Clinical Aspects of Liver Transplantation

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Abbreviations
  AIDS acquired immunodeficiency syndrome
  AIH autoimmune hepatitis
  ALD alcoholic liver disease
  ALF acute liver failure
  ALT alanine aminotransferase
  APACHE Acute Physiology and Chronic Health Evaluation
  AST aspartate aminotransferase
  CMV cytomegalovirus
  CVVH continuous venovenous hemodialysis
  DCD donation after cardiac death
  DRI donor risk index
  EBV Epstein-Barr virus
  ECD extended criteria donor
  ERCP endoscopic retrograde cholangiopancreatography
  ESLD end-stage liver disease
  HAV hepatitis A virus
  HBV hepatitis B virus
  HCC hepatocellular carcinoma
  HCV hepatitis C virus
  HELLP hemolysis, elevated liver tests, low platelets syndrome
  HIV human immunodeficiency virus
  HPS hepatopulmonary syndrome
  HRS hepatorenal syndrome
  HTK histidine-tryptophan-ketoglutarate
  IL-2 interleukin-2 receptor*
  INR international normalized ratio
  LT liver transplantation
  MELD Model for End-Stage Liver Disease
  NAFLD nonalcoholic fatty liver disease
  NOTA National Organ Transplant Act of 1984
  OPTN Organ Procurement and Transplantation Network
  PBC primary biliary cirrhosis

*Other arabic numbers may be used for receptor number.
Liver transplantation (LT) has experienced dramatic growth in recent years as indications for this procedure have broadened and clinical outcomes have improved. In the United States, the willingness of third party payers (including Medicaid and Medicare) to fund organ transplantation has contributed to this increase. Improvements in the transplant surgical procedure, postoperative management, and immunosuppressive agents have led to the saving of thousands of lives on a yearly basis. The majority of these patients return to a good functional status, including many patients who return to work and a high level of physical activity. Unfortunately, such progress has inevitably brought about an increased demand for LT and shortages of ideal donor organs.

Current growth in the field of LT is directly proportional to expansion of the organ donor pool through the use of living donors and the use of nonideal deceased donors, so-called extended criteria donors (ECDs). Indications for LT have expanded to include elderly patients with comorbidities, patients with hepatocellular carcinoma (HCC) and other tumors, and retransplantation in patients with recurrent disease. Current research in the field of LT attempts to provide more donor organs through improvement in organ preservation and procurement techniques, expanded use of ECD organs and living donors, and eventually, the development of an unlimited supply of organs through xenotransplantation. Another impediment in the field of LT is the side effects of immunosuppressive drugs. These powerful agents, although effective at preventing rejection, continue to have major side effects that have an impact on long-term patient morbidity and mortality. This chapter reviews the history of and current trends in LT, recipient selection in LT, organ donor selection, the operative transplant procedure, immunosuppression, and transplant outcomes.

**History of Liver Transplantation**

The idea of organ transplantation in the modern era began with Dr. Alexis Carrel, who pioneered the concept of sewing two individual blood vessels together with sutures to establish alternative vascular flow (Table 41-1). As this technique was refined, the possibility of removing an indigent organ (physiologic disturbances of organs caused by biologic factors) establish basic concepts of transplant immunology, including rejection.

<table>
<thead>
<tr>
<th>Date</th>
<th>Historical Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1900s</td>
<td>Alexis Carrel at the University of Lyon develops surgical technique of performing vascular anastomoses.</td>
</tr>
<tr>
<td>1906–1912</td>
<td>Karl Landsteiner (ABO compatibility) at the University of Vienna and Alexis Carrel (physiologic disturbances of organs caused by biologic factors) establish basic concepts of transplant immunology, including rejection.</td>
</tr>
<tr>
<td>Mid 1940s</td>
<td>Peter Medawar at the University of Oxford elucidates the pathophysiology of skin allograft rejection.</td>
</tr>
<tr>
<td>Early 1950s</td>
<td>Successful renal transplantation in humans occurs.</td>
</tr>
<tr>
<td>1955</td>
<td>Stuart Welch at Albany Medical College describes auxiliary liver transplantation in dogs.</td>
</tr>
<tr>
<td>Late 1950s</td>
<td>Earliest attempts at experimental liver transplantation are made.</td>
</tr>
<tr>
<td>1963</td>
<td>Thomas Starzl attempts first human liver transplant in a child at University of Colorado; patient does not survive surgery. After two additional unsuccessful attempts by Starzl, and failures in Boston and Paris, worldwide moratorium on liver transplantation, which lasts 3.5 years, takes effect.</td>
</tr>
<tr>
<td>1967</td>
<td>Starzl completes first successful liver transplant. Between 1967 and 1979, more than 160 patients undergo liver transplantation at the University of Colorado with marginal success.</td>
</tr>
<tr>
<td>1968</td>
<td>Roy Calne at the University of Cambridge establishes the second liver transplant program.</td>
</tr>
<tr>
<td>1980</td>
<td>Uniform Determination of Death Act (UDDA) provides comprehensive and medically sound basis for determining death in all situations, thus establishing brain death law.</td>
</tr>
<tr>
<td>1983</td>
<td>The National Institutes of Health (NIH) recognizes liver transplantation as a therapeutic modality for end-stage liver disease.</td>
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<tr>
<td>1984</td>
<td>Cyclosporine becomes available as a first clinically effective immunosuppressant. National Organ Transplant Act (NOTA) forbids buying and selling of human organs and establishes the Organ Procurement and Transplantation Network (OPTN) to administer transplantation in the United States.</td>
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<tr>
<td>1984</td>
<td>Henri Bismuth at Paul Brousse Hospital, France, performs first reduced-size liver transplant.</td>
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<tr>
<td>1988</td>
<td>Rudolf Pichlmayr performs first split-liver transplant at Hannover Medical School, Germany.</td>
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<tr>
<td>1989</td>
<td>Tacrolimus (Prograf, FK506) is introduced as an effective immunosuppressant; early reports suggest improved survival compared with cyclosporine.</td>
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<tr>
<td>1989</td>
<td>Christoph Broelsch at the University of Chicago Medical Center performs the first successful left lobe living donor liver transplant (left lateral segment, mother to child).</td>
</tr>
<tr>
<td>1994</td>
<td>Yoshio Yamaoka at Kyoto University, Japan, performs the first successful right lobe living-donor liver transplant.</td>
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<tr>
<td>2002</td>
<td>MELD score for allograft allocation is instituted.</td>
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**Table 41-1. Chronologic History of Liver Transplantation**

PELD: pediatric end-stage liver disease
PSC: primary sclerosing cholangitis
PTC: percutaneous transhepatic cholangiography
PTLD: post-transplant lymphoproliferative disease
rATG: rabbit antithymocyte globulin
SRTR: Scientific Registry of Transplant Recipients
TB: total bilirubin
TIPS: transjugular intrahepatic portosystemic shunt
UCSF: University of California, San Francisco
UNOS: United Network for Organ Sharing
UW: University of Wisconsin

MELD, Model for End-Stage Liver Disease.
Clinical Aspects of Liver Transplantation

Liver transplants were marked by massive blood loss, hemodynamic instability, prolonged hospital stays, and predictably poor clinical outcomes. Early survival was measured in months rather than years. The primary causes of ESLD at that time were alcoholic liver disease (ALD) and hepatitis B (HBV)–related cirrhosis. Growth of LT was understandably slow.

In 1984, cyclosporine was introduced clinically as an immunosuppressive agent and all clinical solid organ transplant outcomes immediately improved. For the first time, 1-year patient survival after liver transplant was greater than 50% because the risk of rejection could be reliably managed in most patients. Critical care management improved, along with advances in surgical technique and immunosuppression, throughout the 1980s and 1990s. One-year survival rates improved to above 80%. With improved outcomes, competition for scarce donor liver allografts increased.

**Legislative Milestones**

The U.S. Congress passed important federal laws facilitating organ donation and procurement as well as allocation and distribution. The National Organ Transplant Act of 1984 (NOTA) strictly forbade the buying and selling of human organs, created the Organ Procurement and Transplantation Network (OPTN), and established a Scientific Registry of Transplant Recipients (SRTR) to follow outcomes. The OPTN is administered through the United Network for Organ Sharing (UNOS), which maintains the national organ waiting list, facilitates organ distribution and transplantation (including computerized donor-recipient matching), and monitors member centers for compliance with OPTN policies.

Another critical law passed at this time was the Uniform Determination of Death Act. This law established a legal definition of death through one of two mechanisms: permanent cessation of function of the cardiopulmonary system or irreversible loss of brain function. Prior to the establishment of a legal definition of brain death, all deceased donor organs were procured only after cessation of cardiopulmonary function. This subjected all donor organs to a period of warm ischemia time, because the initiation of organ procurement could not occur until the declaration of cardiac death. This necessary period between the declaration of death and the initiation of procurement frequently resulted in irreversible injury to the donor organs, which had a direct impact on clinical transplant outcomes. With the legal establishment of brain death, the potential donor could be declared legally dead with a completely intact, clinically stable, cardiopulmonary system. Organ procurement from a donor who has been declared brain dead permits rapid exanguination and cooling of the organs with no warm ischemia time, which improves initial and long-term function of the graft. The legislation to establish a definition for brain death has been critical to the growth of transplantation and today, 96% of all deceased donors have been declared brain dead at the time of organ procurement.

These legislative mandates had a direct impact on the ability of transplant physicians to improve clinical outcomes and save lives. Private and governmental payers accepted LT as an indicated procedure for the treatment of ESLD and established reimbursement mechanisms. With adoption of these measures, there was a dramatic increase in the number of patients listed for transplantation. Broad public media campaigns were initiated to encourage organ donation to supply the burgeoning need for this resource. Soon the demand for donor organs outstripped the need, and living donor LT began to grow. The definition of an acceptable deceased donor was expanded to include liver allografts from the elderly, obese, individuals with known traumatic liver injury, and those with known exposure to infectious diseases. More recently, the use of donors who have already experienced cardiac death has started to increase. Today, the bulk of research in clinical LT focuses on expanding the use of available donor organs.

**Current Trends**

In 2007, there were 96 U.S. LT centers that performed ten or more LTs, with a total LT volume of 6494. Overall, there were 6941 (96%) deceased donors and 266 (4%) living donors (Fig. 41-1). There were 713 livers that were donated and procured for transplantation but were unable to be transplanted. Pediatric LT recipients (younger than 18 years of age) constituted 8% and 16% of the deceased and living donor transplants, respectively. Elderly recipients (age 65 and older) constituted 10% and 8% of the deceased and living donor transplants, respectively. Overall LT outcomes have included graft survival for deceased and living donors of 82% and 85% at 1 year and 67% and 68% at 5 years (Table 41-2). Recent studies have demonstrated a 5% to 10% decrease in patient survival for recipients with hepatitis C virus (HCV) or HCC at 3 to 5 years after LT. Overall, LT patients enjoy a good quality of life. Many patients return to work, and survival for more than 20 years is not uncommon. Many female recipients have reported successful pregnancies, although not without risk of graft injury or loss. Future quality of life research will center around the minimization of immunosuppression-related complications, which remain common.

