transplantation for other reasons. The presence of a florid inflammatory bile duct lesion is highly suggestive of the recurrence of primary biliary cholangitis, but even this lesion can be observed in acute rejection. Hereditary disorders such as Wilson’s disease and α 1 antitrypsin deficiency have not recurred after liver transplantation; however, recurrence of disordered iron metabolism has been observed in some patients with hemochromatosis. Hepatic vein thrombosis (Budd-Chiari syndrome) may recur; this can be minimized by treating underlying myeloproliferative disorders and by anticoagulation. Because cholangiocarcinoma recurs almost invariably, few centers now

offer transplantation to such patients; however, a few highly selected patients with operatively confirmed stage I or II cholangiocarcinoma who undergo liver transplantation combined with neoadjuvant chemoradiation may experience excellent outcomes. In patients with intrahepatic HCC who meet criteria for transplantation, 1- and 5-year survivals are similar to those observed in patients undergoing liver transplantation for nonmalignant disease. Finally, metabolic disorders such as MASLD are seen *de novo* and recur frequently, especially if the underlying metabolic predisposition is not altered. Hepatitis A can recur after transplantation for fulminant hepatitis A, but such acute reinfection has no serious clinical sequelae. In fulminant hepatitis B, recurrence is not the rule; however, in the absence of any prophylactic measures, hepatitis B usually recurs after transplantation for end-stage chronic hepatitis B. Before the introduction of prophylactic antiviral therapy, immunosuppressive therapy sufficient to prevent allograft rejection led inevitably to marked increases in hepatitis B viremia, regardless of pretransplantation levels. Overall graft and patient survival were poor, and some patients experienced a rapid recapitulation of severe injury—severe chronic hepatitis or even fulminant hepatitis—after transplantation. Also recognized in the era before availability of antiviral regimens was fibrosing cholestatic hepatitis, rapidly progressive liver injury associated with marked hyperbilirubinemia, substantial prolongation of the prothrombin time (both out of proportion to relatively modest elevations of aminotransferase activity), and rapidly progressive liver failure. This lesion has been suggested to represent a “choking off” of the hepatocyte by an overwhelming density of HBV proteins. Complications such as sepsis and pancreatitis were also observed more frequently in patients undergoing liver transplantation for hepatitis B prior to the introduction of antiviral therapy. The introduction of long-term prophylaxis with HBIG revolutionized liver transplantation for chronic hepatitis B. Preoperative hepatitis B vaccination, preoperative or postoperative interferon (IFN) therapy, or short-term (≤ 2 months) HBIG prophylaxis has not been shown to be effective, but a retrospective analysis of data from several hundred European patients followed for 3 years after transplantation has shown that long-term (≥ 6 months) prophylaxis with HBIG is associated with a lowering of the risk of HBV reinfection from ~ 75 to 35% and a reduction in mortality from ~ 50 to 20%. As a result of long-term HBIG use following liver transplantation for chronic hepatitis B, similar improvements in outcome have been observed in the United States, with 1-year survival rates between 75 and 90%. Currently, with HBIG prophylaxis, the outcome of liver transplantation for chronic hepatitis B is indistinguishable from that for chronic liver disease unassociated with chronic hepatitis B; essentially, medical concerns regarding liver transplantation for chronic hepatitis B have been eliminated. Passive immunoprophylaxis with HBIG is begun during the anhepatic stage of surgery, repeated daily in the postoperative days for high-risk patients (active viremia at the time of transplantation and/or co-infection with hepatitis D or HIV), and then continued with infusions that are given either at regular intervals of 4–6 weeks or, alternatively, when antibody to hepatitis B surface (anti-HBs) levels fall below a threshold of 100 mIU/mL. The current approach in most centers is to continue HBIG indefinitely in select high-risk cases, which can add $\sim \$20,000$ per year to the cost of care, and to transition to maintenance with antiviral alone in low-risk-hepatitis B liver allograft recipients. Still, “breakthrough” HBV infection occurs occasionally. Further improving the outcome of liver transplantation for chronic hepatitis B is the current availability of such antiviral drugs as entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide (Chap. 352). When these drugs are administered to patients with decompensated liver disease, a proportion improves sufficiently to postpone imminent liver transplantation. In addition, antiviral therapy can be used to prevent recurrence of HBV infection when administered prior to transplantation; to treat hepatitis B that recurs after transplantation, including in patients who break through HBIG prophylaxis; and