**Indications in Adults**

**Noncholestatic Liver Disease**

**Hepatitis C**

The leading indication for LT in the United States is hepatitis C–related cirrhosis (Box 41-1). HCV infects 1.5% of the U.S. population and leads to chronic hepatitis in 65% to 85% of carriers, 15% to 25% of whom develop cirrhosis. HCV transmission occurs primarily though intravenous drug use and sexual contact. There are several HCV subtypes with variable response to treatment, which is primarily aimed at controlling the systemic viral load. HCV genotype 1 accounts for approximately 70% of all infections and has the highest rate of progression to cirrhosis with the poorest response to treatment. HCV accounts for 40% to 45% of all LTs and is usually the result of a chronic and insidious disease progression over 20 to 30 years from the initial infection. A large percentage of transplant recipients who are infected with HCV carry additional diagnoses, including ALD, non-alcoholic fatty liver disease (NAFLD), and HCC. Data assessing the
In the majority of patients, recurrence of HCV post-LT is universal and leads to chronic damage to the liver allograft. Whereas progression of liver disease from chronic HCV infection is a long-term process in the native liver, the course is accelerated in transplant patients. Consequences of this HCV recurrence are not seen in the early

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<td>N</td>
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<td>Allografts from Deceased Donors</td>
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<tr>
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<td>&lt;1</td>
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<td>89</td>
<td>246</td>
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<td>1–5</td>
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<td>50–64</td>
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<td>1078</td>
<td>87</td>
<td>1078</td>
<td>77</td>
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<tr>
<td>Allografts from Living Donors</td>
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<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>640</td>
<td>91</td>
<td>640</td>
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<td>&lt;1</td>
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<td>50–64</td>
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<td>276</td>
<td>80</td>
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<tr>
<td>65+</td>
<td>50</td>
<td>84</td>
<td>50</td>
<td>78</td>
</tr>
<tr>
<td>Primary Diagnosis (% of Total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11,115</td>
<td>89.6</td>
<td>11,115</td>
<td>82.3</td>
</tr>
<tr>
<td>Noncholestatic cirrhosis (61.7)</td>
<td>6863</td>
<td>90.9</td>
<td>6863</td>
<td>83.2</td>
</tr>
<tr>
<td>Cholestatic liver disease–cirrhosis (8.2)</td>
<td>916</td>
<td>90.6</td>
<td>916</td>
<td>84.3</td>
</tr>
<tr>
<td>Acute hepatic necrosis (7.6)</td>
<td>843</td>
<td>84.5</td>
<td>843</td>
<td>78.6</td>
</tr>
<tr>
<td>Biliary atresia (3.2)</td>
<td>358</td>
<td>85.1</td>
<td>358</td>
<td>82.3</td>
</tr>
<tr>
<td>Metabolic diseases (3.1)</td>
<td>349</td>
<td>87.1</td>
<td>349</td>
<td>80.1</td>
</tr>
<tr>
<td>Malignant neoplasms (8.6)</td>
<td>954</td>
<td>90.5</td>
<td>954</td>
<td>82.6</td>
</tr>
<tr>
<td>Other (7.5)</td>
<td>832</td>
<td>83.7</td>
<td>832</td>
<td>76.6</td>
</tr>
</tbody>
</table>

Tx, Period during which liver transplant occurred.
Adapted from Scientific Registry of Transplant Recipients (SRTR). Available at www.ustransplant.org.

impact of hepatitis C combined with other disease processes injurious to the liver are incomplete, and extrapolation regarding long-term disease progression has not been defined. Clinically, however, hepatitis C–infected patients with an extensive history of alcohol abuse appear to progress at a more rapid rate to ESLD.
Hepatitis B and Hepatitis A

Hepatitis B is the most common cause of liver cirrhosis worldwide and affects an estimated 400 million persons. HBV infection was previously a major cause of ESLD in the Western world; however, its prevalence has decreased dramatically with the development of an effective vaccine that is now administered to all children at infancy in many countries. The prevalence of HBV infection remains high in Asia and Africa, where immunization is not yet widely available in many countries. In these areas, HBV remains the leading cause of ESLD, and the development of HCC with chronic HBV hepatitis is common. Post-transplant HBV recurrence was 80% with frequent progression to early graft failure, retransplantation, and death. However, the development of effective antiviral therapies, including hepatitis B immune globulin and lamivudine, has resulted in graft survival results similar to those for patients with nonviral liver disease and low rates of post-transplant recurrence. Acute hepatitis B infection can lead to acute liver failure (ALF) in 1% to 4% of infected patients, but these patients can achieve reasonable survival results with transplantation and appropriate follow-up therapy.

Hepatitis A virus (HAV) infection is unusual in the United States and Europe but, in rare cases, can lead to ALF. In general, HAV infection is self-limited and causes an acute illness that does not lead to chronic liver disease. In countries with poor sanitation and dense population, HAV accounts for 10% of cases of ALF. Older patients (>40 years of age) and those with underlying liver disease (related to chronic HCV infection or ALD) are at increased risk for HAV-related ALF.

Alcoholic Liver Disease

ALD is the second leading indication for LT in the United States and is also a leading indication worldwide. The time interval from the onset of alcohol abuse to ESLD is variable and depends on average daily consumption, alcohol-free intervals, comorbid diseases, and genetic predisposition. According to recent national surveys reported by the U.S. Centers for Disease Control and Prevention, more than 50% of the adult U.S. population drank alcohol in the past 30 days. Approximately 5% of the total population drank heavily, and 15% of the population binge drank. The U.S. prevalence of ALD is reported at 0.75%, and excessive alcohol use is the third leading lifestyle-related cause of death for people in the United States each year.

Approximately 20% of LT recipients have a history of ALD. There is a sizeable percentage of patients with HCV infection who also have ALD. Combining ALD with any other primary liver disease may result in a synergistic effect with more rapid progression to ESLD. Most U.S. centers require a confirmed period of alcohol abstinence of 6 to 12 months before listing for LT. This abstinence period often includes a required period of intensive outpatient addiction-related therapy as well as random alcohol and drug screening. Post-transplant alcohol recidivism is a major concern because post-transplant alcohol intake can be particularly toxic to the transplant liver and can lead to rapid hepatic decompensation and death, depending on total intake. Alcohol recidivism varies widely following transplantation, but most centers quote a 10% to 20% rate within 5 years. Many of these patients have additional addiction issues and require ongoing support and therapy related to the use of both legal and illegal addictive substances. In spite of these statistics, post-transplant survival for patients with ALD is excellent, with results equivalent to those for patients with nonviral liver disease undergoing transplantation.

Nonalcoholic Fatty Liver Disease

NAFLD has grown at a rapid rate in Western countries in recent years as the general population has experienced an epidemic of obesity. Obesity is defined as a body mass index of 30 or higher. The prevalence of obesity has increased dramatically, now affecting one in three persons in the United States, with 5% of the population affected by NAFLD. Currently in the United States, HCV, ALD, and NAFLD are the top three indications for LT. However, although the prevalence of HCV-related and ALD-related cirrhosis has stabilized, NAFLD-related cirrhosis continues to increase yearly and affect persons at younger and younger ages. It is now thought that NAFLD is the primary cause of cirrhosis in many patients previously diagnosed with nonalcoholic steatohepatitis (NASH), a histological entity that is associated with NAFLD. The prevalence of NASH is thought to be extremely high in many populations and is the primary cause of cirrhosis in many patients who are candidates for LT. Post-transplantation, the natural history of NAFLD is similar to that of patients with nonalcoholic steatohepatitis (NASH).
with cryptogenic cirrhosis. Extrapolation of current trends has led researchers to predict that NAFLD as a cause of cirrhosis will surpass HCV cirrhosis as the primary indication for LT in the next 10 to 20 years. Post-transplant recurrence of NAFLD is common. The prevalence of moderate steatosis at 1 year post-transplant is 15% in patients with HCV or ALD but 60% in patients transplanted for NAFLD.5

Autoimmune Hepatitis
Autoimmune hepatitis (AIH) is a chronic, inflammatory liver condition associated with autoantibodies that incite interface hepatitis. This process can result in both ALF and chronic liver disease. The prevalence of AIH is highest in young females (70%), and the disease typically responds to immunosuppressive therapy. Patients progress to LT when their condition becomes decompensated. Unfortunately, a clinical marker for onset of AIH has not been identified, and the exact cause of the condition is unknown. As such, the diagnosis is one of exclusion in which other diseases have been ruled out and the patient fits with a set of clinical, histologic and laboratory parameters. These patients typically do well with the transplant procedure because they tend to be young and otherwise well compensated. However, disease recurrence and liver allograft failure are common; the hyperactive immune system leads to high rates of acute and chronic allograft rejection and difficulty in modulating immunosuppression. Of note, de novo AIH can occur in patients who have undergone LT for another primary disease process.

Cholestatic Liver Disease
Primary Biliary Cirrhosis
Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease resulting from injury to septal and lobular bile ducts. The disease tends to affect middle-aged females, is thought to be immune-mediated, and affects 0.1% of the population in the United States. The primary treatment for PBC is ursodeoxycholic acid, which prolongs transplant-free survival and prevents disease-associated complications such as esophageal varices and severe pruritus. However, no current studies provide evidence that available medical therapy ultimately precludes the need for transplantation or prolongs transplant-free survival. A significant number of these patients, therefore, do progress to transplantation, which prolongs their survival when compared to the natural history of the disease. PBC can recur following transplantation, and the incidence may be as high as 10% to 20% at 5 years.10,11 Post-transplant survival for PBC patients is among the highest of all LT recipients, exceeding 90% at 1 year and 80% at 3 years.

Primary Sclerosing Cholangitis
Primary sclerosing cholangitis (PSC) is characterized by chronic inflammation of the bile ducts of the liver, which leads to loss of ducts and duct strictures. PSC more commonly affects males, and 70% of patients with PSC also have inflammatory bowel disease (primarily ulcerative colitis). Current medical therapy has little impact on the progression of this disease, and the inability of the liver to excrete bile leads to cirrhosis and chronic cholangitis as well as to the need for LT. Importantly, patients with PSC carry an increased risk of cholangiocarcinoma, which occurs in 10% to 20% of cases.12,13 Predictive factors for cholangiocarcinoma are inadequate, which results in patients with PSC undergoing frequent screening with endoscopic retrograde cholangiopancreatography (ERCP) to obtain bile duct brushings for pathologic review.

The transplant procedure for PSC has historically required the use of Roux-en-Y choledochojejunostomy to avoid use of the remaining posthepatectomy bile duct for a duct-to-duct anastomosis. This duct was believed to be at risk for stricture, which could compromise the transplant liver. However, with the increasing safety and utility of ERCP, some centers are now connecting the transplant common bile duct to the native bile duct if it is normal in appearance. The duct-to-duct anastomosis permits ongoing post-transplant ERCP surveillance of the native duct, which remains at risk for cholangiocarcinoma. This surveillance is not possible with the alternative duct reconstruction. Although overall post-transplant survival is excellent, PSC can recur following LT.14 The diagnosis of post-transplant PSC is complicated. A high rate of biliary complications exists for any LT, and these must be ruled out before a diagnosis of post-transplant PSC is entertained. Common transplant issues that affect the biliary system include technical issues (stenosis), poor arterial flow, a cardiac death donor, an episode of profound hypotension, severe preservation injury, and ABO incompatibility.15

Hepatocellular Carcinoma
Early experience with LT for patients with HCC resulted in a high rate of HCC recurrence and patient death. Recurrence frequently occurred within 2 years of transplantation and was localized to the transplant liver. Use of donor liver allografts in these patients was questioned. In 1989, the U.S. Department of Health and Human Services decided that the presence of HCC was a contraindication to LT. At this time, outcomes for LT continued to improve, resulting in an increasing demand for the procedure. LT wait list times increased to well over 1 year, it was impractical to pursue LT in patients with HCC, and the disease would progress and exclude this option. As alternative treatment for these patients, several modalities were studied and showed promise in reducing tumor size and slowing tumor progression. Procedures such as transarterial chemoembolization (TACE), ethanol injection, cryosurgery, and radiofrequency ablation were increasingly used.