to reverse the course of otherwise fatal fibrosing cholestatic hepatitis. Clinical trials have shown that entecavir or tenofovir antiviral therapy reduces the level of HBV replication substantially, sometimes even resulting in clearance of hepatitis B surface antigen (HBsAg); reduces alanine aminotransferase (ALT) levels; and improves histologic features of necrosis

and inflammation. Currently, most liver transplantation centers combine HBIg plus one of the high-barrier-to-resistance oral nucleoside (entecavir) or nucleotide analogues (tenofovir). In low-risk patients with no detectable hepatitis B viremia at the time of transplantation, results from a number of clinical trials have suggested that antiviral prophylaxis can suffice, without HBIg or with a finite duration of HBIg, to prevent recurrent HBV infection of the allograft. In patients documented at the time of liver transplantation to have undetectable HBV DNA in serum and covalently closed circular DNA in the liver (i.e., with low risk for recurrence of HBV infection), results of a clinical trial suggested that, after receipt of 5 years of combined therapy, both HBIg and oral-agent therapy can be withdrawn sequentially (over two 6-month periods) with a success rate, as monitored over a median of 6 years after withdrawal, of 90% and an anti-HBs seroconversion rate of 60% (despite transient reappearance of HBV DNA and/or HBsAg in some of these patients). Antiviral prophylactic approaches applied to patients undergoing liver transplantation for chronic hepatitis B are being used as well for patients without hepatitis B who receive organs from donors with antibody to hepatitis B core antigen (anti-HBc) but who do not have detectable HBsAg. Patients who undergo liver transplantation for chronic hepatitis B plus D are less likely to experience recurrent liver injury than patients undergoing liver transplantation for hepatitis B alone; still, such co-infected patients would also be offered standard posttransplantation prophylactic antiviral therapy for hepatitis B. Until recently, the most common indication for liver transplantation was end-stage liver disease resulting from chronic hepatitis C (Fig. 356-2). For patients undergoing liver transplantation for hepatitis C, because of an aggressive natural history of recurrent allograft hepatitis C, graft and patient survival were diminished substantially compared to other indications for transplantation. The approval over the last decade of several DAA agents and of IFN-free DAA regimens against HCV has had a major impact on the

Percent

A Year FIGURE 356-2 Trends in liver transplantation. A. Candidates waiting for liver transplantation by indication at any time in the given year. Candidates listed at more than one center are counted once per listing. Active and inactive patients are included. B. All liver allograft recipients by indication, including adult and pediatric, retransplantation, and multiorgan recipients. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MASH, metabolic dysfunction-associated steatohepatitis. (From the Scientific Registry of Transplant Recipients (SRTR.org).)

management and outcome of both pretransplantation and posttransplantation HCV infection. Such therapeutic approaches (1) permit the clearance of viremia in a substantial proportion of decompensated cirrhotics, thereby preventing recurrent allograft infection and even improving the clinical status of most of these patients, delaying or obviating the need for liver replacement; and (2) achieve sustained virologic responses in a much higher proportion of persons with allograft HCV infection, because of improvements in antiviral treatment efficacy and tolerability. Ideally, patients should be treated prior to liver transplantation. This approach has already reduced the numbers of patients with HCV infection referred for liver transplantation and led to delisting of others. A

concern, however, is that eradication of HCV infection will reduce the MELD score and lower the priority for a donor organ in some patients who still require transplantation because of continued hepatic decompensation and profound reduction in quality of life (a situation referred to as MELD purgatory). In addition, elimination of HCV infection prior to transplantation, historically, would have disqualified such patients as recipients of donor livers from persons with HCV infection, contracting the potential donor pool and limiting accessibility to donor organs and timely transplantation. With the advent of highly effective DAAs, however, allografts from HCV-infected donors are being transplanted into both HCV-infected and HCV-uninfected recipients, who can be treated posttransplantation with DAAs. Thus, earlier concerns about the potential impact of pre transplantation DAA treatment on limiting the donor pool are no longer an issue. The approach to HCV treatment should be individualized thoughtfully for each patient, based on such factors as MELD score, time anticipated prior to availability of a donor organ, relative clinical stability, and comorbidities.