Eventually, scoring systems were developed to prioritize patients with liver cirrhosis and HCC; select patients have been found to have survival rates similar to those for other LT patients when falling within these criteria. It was soon proven that LT is the most effective treatment for patients with HCC, addressing not only the primary tumor but also the “at-risk” liver that remains highly susceptible to the development of additional tumors. Optimal outcomes are seen in patients who have a solitary tumor less than 5 cm in diameter, or three or fewer tumors, with no tumor greater than 3 cm in diameter (Milan criteria). The Milan criteria are the most commonly used parameters today, although the University of California, San Francisco (UCSF), criteria are more liberal and have been shown to have similar results (Table 41-3).

Patients who fall outside of the Milan or UCSF criteria may be denied transplantation. Recent progress has been made in down sizing HCC to decrease total tumor volume, which may permit individual patients to undergo LT at certain centers. Patients may be outside of acceptable criteria either because of too many discrete tumors (i.e., multifocal HCC, four or more tumors) or a single tumor that is too large for transplantation. Early experience with transplantation for HCC has resulted in a high rate of HCC recurrence and patient death. Recurrence frequently occurred within 2 years of transplantation and was localized to the transplant liver. Use of donor liver allografts in these patients was questioned. In 1989, the U.S. Department of Health and Human Services decided that the presence of HCC was a contraindication to LT. At this time, outcomes for LT continued to improve, resulting in an increasing demand for the procedure. LT wait list times increased to well over 1 year, it was impractical to pursue LT in patients with HCC, and the disease would progress and exclude this option. As alternative treatment for these patients, several modalities were studied and showed promise in reducing tumor size and slowing tumor progression. Procedures such as transarterial chemoembolization (TACE), ethanol injection, cryosurgery, and radiofrequency ablation were increasingly used.

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### Table 41-3. Milan and UCSF Eligibility Criteria for Transplantation for Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>System</th>
<th>Single Tumor</th>
<th>Multiple Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum Diameter</td>
<td>Maximum Number</td>
</tr>
<tr>
<td>Milan criteria</td>
<td>5 cm</td>
<td>3</td>
</tr>
<tr>
<td>UCSF criteria</td>
<td>6.5 cm</td>
<td>3</td>
</tr>
</tbody>
</table>

UCSF, University of California, San Francisco.
Acute liver failure (ALF) is a consequence of severe liver damage from a nonchronic process that results in encephalopathy and cerebral edema, acute renal failure, coagulopathy, and physiologic disturbances of blood glucose and acid-base status. Depending on the amount of hepatic damage present, patients with ALF have the potential for complete recovery with return to normal liver function. Unfortunately, many of those affected progress to massive, irreversible end-organ damage requiring LT. The primary cause of death in these critically ill patients is brain herniation related to severe cerebral edema and multiorgan failure related to severe acidosis. Patients who do recover may have persistent neurologic damage, and many have persistent renal failure, which improves over weeks to months either with liver regeneration or LT. ALF accounts for 10% of all LTs in the United States, Europe, and Australia.

The most common etiology of ALF in Western countries is acetaminophen toxicity, most frequently related to an intentional overdose, although unintentional overdoses are common. Another important etiology is drug toxicity related to other agents such as methotrexate, antituberculosis drugs, and anticonvulsants. Unintentional overdoses commonly occur when a combination of a hepatotoxic prescribed drug is combined with a high level of over-the-counter acetaminophen. In patients with moderate to heavy daily alcohol use, ALF may occur when this alcohol use is combined with otherwise acceptable levels of one or two other hepatotoxic drugs over several consecutive days or weeks. Other causes of ALF are much less common. Any virus that affects the liver can give rise to ALF. LT in a child without end-stage liver failure can result from debilitating symptoms such as pruritus, which leads to chronic skin lesions, malnutrition, and growth failure, or fatigue, which impedes the ability to participate in school.

Another cause of secondary liver disease is related to chronic parenteral nutrition in children with short gut syndrome. Parenteral nutrition can be especially toxic to the immature pediatric liver, and progression to liver failure is more rapid at younger ages. However, in these children consideration should be given to multivisceral transplants and/or radiofrequency ablation, whereas single large tumors often respond well to these treatments. The estimated survival for patients with multifocal disease who do not undergo transplantation is 9 to 12 months.

### Indications in Children

The primary indication for LT in children is hepatic failure (Box 41-2). Hepatic failure can result from a chronic primary disease process, such as biliary atresia, alpha-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis, PSC, or AIH. LT may also be indicated in children with a nonprogressive primary liver disease in which the symptoms or morbidity of the disease outweigh the risks of transplantation. Examples of these diseases include Alagille syndrome and inborn errors of metabolism. Cystic fibrosis is an example of secondary liver disease in which the primary disease process is systemic but results in life-threatening liver dysfunction. The decision to perform LT in a child without end-stage liver failure can result from debilitating symptoms such as pruritus, which leads to chronic skin lesions, malnutrition, and growth failure, or fatigue, which impedes the ability to participate in school.

### Box 41-2. Indications for Liver Transplantation in Children

**Cholestatic Diseases**
- Biliary atresia
- Alagille syndrome
- Progressive familial intrahepatic cholestasis
- Giant cell hepatitis or neonatal hepatitis of unknown etiology
- Chronic parenteral nutrition therapy–induced liver damage

**Hepatocellular Diseases**
- Acute and subacute hepatic failure
- Hepatoxins
- Acute Wilson disease
- Autoimmune liver disease
- Chronic hepatitis B or C
- Polycystic liver disease

**Metabolic Diseases**
- Alpha-1 antitrypsin deficiency
- Tyrosinemia type 1
- Wilson disease
- Neonatal hemochromatosis
- Glycogen storage disease type 1
- Cystic fibrosis
- Inborn errors of metabolism
- Crigler-Najjar syndrome type I
- Ornithine transcarbamylase (OTC) deficiency
- Maple syrup liver disease (MSUD)
- Familial hypercholesterolemia

**Tumors**
- Hepatoblastoma
- Hepatocellular carcinoma
transplantation (liver and intestine) to correct the short gut and liver failure simultaneously. Interestingly, isolated intestinal transplant performed prior to the development of bridging liver fibrosis can lead to complete recovery from the liver dysfunction as parenteral nutrition is stopped and the child is able to receive all nutrition enterally.

Finally, LT can be an effective therapy for children with primary hepatic malignancy. HCC can develop in children and, although rare, tends to occur in those patients with a metabolic liver disease. LT in these HCC patients has excellent survival if the HCC is small with few discrete nodules. For those with large or multiple nodules, post-transplant survival is poor. Hepatoblastoma can also be treated with LT. Unlike HCC, hepatoblastoma with a large tumor mass is not a contraindication to LT because these tumors are generally responsive to chemotherapy and can be controlled, or reduced in size, prior to transplantation.25,26

**Patient Evaluation**

Patient evaluation for LT is extensive and thorough. Although there are no strict age criteria, all patients must demonstrate acceptable cardiopulmonary function and risk, be free from active infection, have no recent history of malignancy, have no recent history of substance abuse, and demonstrate sufficient coping ability to comply with a strict post-transplant health and medication regimen. Absolute and relative contraindications are listed in Box 41-3. There are no contraindications based on gender or race, because these have not been clearly demonstrated to have an impact on clinical outcome.

The decision to list a patient for LT is not undertaken lightly. Each year there are three times more patients on the waiting list for LT than the number of transplants performed. Therefore, the listing process is multidisciplinary and includes input from hepatology, transplant surgery, social work, psychology, and financial counselors. The patient’s history is formally presented at a listing meeting in which all involved services participate and contribute to the final decision. After listing, the patient maintains regular contact with a designated transplant coordinator to obtain routine follow-up testing and to notify the team if the patient has an important medical event that may require him or her to become inactivated or removed from the list.

**Box 41-3. Contraindications for Liver Transplantation**

**Absolute**

- Tumors other than primary hepatic tumors (extrahepatic malignancy)
- Active alcoholism or substance abuse
- Metastatic cancer
- Psychosocial and economic factors such as inability to understand the implications of the procedure (lack of insight) or inability to pay
- Multisystem organ failure
- Severe and uncontrolled extrapulmonary infection
- Acquired immunodeficiency syndrome (AIDS) in adults
- Severe cardiovascular, pulmonary, or neurologic disease
- Lack of informed consent
- Terminal nonhepatic disease

**Relative**

- Active infection
- Significant cardiovascular, pulmonary, or neurologic disease
- Portal vein thrombus
- Compensated cirrhosis
- Anatomic abnormalities that preclude safe completion of the transplant
- Human immunodeficiency virus (HIV) infection in adults and children
- AIDS in children

**Older Age**

Recipient age, per se, is not an exclusionary criterion for transplantation. However, elderly recipients certainly have worse long-term outcomes when compared with younger recipients.27 Elderly recipients are more likely to have preexisting conditions that may affect survival, including cardiovascular and pulmonary disease, an increased risk of malignancy and stroke, and less physiologic reserve to withstand the transplant procedure and perioperative recovery. Several studies have demonstrated that elderly patients have poorer LT outcomes. According to a 2004 projection by the U.S. Census Bureau, the population of persons older than 65 years of age will increase from 12.4% to 16.3% of the total U.S. population by the year 2020. This corresponds to an absolute increase of 20 million elderly persons within the next 10 years. Providing health care for these elderly persons will represent not only an enormous economic drain on national health care expenditures but will stress resources such as medical personnel staffing and the capacity of health care facilities. This strain may be especially problematic in the field of organ transplantation. The currently available number of donor organs provides only a fraction of those needed to supply all patients who could benefit from transplantation. With an aging population, which is overall healthier than in past decades, the organ shortage will become more acute as a greater number of these people meet listing criteria for transplantation of all organs. With a rapidly aging population in need of donor organs from a limited nationwide supply, the ability to routinely transplant expanded criteria donor organs into the elderly is of critical importance.

Despite general support in the literature for LT in individuals older than 60 years of age, some authors advocate caution in allocating valuable donor livers to this high-risk population. Proponents of elderly LT have demonstrated outcomes comparable to younger recipients in appropriately selected patients. However, Levy and colleagues clearly demonstrate a decreased long-term survival with increasing age in their single center review of 1446 consecutive LTs over a 13-year period.27 They found age older than 60 years to be an independent risk factor for a worse outcome in elderly recipients. Importantly, elderly patients in this study with better preserved hepatic function or with a lower pretransplant bilirubin level had outcomes similar to younger recipients. This finding underscores the importance of carefully selecting elderly LT recipients and matching them to an appropriate donor liver.

With improvements in the management of chronic liver disease, and the overall aging of the population, an increasing number of elderly are being listed for LT. This may have an effect on long-term LT outcomes in the elderly because, as more elderly patients are listed, the wait time increases. Increasing wait time is particularly dangerous to elderly recipients. As older patients accumulate wait list time, they have a higher risk of developing significant comorbidities such as symptomatic coronary artery disease, renal insufficiency, and malignancy, as well as chronic lung disease and peripheral vascular disease in smokers. Use of the current MELD allocation system forces the less healthy elderly patients to the top of the transplant wait list. When transplanted, previous studies indicate that these less healthy elderly have a worse transplant outcome when compared with their healthy counterparts. One way to usurp this process is to keep the wait list time short for the elderly recipient to facilitate transplantation at an earlier stage of disease. A key component of decreasing transplant list wait time for all age groups is the routine use of ECD livers. To this point, there have been no large-scale studies of the use of marginal donor livers in elderly recipients. Results from our center suggest that elderly recipients can not only successfully be transplanted with outcomes similar to younger recipients, but they can, on a selective basis, receive donor livers from a broad selection of potential donors.
Obesity

Obese recipients undergoing LT have risks that pertain specifically to the transplant procedure. Patients with severe obesity, requiring a larger incision and additional intraoperative assistance, are technically more difficult for the transplant surgeon to manage. Postoperative complications are more frequent and include incisional hernia, venous thromboembolus, pneumonia, and wound infections. Obese patients also have an increased risk of vascular disease, which may predispose them to arterial complications.

Substance Abuse

Alcohol abuse and other substance abuse are common among LT recipients, with prevalence as high as 50% for any lifetime history of alcohol abuse. Additionally, a large percentage of these patients have a history of previous arrest, and many are chronically noncompliant with their medical care. This unstable social history can lead to post-transplant difficulties, and careful social and psychological screening is required. In general, 6 to 12 months of complete abstinence from all substances of abuse is required prior to listing for transplantation. A recent history of alcohol abuse (within 5 years) often necessitates completion of an intensive outpatient substance abuse treatment program. This program combines counseling and therapy with frequent laboratory testing for substance use. Fortunately, close pretransplant screening has proven successful, and post-transplant survival for patients with ALD is equivalent to that for patients transplanted for other diseases.

Comorbidities

ESLD is frequently accompanied by a host of comorbidities that may affect the outcome of the transplant. Hepatorenal syndrome (HRS) is a condition in which chronic liver disease leads to renal insufficiency. The presence of renal failure is an important predictor of survival in patients with cirrhosis and in those who undergo LT. A significant proportion of LT recipients develop chronic kidney disease as a direct result of pretransplant renal injury, and this frequently leads to dialysis following the transplant. Application of the National Kidney Foundation chronic kidney disease classification is important in liver failure patients to determine their need for a possible combined liver/kidney transplant.

HRS is part of a spectrum of illness associated with increased pressures in the portal vein circulation, which begins with the development of ascites in the abdomen. The spectrum continues with diuretic-resistant ascites, where the kidneys are unable to excrete sufficient sodium to clear the fluid, even with the use of diuretic medications. Most individuals with HRS have diuretic-resistant ascites before they develop deterioration in kidney function. The predominant theory (termed the underfill theory) is that blood vessels in the renal circulation are constricted due to the dilation of blood vessels in the splanchic circulation, which is mediated by factors released because of the liver disease. The consequence of this phenomenon is a decrease in the "effective" volume of blood sensed by the juxtaglomerular apparatus, leading to the secretion of renin and the activation of the renin-angiotensin system, which results in the vasoconstriction of vessels systemically and in the kidney specifically. However, the effect of this is insufficient to counteract the mediators of vasodilation in the splanchic circulation, leading to persistent "underfilling" of the renal circulation and worsening renal vasoconstriction, resulting in renal failure. Studies to quantify this theory have shown that there is an overall decreased systemic vascular resistance in HRS, but that the measured femoral and renal fractions of cardiac output are increased and reduced, respectively, suggesting that splanchic vasodilatation is implicated in the renal failure. Although some of the effects of HRS are reversed with LT, patients do not generally return to completely normal renal function.

Hepatopulmonary syndrome (HPS) also results from differences in vascular pressures related to the primary liver disease. The vasodilation caused by liver failure has a direct vasodilatory effect in the lungs, leading to increased blood flow in relation to ventilation and a ventilation-perfusion mismatch. This is seen clinically as a right-to-left shunt, and the patient experiences dyspnea. As with HRS, HPS is an important marker of disease severity, and prognosis is poor without a timely LT. Symptoms of HPS improve markedly with LT.

Patients with ESLD have many other signs and symptoms of their liver disease. Jaundice, ascites, edema, malnutrition, fatigue, and encephalopathy are all commonly seen. Resolution of these derangements can be immediate, as with encephalopathy, or may take months to reverse, as with malnutrition. Post-transplant supportive care is critical, and many of these patients require intensive physical and occupational therapy before they are able to safely return to normal activities of daily living.

Retransplantation

Retransplantation is a complex issue in the field of LT. With a large number of persons awaiting a first LT, and many others dying each year while awaiting an LT, it is difficult to justify a second or third LT. The most common indication for retransplant is failure of a primary LT in the immediate post-transplant period secondary to vascular thrombosis, primary nonfunction, or hyperacute rejection. Thereafter, retransplantation occurs in the setting of recurrence of the primary disease, chronic rejection, or chronic biliary complications. Nearly all liver diseases that can lead to cirrhosis can recur in the transplant liver; therefore, the issue of retransplantation is not inconsequential. In the United States, approximately 8% of all LTs are performed on a patient who has had a previous transplant. Retransplantation raises many clinical, financial, and ethical questions. Technically, retransplantation is significantly more complex than a primary LT, resulting in increased risk of complications and prolonged post-transplant recovery with higher costs. Data suggest that 3-year survival after retransplantation is 70%, compared with 75% to 80% for first-time recipients, which provides evidence that these transplants may not optimize the use of individual liver allografts.

Transplant centers most active in trying to use all available liver allografts may be those with the highest retransplant rates. Certain deceased donor liver allografts carry a higher risk of early failure or complications. Use of these grafts may lead to a higher rate of graft loss with need for early retransplantation. Examples of these donors include organs procured under a donation after cardiac death (DCD) protocol, allografts with a high percentage of steatosis, and those from the elderly. Many of these grafts from marginal donors are successfully transplanted, resulting in a decreased wait list time and a higher transplant rate, with the cost being a higher risk of early graft failure (requiring retransplantation).

Young Age

LT is an effective and appropriate therapy for children with liver disease. Unfortunately, outcomes very greatly depending on the age, size, and general health status of the child at the time of transplant. Infants undergoing LT are at high risk for mortality, both while they are on the wait list and in conjunction with the transplant itself. These children have limited reserve, can be very ill, and are at high risk for hepatic artery thrombosis, which is often a fatal complication. The wait list time for a small child can be prolonged because deceased donor organs of the necessary size are infrequently available. Many centers now offer living donor transplantation using the left lateral segment of an adult liver if it is of an appropriate size. These reduced-size grafts
now have survival rates in the pediatric population that are similar to or better than whole organ grafts. Children older than 3 years of age have significantly better outcomes because they have more physiologic reserve and are often not as severely decompensated. Also, there are more viable organs available for these children, simply because of the increasing size of the abdomen. Older children, who have a larger blood vessel diameter and higher baseline blood pressure, are also less likely to develop hepatic artery thrombosis.

Workup for LT in children is similar to that for adults. Severe cardiopulmonary disease must be ruled out. Although chronic diseases are less common, pediatric patients can experience significant decompensation from their liver disease and present with severe malnutrition, ascites, edema, portal hypertension, and HRS and HPS. Patients who become critically ill prior to transplantation and require mechanical ventilation or dialysis have markedly diminished post-transplant survival. As with adults, there is a scoring system to predict wait list mortality. However, the pediatric end-stage liver disease (PELD) score takes into account age and growth failure, in addition to the liver factors of international normalized ratio (INR), serum bilirubin, and serum creatinine seen in the adult MELD score. Most common indication for retransplantation for all children is hepatic artery thrombosis, which occurs in children at a higher frequency than in adults with LTs. These retransplants may be urgent and carry a high risk of mortality because of the difficulty in finding a replacement allograft of the appropriate size. Other indications for retransplantation include disease recurrence, primary nonfunction, and chronic rejection. Chronic rejection is commonly related to noncompliance and is often seen in the teenage years.

**Donor and Allograft Evaluation**

Although indications for organ transplantation broaden each year, and the number of listed patients consequently increases, organ donation rates have leveled off in recent years. This has resulted in an increased wait list time at many centers. Efforts to increase donation rates and to expand the donor supply in recent years have met with limited success (Box 41-4). Use of partial grafts has become more common in providing donor organs in a timely fashion to recipients in need. This approach takes advantage of the unique ability of the liver to regenerate rapidly and may provide additional organs not previously available. Unfortunately, recent studies suggest that use of these partial liver grafts imparts a significant risk to live donors, and this use may lead to a lower recipient and graft survival than in deceased donor livers in select patients. The newly derived donor risk index (DRI) includes a partial graft transplant as an independent predictor of worse transplant outcome. Partial graft transplant in this DRI formula carries a risk of graft loss similar to a donor older than 60 years of age or to DCD. Additionally, for living donation, there are societal costs in subjecting some of the healthiest persons in the general population to the elective donor surgery with significant risk of morbidity and mortality.

**Extended Criteria Donors**

Another approach to increase organ availability is the use of ECDs—using already available deceased donor organs from patients who would traditionally be excluded from consideration. Examples of expanded criteria include donors at the extremes of age or with morbid obesity, human immunodeficiency virus (HIV) or hepatitis B or C infection, non–heart-beating status, severely elevated liver enzymes, severe hypernatremia, prolonged intensive care unit stay or pressor use, prolonged cold ischemia time, and high-risk social history (Box 41-5). Data from our institution and other centers confirm that ECD organs, if placed into appropriate recipients, can be transplanted successfully with little impact on patient and graft survival. Frequently, patients with HCC are ideal candidates for ECD organs, because these patients are less likely to have decompensated liver failure. With a lower average MELD at transplant, patients with HCC can better tolerate a graft that may experience a delay in optimal function. The lack of efficacious treatment alternatives for patients with HCC makes this particular patient population a target group that may benefit from expanded use of ECD liver allografts.

A commitment to the use of ECD livers has led to a wide disparity in wait list times at U.S. transplant centers. Several U.S. centers offer a wait list time of less than 3 months, whereas others have a median wait list time of more than 3 years. There are ongoing efforts to address this disparity; however, a solution is not straightforward. Some centers develop an expertise in the use of ECD livers and increase their transplant volume, which results in a short wait list time to transplant. In these situations, patients may self-select by referral to these centers or by being listed simultaneously at multiple centers. These options are acceptable within the current system but tend to discriminate against

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**Box 41-4. Strategies Available to Increase Available Donor Liver Allografts**

<table>
<thead>
<tr>
<th>Currently Used</th>
<th>Potential Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public education and media awareness</td>
<td>Altering consent laws to use transplantable organs without first obtaining donor consent</td>
</tr>
<tr>
<td>Donation after cardiac death</td>
<td>Xenotransplantation</td>
</tr>
<tr>
<td>Use of extended criteria donors (nonideal donors)</td>
<td>Hepatocyte transplantation in patients with acute liver failure*</td>
</tr>
<tr>
<td>Living donor transplantation</td>
<td>Liver dialysis in patients with acute liver failure*</td>
</tr>
<tr>
<td>Use of split or reduced-size allografts</td>
<td></td>
</tr>
<tr>
<td>Use of temporary auxiliary grafts</td>
<td></td>
</tr>
</tbody>
</table>

*Although this therapy does not directly increase the number of donor organs, it may obviate the need for scarce donor organs by maintaining hepatic function until the acute injury heals and the native liver attains functional recovery.