CHAPTER 356 DAA combinations that are being used successfully against allograft HCV include ledipasvir plus sofosbuvir; velpatasvir plus sofosbuvir; and grazoprevir plus pibrentasvir. (For updated guidelines, see www.hcvguidelines.org.) In patients with recurrent HCV infection after Liver Transplantation Acute liver failure HCV Alcoholic liver disease Cholestatic disease HCC MASH Other/unknown

Transplants

PART 10 Disorders of the Gastrointestinal System

Year B FIGURE 356-2 (Continued) liver transplantation, each of these regimens has yielded response rates approaching those seen in compensated nontransplant patient populations. Historically, small numbers of allograft recipients have succumbed to early HCV-associated liver injury, and a syndrome reminiscent of fibrosing cholestatic hepatitis (see above) has been observed rarely. Currently, however, the routine use of DAA regimens early after transplantation, before the onset of these variant presentations, has already had a profound impact on the frequency of severe recurrent allograft hepatitis C. Patients who undergo liver transplantation for end-stage alcohol-associated cirrhosis are at risk of a return to drinking again after transplantation, a potential source of recurrent alcohol-associated liver injury. Currently, alcohol-associated liver disease is the most common indication for liver transplantation, accounting for 40% of all liver transplantation procedures, and most transplantation centers screen candidates carefully for predictors of continued abstinence. Return to alcohol use is more likely in patients whose sobriety prior to transplantation was <6 months. For abstinent patients with alcohol-associated cirrhosis, liver transplantation can be undertaken successfully, with outcomes comparable to those for other categories of patients with chronic liver disease, when coordinated by a team approach that includes substance use counseling. The syndemic of hazardous alcohol consumption, opioid use, and obesity continues to influence important changes in liver disease epidemiology, health disparities, indications for transplant (Fig. 356-2), and disease recurrence. ■

■ **POSTTRANSPLANTATION QUALITY OF LIFE** Full rehabilitation is achieved in most patients who survive the early postoperative months and escape chronic rejection or unmanageable infection. Psychosocial maladjustment interferes with medical compliance in a small number of patients, but most manage to adhere to immunosuppressive regimens, which must be continued indefinitely.

Acute liver failure HCV Alcoholic liver disease Cholestatic disease HCC MASH Other/unknown In one study, 85% of patients who survived their transplant operations returned to gainful activities. In fact, some women have conceived and carried pregnancies to term after transplantation without demonstrable injury to their infants. ■ ■FURTHER READING Bethea E et al: Immediate administration of antiviral therapy after transplantation of hepatitis C-infected livers into uninfected recipients: Implications for therapeutic planning. *Am J Transplant* 20:1619, 2020. Bhattacharya D et al: Hepatitis C Guidance 2023 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis* 2023. (Updated regularly, available at <http://www.hcvguidelines.org>. Accessed September 23, 2023.) Brustia R et al: Guidelines for perioperative care for liver transplantation: Enhanced Recovery After Surgery (ERAS) recommendations. *Transplantation* 106:552, 2022. European Association for the Study of the Liver: EASL Clinical Practice Guidelines on acute-on-chronic liver failure. *J Hepatol* 79:461, 2023. Goldberg D et al: Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. *Gastroenterology* 152:1090, 2017. Kim WR et al: MELD 3.0: The Model for End-Stage Liver Disease updated for the modern era. *Gastroenterology* 161:1887, 2021. Louvet A et al: Early liver transplantation for severe alcohol-related hepatitis not responding to medical treatment: A prospective controlled study. *Lancet Gastroenterol Hepatol* 7:416, 2022. Lucey MR et al: Liver transplantation. *N Engl J Med* 389:1888, 2023. Nephew LD, Serper M: Racial, gender, and socioeconomic disparities in liver transplantation. *Liver Transpl* 27:900, 2021. Terrault NA et al: Liver transplantation 2023: Status report, current and future challenges. *Clin Gastroenterol Hepatol* 21:2150, 2023.

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