**Box 41-5. Extended Criteria Donors**

<table>
<thead>
<tr>
<th>Donor History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of brain tumor*</td>
</tr>
<tr>
<td>Reactive serology for hepatitis C</td>
</tr>
<tr>
<td>High-risk social behavior</td>
</tr>
<tr>
<td>History of malignancy†</td>
</tr>
<tr>
<td>Significant and prolonged alcohol abuse</td>
</tr>
<tr>
<td>Current active infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor Physiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very old or very young age</td>
</tr>
<tr>
<td>Severe steatosis</td>
</tr>
<tr>
<td>Requirement for high-dose pressors</td>
</tr>
<tr>
<td>Prolonged stay in the intensive care unit</td>
</tr>
<tr>
<td>Split or reduced-size graft</td>
</tr>
<tr>
<td>Evidence of liver injury</td>
</tr>
<tr>
<td>Donation after cardiac death</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prolonged Procurement/Preservation Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged cold ischemia time</td>
</tr>
<tr>
<td>Prolonged warm ischemia time</td>
</tr>
</tbody>
</table>

*Only patients with low grade (grade 1 and 2) central nervous system tumors are recommended as non–extended criteria donors.
†Metastatic disease is a contraindication for donation.
patients without the resources to seek care at multiple sites. A systematic patient referral mechanism may be appropriate in which high-risk patients, including those with HCC and the elderly, are referred to waitlist centers with a short wait list time when the anticipated wait list time to transplant is excessive. The DRI, derived from data from 20,023 U.S. subjects over 5 years, is a regression formula with primary outcome being graft loss. The only deceased ECD criteria found to incur greater risk, and to be included in the final formula, were donor age and DCD. This suggests that greater use of ECDs is warranted, whereas use of partial graft donors should be minimized when possible.

Because of the complexity of this decision process of matching a donor organ to a specific recipient, a surgeon at one center may choose to use a particular organ, whereas a surgeon at another center may reject the organ for use. Additionally, at our center, we have made an effort to categorize ECD allografts according to their risk based on donor medical history or actual physiologic insult to the graft.40 Non-donor–related issues, such as anticipated cold and warm ischemia times, the urgency of need for the recipient, blood type, the availability of the transplant team, and recipient operative risk, also contribute to the decision to use a graft. Presumably, however, when a given liver graft has been rejected by multiple centers, it carries an accumulated risk believed by many surgeons to be excessive. In the United States, liver allograft allocation is strictly regulated. Local centers have the first option to accept a donor liver, followed by regional allocation for those donor livers not accepted locally, and finally, national allocation for those donor livers not accepted regionally (Box 41-6). For an organ to be offered for national sharing in the United States, it has to have been previously rejected by a minimum of five, and as many as 20, other LT centers.

Physiologic Extended Criteria Donors
The routine use of ECD livers in LT has increased with the worsening shortage of donor organs. There is no consensus definition for extended criteria organs in LT. Factors thought to be associated with worse outcomes and increased risk of primary nonfunction and graft failure include increasing donor age, DCD, increasing percentage of steatosis, elevated liver enzymes, severe hypernatremia, cold ischemia time greater than 12 hours, prolonged donor intensive care unit stay with pressor use, and serology positive for HCV, hepatitis B core antibody, or human T lymphotrophic virus types 1 and 2. Use of these organs nationwide ranges between 10% and 20%. Recently, a DRI has been proposed with a regression model that suggests an increasing donor risk for increasing donor age, death from stroke or anoxia, African-American race, DCD, partial/split graft, decreasing donor height, increasing cold ischemia time, and regional or national sharing. Of all deceased liver donor physiologic and medical history characteristics, the only two factors that consistently demonstrate decreased allograft survival are donor age and severe steatosis. Older donor livers have higher rates of primary nonfunction and delayed graft function and lower long-term survival rates.42–45 These allografts also have a higher rate of HCV recurrence.42–44 Studies reporting these results are those analyzing outcomes on thousands of LT recipients with years of follow-up from large databases. These studies do not negate the ability of an individual center to transplant liver allografts from elderly donors into appropriate recipients successfully. However, care must be taken to match the donor and recipient and to minimize any other additional high-risk factors in the donor other than old age. The use of elderly donor livers may be most appropriate for a similarly aged recipient, and their use should be minimized in patients with HCV, those who are very young, and those who are critically ill. There are several factors that may contribute to the lower survival for elderly livers. Certainly, there are physiologic changes, including decreased total hepatocyte mass and total gross size; increased baseline stiffness to the liver, which may result in increased portal pressures; and possibly thickened arterial vasculature with poorer flow. Older donor livers do not tolerate cold ischemia well. In general, we will not accept an older donor liver if we anticipate cold ischemia time greater than 8 hours. Frequently, these livers can be reperfused at our center within 4 hours of donor aortic cross clamping. Again, these allografts can and should be used, but the older donor liver must be carefully scrutinized. For example, at our center, the older donor liver must have no appreciable steatosis, must not be infected with hepatitis C, and must not have a significant elevation of liver enzymes, and in addition, it must be from a clinically stable deceased donor (not a DCD).

Hepatic steatosis in the donor liver has a well-known association with primary nonfunction. This steatosis is generally described as macrovesicular, microvesicular, or total. Most centers consider macrosteatosis to be more important in the evaluation of the donor organ, although other centers consider total steatosis in their decision. Most graft losses associated with a steatotic liver occur in the first few weeks after transplant, with long-term survival being equivalent to nonsteatotic livers when these early graft losses are censored. Resolution of the steatosis in the transplant liver occurs rapidly, and complete resolution can be seen in as few as 5 to 7 days. This suggests that hepatic steatosis is a very dynamic process, and resolution of the steatosis seems to persist when the liver is placed into the new physiologic environment of the recipient. Hepatic macrosteatosis of 20% to 30% is considered the upper range for transplantation depending on donor age (less for older donors). Although steatosis is more commonly seen in obese donors, normal liver allografts are frequently procured from donors with a body mass index greater than 40, and these potential donors should be carefully evaluated, especially those of a younger age.

Liver allografts are frequently refused for transplantation because of elevated liver function enzymes in the donor. The enzymes may be elevated for a variety of reasons, including donor hypotension, mechanical trauma, drug toxicity, administration of parenteral nutrition in the intensive care unit, hepatic vascular injury, and simultaneous presence of a severe brain injury. Careful analysis of the etiology of the enzyme elevation is critical in determining the transplant potential for the liver. Bedside biopsy is often helpful and may reveal information useful in the decision-making process. Our center has successfully used livers with peak aspartate aminotransferase (AST) greater than 5000 μL/L in the appropriate clinical setting. We have previously published our results of 117 patients with peak AST or alanine aminotransferase (ALT) greater than 500 μL/L or total bilirubin (TB) greater than 2, and found no difference in 1-year survival rates compared with those in donors with liver function enzymes lower than these values.46

Box 41-6. Order of Allocation of Liver Allografts from Deceased Donors

<table>
<thead>
<tr>
<th>Status</th>
<th>Allocation Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local: status 1</td>
<td>by wait time as status 1</td>
</tr>
<tr>
<td>Regional:</td>
<td>MELD/PEDL ≥ 15, in descending order of mortality risk score (MELD/PEDL)</td>
</tr>
<tr>
<td>Regional:</td>
<td>MELD/PEDL ≥ 15, in descending order of mortality risk score (MELD/PEDL)</td>
</tr>
<tr>
<td>Regional:</td>
<td>MELD/PEDL &lt; 15, in descending order of mortality risk score (MELD/PEDL)</td>
</tr>
<tr>
<td>National:</td>
<td>MELD/PEDL any, in descending order of mortality risk score (MELD/PEDL)</td>
</tr>
</tbody>
</table>

Status 1 refers to a patient with acute hepatic failure with anticipated life expectancy less than 7 days.

Model for End-Stage Liver Disease (MELD) score = 9.597 × log N (LN (creatinine) + 0.378 × LN (bilirubin)) + 1.12 × LN (INR) + 0.643

Pediatric End-Stage Liver Disease (PEDL) score = 0.480 × LN (bilirubin) + 1.857 × LN (INR) – 0.687 × LN (albumin) + 0.436 (patient less than 1 year of age) + 0.667 (patient with growth failure)
With the ongoing shortage of donor liver allografts, there has been an increased use of organ donors under the DCD protocol. DCD organs are procured after cessation of cardiopulmonary function. The DCD protocol is used in organ donors who do not meet brain death criteria but who have nonrecoverable illness for which medical support will be electively withdrawn. For these patients, consent can be obtained for withdrawal of life support under controlled conditions. A physician who is not affiliated with the organ procurement team independently declares death after withdrawal of support. From the time of the declaration of death, a waiting period is then observed to ensure no recovery of cardiovascular function (usually 5 minutes), after which the donor surgeon can begin the procurement procedure. The organ procurement proceeds rapidly with cannulation of the aorta to begin exsanguination and cold flushing of the organs, followed by rapid cooling with topical ice and, finally, removal of the organs with placement in cold preservation solution. The DCD protocol of necessity imposes a period of warm ischemia on the procured organs, which has been shown to worsen transplant outcomes. In LT, the most commonly described complication of the DCD protocol is diffuse intrahepatic biliary strictures. These strictures are thought to arise from an interruption or impediment of arterial flow to the biliary system. This ischemic damage to the biliary system is generally not seen until several days or several weeks after transplant but frequently leads to early graft loss as this condition is generally not amenable to therapeutic intervention. Warm ischemic damage may result either directly during the donor warm ischemia time or at the time of organ reperfusion. It has been suggested that microthrombi form in the microvasculature of the biliary system during the warm ischemia period, and this impedes arterial flow to the biliary system after reperfusion. Graft survival for DCD liver allografts is generally 10% to 15% less at 1 year (75% survival) when compared with non-DCD donors. In the majority of patients who do not develop diffuse intrahepatic biliary strictures, DCD allografts seem to have normal function and long-term survival. DCD livers currently account for 4% of transplanted allografts in the United States. Results at our center have improved in recent years, with more stringent criteria regarding acceptable DCD livers. Important factors predictive of successful use of DCD liver allografts include donor age, presence of steatosis, time to arrest, and cold and warm ischemia time.

Medical History of Extended Criteria Donors

The other category of ECD livers are those from donors with a high-risk social history, placing them at risk for infectious diseases such as HIV, HCV, and HBV, including certain sexually transmitted diseases such as syphilis, or cancer. Previously observed exclusionary criteria included intravenous drug use, trading sex for money or drugs, previous incarceration, male-to-male sexual contact, or any history of cancer. Although these factors continue to be investigated and recorded for all deceased donors, they are now considered relative exclusionary factors. Current testing for common infectious diseases provides a relatively short window for incubation prior to testing positive. This has lowered the risk of transmission significantly, although this risk is not zero. The natural history of many cancers has now been categorized sufficiently to assess the risks of disease recurrence in a potential organ donor who has been cancer free for many years. Along with this group is the subset of patients with known brain tumors. These tumors tend to remain localized to the brain; therefore, the thoracic and abdominal organs can frequently be transplanted.

An important group of deceased liver donors within the high-risk medical history are those who are infected with HCV. There are 4 million persons in the United States (~1%) who are infected with this virus. However, the rate of HCV infection in otherwise eligible organ donors is ten times higher than the prevalence in the general pop-

ulation. This finding results from the considerable overlap between those persons infected with HCV and those who live a high-risk lifestyle of intravenous drug use, prostitution, and gang and criminal activity. People who suffer an unexpected death in relation to these activities are over-represented by teens and young adults—persons who are the ideal organ donors. Therefore, there has been an increasing emphasis on using HCV-infected liver allografts to help ameliorate the organ shortage. HCV-infected liver allografts transplanted into HCV-infected recipients have similar, if not improved, outcomes when compared with noninfected grafts 5 years after LT. Results from our center suggest that fibrosis progression in the first year post-transplant is decreased for HCV-infected grafts. These findings may result from a previously upregulated defense, or an inherent resistance, to the HCV virus in previously infected grafts. It has also been suggested that HCV-infected allograft recipients may experience genotype switching, in which the more virulent virus that led to cirrhosis in the recipient is downgraded to a less virulent strain through replacement of the liver. These findings are particularly important in the HCV-infected population because data suggest that living donor split allografts have worse outcomes in HCV recipients, and many centers will not use split grafts in patients with HCV. It has been hypothesized that the active regenerative physiology of the split liver graft stimulates a more aggressive infection of the transplant liver graft with HCV by an unknown mechanism. Whether a similar process could occur in an extended criteria deceased donor organ, which may also require significant regeneration after procurement damage or ischemic injury, is unknown.

Liver allograft donors with previous exposure to HBV have also been used extensively in recent years. With the successful control of HBV with immunization and lamivudine, deceased donors who have had previous infection with HBV (positive for hepatitis B core antibody) can be transplanted with a near-zero risk of HBV transmission.

Partial Liver Allografts

As a consequence of the shortage of deceased donor liver allografts, partial liver allografts are now used. In countries with limited access to deceased donors, partial liver allografts from living donors may be the only option available for patients in need of LT. Also, splitting of a deceased donor liver can result in two viable grafts, although each split portion carries an increased risk of complications when compared with a whole organ allograft. Much of the impetus for the development of split liver transplants grew from two areas of need: pediatric LT and transplantation in countries with few deceased donor organs. A recent review of 10-year clinical outcomes demonstrates similar outcomes for whole organ and partial liver grafts in children but a significant decrease in survival for split liver grafts in adults.

Pediatric patients have a high rate of decompensation and death on the LT wait list—as high as 25% to 50%. Because the death rate among healthy children is very low, there are few whole-organ deceased donors of an appropriate size. For small infants, the left lateral segment (segments 2 and 3) or left lobe (segments 2, 3, and 4) of an adult liver provides adequate hepatic function and can be obtained from either a living donor or a deceased donor. As with a standard LT, there are three requirements for a partial organ graft: vascular inflow (including both arterial and portal), venous outflow, and biliary drainage. The graft must be of adequate size to provide the hepatic mass required to support normal physiologic processes. The liver graft will then regenerate to a mass determined by both available space and functional capacity. Partial grafts for pediatric transplantation can be obtained through a variety of mechanisms.
A reduced-size graft is one in which the whole organ is procured for a single recipient and the graft is reduced in size to match the recipient. This approach does not increase the number of available organs but does shorten the wait list time for small children. A living donor graft is one in which a segment of the liver, the right lobe, left lobe, or left lateral segment, is procured from a healthy living donor as an elective procedure. This approach does increase the number of available organs and also decreases wait list time. A split liver graft is taken from a deceased donor. The liver is divided into right and left portions, and the two grafts are transplanted into two separate recipients, commonly an adult for the right portion and a child for the left portion. The split procedure can occur either in situ at the time of organ procurement or ex vivo under cold ischemic conditions after the liver has been procured. Splitting a deceased donor liver into two grafts, namely right and left lobe grafts for an adult and pediatric recipient respectively, increases the number of available organs and decreases the wait list time. Similarly, right lobe and left lobe grafts from living donors increase the donor pool (Figs. 41-2 and 41-3). Living donor transplantation is more common in Japan and Southeast Asia than in the Western hemisphere.

Liver Allograft Allocation

The MELD score is a continuous variable of disease severity that was developed to assess short-term prognosis in patients with liver failure undergoing transjugular intrahepatic portosystemic shunt (TIPS) placement. It was subsequently found to be a sensitive and specific predictor of short-term mortality for patients with liver failure awaiting transplantation. In 2002, the LT wait list was transitioned from a wait time–based allocation system to a MELD-based system in which wait time was de-emphasized, and disease severity (MELD score) became the primary criterion for organ allocation. Early reviews of the MELD system demonstrate that deaths on the LT wait list have decreased. Attempts have been made to associate the pretransplant MELD score with post-transplant outcomes, but results of these studies have been less clear. National implementation of the MELD system has provided a predictable and reproducible means for clinicians to assess the severity of ESLD and to appropriately list patients for transplantation.

The MELD score has three components, which reflect the synthetic function of the liver, the excretory function of the liver, and the overall systemic effect of the liver disease. The synthetic function of the liver is assessed through the INR, which reflects the ability of the liver to produce coagulation factors. Within the regression analysis that calculates MELD, INR has the largest covariate, which results in a disproportionate weight on this value in predicting liver disease severity. The excretory function of the liver is assessed through its ability to produce and excrete bile, as reflected in the serum total bilirubin (TB) level. Finally, a surrogate for the systemic effect of the liver disease is assessed through its impact on renal function, generally from HRS, and is reflected in the serum creatinine. The INR, serum TB level, and serum creatinine are readily available and easily calculated, making them ideal markers from a clinical standpoint. Additionally, because these are all

Figure 41-2. A, A right lobe graft from a living donor consists of segments 5, 6, 7, and 8 and is procured along with the right branches of the hepatic artery, portal vein, hepatic duct, and hepatic vein. B, A right lobe allograft implanted into an adult recipient.

Figure 41-3. A left lobe allograft from a living donor consists of segments 2 and 3 only and is procured along with the left branches of the hepatic artery, portal vein, hepatic duct, and hepatic vein.
independent laboratory values, there is no subjective component to the MELD score, which increases fairness for all LT recipients on the wait list. The MELD score ranges from a low of 6 to a high of 40. There is a pediatric version of the MELD score (P Feld), which is also composed of INR, TB, and creatinine; it also includes a variable for recipient age and growth (see Box 41-6).36

There has been considerable discussion regarding the appropriate timing for listing a patient for transplantation. Clearly, patients with severe disease should be listed and transplanted in an expedited fashion. Those patients with a very low MELD score, who are well compensated, may better await progression of their disease prior to taking on the risks of the LT. Recent studies suggest that patients with a MELD score as low as 11 to 12 derive a better clinical outcome from LT as opposed to delaying the procedure.40 However, all patients with cirrhosis retain the underlying risks of the disease, including an increased risk of gastrointestinal hemorrhage, development of HCC, encephalopathy, malnutrition and debility, and worsening HRS and HPS.

Organ Matching

Matching a donor liver to a specific recipient is primarily based on two factors: blood type and size match. However, organ/graft-recipient matching can be much more complex than simply choosing the next person of the appropriate blood type that the liver allograft will fit in terms of size. For example, many liver recipients are also on the transplant list for additional organs, such as a kidney (combined liver and kidney), and all organs to be included in the transplant must be evaluated individually. With the ongoing shortage of donor organs, a greater number of ECD livers must be assessed. Critically ill patients in the intensive care unit may not tolerate transplantation with a donor liver that has little reserve or is at risk for delayed graft function, such as those from older donors or those with severe steatosis. There is increasing use of liver allografts from donors infected with HCV. Although these HCV grafts can be successfully transplanted with good outcomes, they must be carefully evaluated and transplanted only into a consenting recipient with genotype 1 HCV. The transplant team and the organ recipient must remain somewhat flexible in allocating the organ to the most appropriate recipient.45 Organ–recipient matching is a complex process that is best managed by an experienced surgeon, who has the final responsibility for transplant success. As the liver transplant system continues to accumulate outcomes data, clinicians will gain more experience in using extended criteria allografts.

Donor and Recipient Operation

Organ Procurement from Deceased Donors

The organ procurement operation from a deceased donor is well standardized, with little variation among surgeons. The primary goal of the procurement procedure is the safe removal of organs, all of which remain viable for transplantation. Safe preservation of the organs depends on two primary principles: (1) rapid exsanguination and vascular flushing with an appropriate preservation solution and (2) rapid cooling. The involved organs are carefully dissected and prepared simultaneously. For the abdominal organs, an aortic cannula, which is used to flush the arterial system of the abdominal cavity, is placed. Some surgeons choose to place a second cannula in the portal vein (through the inferior mesenteric vein) to flush the portomesenteric system. The abdominal aorta is clamped superior to the celiac trunk and near the iliac bifurcation to isolate the abdominal organs. The outflow for the blood and preservation solution is generally through the suprahepatic vena cava at its junction with the right atrium. As the clamps are placed and the preservation solution is infused, iced normal saline is placed throughout the abdominal cavity to topically cool the organs. For partial liver procurement from a living donor, the liver resection is performed in the donor with total dissection completed while vascular inflow and outflow remain intact. Clamps are applied simultaneously and the donor graft is removed, followed by rapid flushing and cooling.

The choice of preservation solution has recently engendered some discussion. In the United States, two primary solutions are used for abdominal organ preservation: University of Wisconsin (UW) and histidine-tryptophan-ketoglutarate (HTK) solutions. The composition of UW and HTK preservation solutions and the history behind their development have been published previously.49 UW is a much more viscous solution that flushes at a slower rate and with a lower total volume. HTK is a very-low-viscosity solution that is based on a buffer system (histidine), with two additional substrates (tryptophan and ketoglutarate). With either solution, preservation of the organs is based on the primary principle that the osmotic concentration is maintained by metabolically inert substrates with the addition of oxygen radical scavengers. UW is believed to provide organ tolerance to long cold ischemia times in a predictable manner. UW was first compared with HTK in a randomized fashion in LT more than a decade ago and demonstrated clinical equivalence.50 Subsequent clinical studies have demonstrated essentially equivalent outcomes for these two solutions in deceased donor LT.49,51 The solutions have also been found to be similar in living donor LT.52,53 HTK, with its lower viscosity, may result in better penetration of the microcirculation for a better flush. This may lead to a lower rate of biliary complications and may provide a more thorough flush in livers procured using DCD.49

Once procured, the liver allograft must be transplanted and reperfused within a strict time limit. Whereas the heart and lung can only tolerate cold ischemia times of 4 and 6 hours, respectively, the liver can routinely be transplanted with up to 12 hours of cold ischemia time. Beyond this time period, successful transplantation is possible, but potential complications arise, and the risk of primary nonfunction and patient death increases. While experiencing cold ischemia, the hepatocytes continue to have cellular metabolism but at a much lower rate. By-products of this anaerobic metabolism may accumulate in the liver graft and are released at the time of reperfusion. Therefore, most centers flush the liver allograft immediately prior to reperfusion in the recipient to avoid hemodynamic instability and cardiac dysrhythmias.

Liver Transplant Operation

There are three components of the LT operation: (1) preparation of the transplant organ, (2) recipient hepatectomy, and (3) implantation of the graft.

Preparation of Allograft

Preparation of the graft involves removal of residual tissue, including residual diaphragm and pericardium around the vena cava and hepatic veins, during the donor operation. The gallbladder is always removed from the donor liver, and the cystic duct is ligated. Accessory hepatic arteries are carefully dissected and preserved. An accessory right hepatic artery requires reconstruction prior to transplantation and can be reconstructed directly to the gastroduodenal artery or the splenic artery. Alternatively, the origin of the accessory right hepatic artery at the superior mesenteric artery can be preserved, with the superior mesenteric artery being reconstructed to the splenic artery. In general, an accessory left hepatic artery cannot be safely reconstructed, and it is dissected and preserved in situ with careful ligation of small vessels, including the distal left gastric artery after the takeoff of the left accessory hepatic artery.
Recipient Hepatectomy
The conventional or standard bicaval method and (2) the piggyback technique. Both approaches to the hepatectomy require initial takedown of the falciform and gastrohepatic ligaments, followed by dissection of the hilum of the liver with transection of the hepatic artery, common bile duct, and portal vein. The conventional approach then proceeds with clamping of the vena cava above and below the liver, with transection of the vena cava between the clamps and removal of the liver. This method necessarily requires complete clamping of the vena cava, although a shunt can be formed (Fig. 41-4). The piggyback technique, which does not require clamping of the vena cava, differs. It involves the careful retraction of the liver away from the vena cava, with perforating branches between the vena cava and the liver individually ligated and transected. Eventually, the liver remains attached only by the hepatic veins. After clamping and transecting these veins, the surgeon removes the liver.

The piggyback technique is technically more difficult than the conventional approach, but the recipient tends to remain more hemodynamically stable because the preload to the heart from the lower body is never interrupted (see Fig. 41-4). Some surgeons who use the piggyback approach construct a temporary portocaval shunt to decompress the portomesenteric system until the time of liver allograft reperfusion. For transplant recipients with HCC, surgeons may choose to use the conventional approach to minimize the risk of retaining the native vena cava, which may have macrovascular invasion or through which hematogenous spread may occur during the hepatectomy. Our center uses the piggyback approach for nearly all patients with HCC and has demonstrated no difference in clinical outcomes.\(^\text{54}\) The piggyback approach may be the preferred method in high-risk patients such as the elderly, those with poor physiologic reserve, or those who are hemodynamically unstable. The piggyback technique tends to preserve hemodynamic and physiologic stability throughout the transplant process, which may be associated with less perioperative morbidity and mortality.

Implantation of Allograft
Finally, the transplant is performed. For the conventional approach, the vena cava must be reanastomosed both above and below the liver. An additional benefit of the piggyback hepatectomy is that one less anastomosis is required during the transplant. For the piggyback hepatectomy, the liver outflow is through the clamped hepatic veins so that a single anastomosis is required. This reductive from two anastomoses to one anastomosis can decrease critical warm ischemia time by as much as 5 to 10 minutes. Next, the portal vein and hepatic artery are anastomosed and the liver is reperfused. Again, the liver is generally flushed immediately prior to reperfusion to minimize the cardiac and hemodynamic effects of reperfusion. Finally, the common bile duct can be anastomosed either to the recipient common bile duct or to a Roux-en-Y limb of the small intestine.

The living donor partial liver transplant requires use of the piggyback hepatectomy because there is no vena cava available from the living donor. Therefore, the donor hepatic vein is anastomosed to the recipient hepatic veins, with portal and arterial inflow constructed directly to the native portal vein and hepatic artery. The bile duct is transected close to the liver graft and can be anastomosed to either the residual native bile duct or to a Roux-en-Y reconstruction to the intestine with a choledochojejunostomy.

Closure of Abdomen
Closure of the abdomen in conjunction with aggressive fluid resuscitation can result in elevated intra-abdominal pressures and post-transplant abdominal compartment syndrome. This increased pressure can compromise the newly transplanted liver, resulting in hepatic congestion. Additionally, systemic effects of abdominal compartment syndrome can lead to increased inspiratory pressures and slow weaning from the ventilator, as well as poor renal vein outflow and compromised renal function. The decision to delay final closure of the abdomen for 24 to 72 hours post-transplant is center dependent. Venous outflow for the liver is critical to avoid hepatic congestion, which can lead to graft injury and vascular thrombosis. Maintaining the post-transplant patient with a low central venous pressure in the immediate post-transplant period optimizes liver allograft blood flow and may improve early function.

Anesthesia
The role of the anesthesiologist is critical in the LT procedure. Prior to initiating the procedure, large-bore vascular access is generally placed to allow rapid infusion of blood products, if necessary. Many centers routinely place a pulmonary artery catheter for continuous monitoring of cardiac function and fluid status. Two arterial catheters are placed

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**Figure 41-4.** A, Conventional technique with bicaval anastomosis: The retrohepatic vena cava from the donor replaces the retrohepatic vena cava of the recipient, which is excised along with the diseased liver. This procedure necessitates interruption of caval blood flow and requires two caval anastomoses. B, Piggyback approach for caval anastomosis: The retrohepatic vena cava of the recipient is not excised and blood flow is never interrupted. The donor cava is simply anastomosed to the recipient hepatic veins, which flow immediately into the vena cava.
to allow continuous monitoring of systemic blood pressure and frequent review of blood gases. LT has historically been associated with massive blood loss related to the presence of portal hypertension and varices, the underlying coagulopathy and thrombocytopenia, and the overall complexity of the procedure. Patients with liver failure maintain a baseline vasodilatory status which, when added to intraoperative blood loss, can lead to significant hemodynamic instability. As surgeons have gained increasing experience with LT, blood loss has improved and the procedure has become safer. Additionally, the increased use of the TIPS serves to decompress the portomesenteric system, which lessens variceal-related bleeding. The use of antifibrinolytics varies but may have a role in minimizing perioperative blood loss.

**Post-transplant Course**

**Surgical Complications**

Immediate post-transplant complications may result from technical issues related to the transplant procedure, poor function of the graft, or recipient health issues. The most critical early post-transplant complication is thrombosis of the hepatic artery or the portal vein. Thrombosis of the hepatic vein anastomosis is uncommon. The liver requires both hepatic artery and portal vein inflow for survival, and thrombosis of either anastomosis places the graft at imminent risk of failure. Post-LT, Doppler ultrasound is used to ensure that vascular flow remains adequate. A loss of flow in either vessel generally necessitates emergent return to the operating room to reestablish flow. Post-transplant bleeding in the first 24 to 48 hours is not uncommon and requires re-exploration to identify and control the source.

**Primary Nonfunction**

Primary nonfunction is a definition of exclusion in which there is graft failure within 7 days of the transplant with no other identifiable cause. This failure occurs in 1% to 5% of LTs and may be related to prolonged ischemia time, old donor age, and severe steatosis. Liver recipients who experience primary nonfunction are immediately relisted for transplantation, but they experience a high death rate, both while waiting for the second transplant and after they have received the second transplant. Delayed graft function is not well defined, but it may be manifest as prolonged elevation of the serum bilirubin level, a prolonged elevation of the INR, renal dysfunction, and persistent encephalopathy. Patients experiencing poor early graft function may have deterioration of renal function and require continuous venovenous hemodialysis (CVVH). This therapy permits the clinician to closely modulate patient fluid status when the renal function is marginal. A small-for-size graft is a syndrome seen almost exclusively in partial LT. The small size of the transplant graft in relation to the recipient blood flow results in persistent portal hypertension and liver congestion because the portomesenteric flow is too great for the liver segment. This syndrome is a major cause of early graft loss in living donor transplantation.

**Biliary Complications**

Biliary complications may be seen within the first post-transplant week but may also occur several weeks or months later. There are three primary complications of the bile duct: (1) biliary leaking, (2) anastomotic stricture, and (3) intrahepatic strictures. Biliary leaking is encountered in the perioperative period and may be technical in nature or may result from bile duct necrosis. Because the common bile duct protrudes from the liver, its blood supply lessens with increasing distance from the hilum of the liver. The recipient duct receives its blood supply from the native recipient pancreaticoduodenal complex and does not have the same blood supply issue. When duct necrosis occurs, a revision can be performed operatively, with a shortening of the duct followed by reanastomosis to the recipient duct or construction of a Roux-en-Y choledochojejunostomy. Biliary complications are particularly problematic in living donor LT and are a major cause of graft loss and patient death in affected patients.

Development of an anastomotic stricture is the most commonly encountered bile duct complication and may occur in up to 25% of patients. The anastomosis between the donor and recipient bile ducts forms a scar as it heals. The development of a stricture, or excessive scar, may depend in some measure on the surgical reconstruction of the duct; however, the size of the ducts and the strength of the donor blood supply to the duct are also important determinants of anastomotic narrowing. Most anastomotic strictures can be treated nonoperatively with ERCP or percutaneous transhepatic cholangiography (PTC). Through these techniques, stents can be placed across the narrowed anastomosis to permit drainage, and these can be increased in size over time to dilate the duct.

Finally, intrahepatic strictures can develop. This complication is rare but is the most difficult to diagnose and treat. Intrahepatic strictures appear as multiple diffuse strictures within a region of the liver or across the entire liver. Diffuse intrahepatic stricturing points to a systemic problem usually related to arterial blood flow. The biliary system is supplied through the arterial microcirculation of the liver. An arterial anastomotic stricture may result, and placing a vascular stent across the arterial anastomosis may improve blood flow and minimize the stricturing problem. Liver allografts procured from deceased donors using a donation after cardiac death protocol are at increased risk for diffuse intrahepatic strictures. The etiology of this association is unknown. DCD requires a time period of 8 to 10 minutes of warm ischemia at the point of procurement. This period may result in direct damage to the biliary system, or the biliary microvasculature may develop diffuse microthrombi, which impede arterial blood flow after reperfusion. Patients who develop diffuse intrahepatic biliary strictures have a high rate of graft loss and frequently require retransplantation within 1 year.

**Hepatic Outflow Obstruction**

Hepatic outflow obstruction is relatively rare but occurs more frequently in patients who have undergone LT with piggyback hepatectomy. The etiology of this process is unclear but appears to be directly involved with the anastomosis between the donor and recipient hepatic veins or with a mechanical obstruction of the outflow of this anastomosis because of the orientation of the liver. The result is a pressure gradient that leads to chronic congestion of the liver. This pressure gradient can result in parenchymal damage to the liver, chronic ascites, or splenomegaly related to portal hypertension. Treatment can be performed using interventional radiology with balloon angioplasty to widen the outflow or placement of a stent across the hepatic vein outflow tract to reduce the pressure gradient.

**Rejection**

Rejection of the liver allograft is less common than that seen with other solid organs. In fact, the liver appears to lessen the rejection risk of other organs when they are transplanted simultaneously. The reason for this finding is unclear. Unfortunately, the diagnosis and treatment for acute and chronic rejection in LT varies widely among LT centers. This lack of standardization impedes research in this area. Individual centers report acute rejection rates ranging from less than 5% to nearly 50%. This raises the question of diagnostic criteria used; such disparity is unlikely to result simply from intercenter variability. The patient with rejection generally presents with elevated liver function enzymes and may have fever and abdominal pain. Commonly
accepted liver biopsy criteria for acute cellular rejection in LT include (1) periportal inflammation, (2) bile duct damage, and (3) endothelialitis. Treatment may include pulse steroids and/or antibody therapy with an increase in baseline immunosuppression. Successfully treated acute rejection of the liver is not believed to have an impact on the long-term survival of the liver graft. Late acute rejection can occur, but chronic rejection of the liver is rare. Groups at increased risk for acute rejection include younger patients, females, patients of African descent, and those with autoimmune diseases. Ultimately, the most common etiology of rejection may be related simply to patient compliance with medications, although this is difficult to prove definitively.

Infections
Post-LT infectious complications are not uncommon but can be minimized with appropriate patient management. The LT procedure itself is clean, which means that intra-abdominal infections post-LT are rare. However, bacterial wound infections are common for a variety of reasons. The LT incision is quite large, and patients with liver failure are malnourished and have poor healing capacity. Many LT recipients receive perioperative steroids, which has a direct effect on wound healing. Finally, clinical comorbidities such as diabetes and obesity contribute to poor wound healing and infection.

The most common viral infection in the LT patient is cytomegalovirus (CMV) infection, which has a 1-year risk of 5% to 20%. Anti-CMV prophylaxis with ganciclovir and minimization of immunosuppression lowers the rate of this infection. Fungal infections can occur in up to 20% of patients and are most commonly seen in the mouth, esophagus, and urinary tract. These infections almost always result from Candida species and respond to standard treatments.

Long-term Renal Failure
Nearly all post-LT immunosuppression protocols use calcineurin inhibitors as the primary immunosuppressant drugs. Use of these agents has resulted in nephrotoxicity as the primary long-term major complication associated with solid organ transplantation. The insidious loss of renal function has a direct impact on transplant outcome, and many solid organ transplant recipients develop end-stage renal disease and require dialysis or kidney transplantation. These same immunosuppressive agents also increase the incidence of diabetes and hypertension, which contributes to the progressive decline in renal function. Attempts have been made to minimize exposure to calcineurin inhibitors by using two- and three-drug regimens, but these additional agents carry their own unique side effects.

Malignancy
The immune system plays a critical role in neoplasm surveillance in the human body. The chronic immune suppression required by all transplant patients places them at increased risk for the development of cancer. Unfortunately, the registries that follow post-transplant cancer are limited, with voluntary reporting and incomplete follow-up. Therefore, the reported incidences by organ and tumor type vary widely. The cancers found in transplant patients tend to mirror those seen in the general population but with increased frequency. Therefore, the cancer most commonly seen in transplant patients is skin cancer (squamous and basal cell). Patients with HCC at the time of transplant have a risk of post-transplant HCC recurrence, but their survival is similar to that for non-HCC patients if they are within the Milan criteria at the time of transplant. Post-transplant lymphoproliferative disease (PTLD) is well described, and the risk appears to increase with increasing levels of immunosuppression.

Complications in Pediatric Recipients
In children older than 3 years of age or larger than 10 kg, the spectrum of post-LT complications is similar to that in adults. Surgical complications can be life-threatening in children. Thrombosis of the hepatic artery or the portal vein can lead to rapid failure of the liver graft. It is very difficult to obtain a pediatric graft in an expeditious fashion, which can result in the death of the recipient. Thrombosis is particularly problematic in infants because they have very small vessels with a low blood pressure, which predisposes to thrombus formation. Children also have a high risk of biliary complications because of the small size of the bile duct. Postoperative edema or duct ischemia can lead to duct narrowing or stricture, which may require intervention. Unique to the infant population is the risk of spontaneous intestinal perforation, which can also be life-threatening if not detected in a timely fashion. Spontaneous perforation may be related to perioperative steroid dosing, pressor use, or surgical stress or unrecognized injury.

The rate of acute rejection is higher in older children and adolescents; these groups have a more active immune system. For this reason, children often receive higher dosing of immunosuppressive medications. Although children have more renal reserve and tolerate the nephrotoxicity of the calcineurin inhibitors better than adults, they still have a high rate of chronic renal dysfunction. Very young children may actually develop a degree of tolerance to the graft, and it is not unusual to have adolescents and young adults who were transplanted as infants, stop their immunosuppression completely. The immunosuppressive agents used in children are essentially the same as those used in adults.

Children have a much better healing capacity than adults so that wound and postoperative infections are rare. These patients are at higher risk for opportunistic infections when compared with nonimmunosuppressed children, but the rates are still lower than those seen in adults. Common infectious agents seen in pediatric transplantation include CMV, respiratory syncytial virus, rotavirus, Candida species, and common bacteria. Post-LT prophylactic medications are the same as those used in adults.

PTLD is a serious complication of transplant immunosuppression that may occur in children within months of immunosuppression induction. The risk of PTLD increases with increased levels of immunosuppression. With increasing immunosuppression, there are fewer T cells in circulation. This T-cell suppression permits the systemic propagation of Epstein-Barr virus (EBV), which stimulates the clonal expansion of B cells, leading to PTLD. As with CMV disease, the children at highest risk are those who are EBV-negative but receive an EBV-positive donor organ. This disease is manifest by lymphadenopathy or the presence of any mass lesion after transplant. Treatment for PTLD includes resection of mass lesions and chemotherapy, including rituximab (anti-CD 20 receptor antibody).

Elevation of liver function enzymes in the post-LT period is often the first indication of a complication. Workup starts with liver Doppler ultrasound to evaluate the vascular flow to the graft. If this study is normal, evaluation of the biliary system is next indicated. Finally, percutaneous liver biopsy can be obtained and often uncovers the etiology when other studies are inconclusive. The liver biopsy in this scenario can frequently differentiate etiologies as diverse as drug effects, biliary obstruction, graft congestion, ischemia, rejection, or recurrent disease. Serial surveillance liver biopsies are used at many centers and may provide predictive information of long-term outcomes.
Post-transplant Immunosuppression

The liver is a large-volume organ and represents a significant tissue mass within the human body. The liver allograft is certainly recognized as "foreign" by the recipient and can experience rejection. However, the liver is less subject to rejection when compared with other solid organs such as the kidney. In fact, cotransplantation of the liver and kidney from the same donor results in a lower rate of rejection of the kidney when compared with kidney transplant alone. Therefore, the liver has some inherent ability to resist rejection, although the mechanism is poorly understood. Management of post-transplant immunosuppression is an ongoing balancing act between preventing host rejection of the transplant organ versus the development of host infection or neoplasm related to overimmunosuppression.

The majority of current immunosuppressive drugs nonspecifically target T-cell activation, clonal expansion, or differentiation in the effector cells. The process of T-cell activation is highly coordinated and involves binding of the T-cell receptor–CD3 complex to antigen expressed on the surface of antigen-presenting cells. Additional cell-bound and secreted costimulatory molecules contribute to augmentation of the T-cell activation. As a result of these interactions, multiple signal transduction pathways become operational, leading to induction of cytokine gene expression and stimulation of cellular activation. Interruption of any of the events of T-cell activation by immunosuppressive drugs results in downstream inhibition of cytokine expression and T-cell proliferation. The immunosuppressants cyclosporine, tacrolimus, and sirolimus suppress the immune response by inhibiting signal transduction pathways within the T cell. These drugs bind to their intracellular targets, immunophilins, creating composite surfaces that block the activity of unique pathways. For cyclosporin–cyclophilin and tacrolimus–FK-binding protein, the target is calcineurin. Sirolimus and everolimus inhibit the T-cell cycle downstream from the interleukin-2 (IL-2) receptor. Other available agents include polyclonal and monoclonal antibodies against T-cell receptors, anti-IL-2 receptor monoclonal antibodies, and antiproliferative agents such as mycophenolate mofetil. Table 41-4 summarizes the properties of these agents.

The first immunosuppressive agents included corticosteroids and antiproliferative agents (azathioprine). These drugs, both alone and in combination, were inadequate to prevent rejection, and transplant outcomes remained universally poor throughout the 1960s and 1970s. The modern era of immunosuppression started with the discovery of cyclosporine. Cyclosporine is a calcineurin inhibitor that selectively impedes IL-2 production and recognition in T cells while leaving non-specific host resistance relatively intact. This drug class first allowed the host to avoid acute cellular rejection while maintaining the ability to repel infectious organisms. Tacrolimus was later introduced as a second calcineurin inhibitor and has been shown to be equally efficacious, perhaps even more so under specific circumstances, with a lower rate of steroid-resistant allograft rejection.

Immunosuppressive Agents

Cyclosporine

The calcineurin inhibitor cyclosporine (Sandimmune, Neoral) came into accepted clinical use in 1979 and quickly revolutionized immunosuppression therapy. This agent permitted solid organ transplantation to emerge as an accepted and viable option for individuals with end-stage organ failure. Cyclosporin A is a product of a fungus and inhibits cell-mediated immunity through suppression of T-cell function. It does not impede phagocytosis or hematopoiesis but does have numerous negative side effects including renal impairment, hypertension, gingival hyperplasia, and hirsutism. Cyclosporine was first used in combination with corticosteroids at the time of its introduction and was subsequently combined with both azathioprine and corticosteroids, depending on the clinical situation. These regimens resulted in dramatically improved graft and patient survival rates. In recent years, tacrolimus has become the preferred calcineurin inhibitor, but cyclosporine remains clinically available and is often used interchangeably with tacrolimus depending on the desired side-effect profile for a particular patient.

Tacrolimus

The calcineurin inhibitor tacrolimus (Prograf) was initially used in clinical practice in 1989. Its mechanism of action is similar to that of cyclosporine, and it is also derived from a fungus. However, tacrolimus has a different side-effect profile than cyclosporine. Although tacrolimus is nephrotoxic, tacrolimus leads to less gingival hyperplasia and hirsutism and has better oral absorption and higher potency. Other side effects reported for tacrolimus include post-transplant diabetes, hypertension, hair loss, hyperkalemia, hypertriglyceridemia, tremor, headaches, and a lowered seizure threshold. This agent has also been linked to an increased prevalence of cardiomyopathy, particularly in pediatric patients, which is not reported with cyclosporine use. This condition appears to resolve with a change from tacrolimus to cyclosporine.

At first, tacrolimus was used primarily as a rescue agent in patients with refractory rejection under cyclosporine. Recent data support the use of tacrolimus monotherapy with low rejection rates in LT. A recent study suggests almost all children can be weaned off steroids by using tacrolimus as the primary immunosuppressive agent after LT. Post-transplant immunosuppression protocols usually dictate use of a calcineurin inhibitor, either cyclosporine or tacrolimus, for children and adults. Many centers augment this with an antiproliferative agent and/or steroids for some time. Studies suggest a lower incidence of rejection with tacrolimus when compared with cyclosporine, and tacrolimus has become the calcineurin inhibitor of choice at most centers. The variety of available immunosuppressants now affords the clinician a choice of medications that can be tailored to each recipient.

Sirolimus/Everolimus

Sirolimus (rapamycin), a target of rapamycin inhibitor, is the product of the bacterium Streptomyces hygroscopicus, which was originally found in a soil sample from Easter Island, also known as “Rapa Nui.” Because of this history, sirolimus has been marketed as rapamycin. It has been found to be an effective immunosuppressant as well as an antiproliferative agent. Sirolimus inhibits the response to IL-2 and thereby blocks activation of T cells and B cells. The mode of action of sirolimus is to bind an intracellular protein, FK-binding protein, in a manner similar to tacrolimus. However, unlike the tacrolimus-bound complex, which inhibits calcineurin, the sirolimus-bound complex inhibits the target of rapamycin pathway. Inhibition of target of rapamycin activation results in the inhibition of T-lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation, and the inhibition of antibody production.

The chief advantage sirolimus has over calcineurin inhibitors is that it is less toxic to kidneys. Transplant patients maintained on calcineurin inhibitors long-term tend to develop impaired kidney function or even chronic renal failure. It is possible that this effect can be minimized by using sirolimus instead. Sirolimus can be used alone, in conjunction with calcineurin inhibitors, or with mycophenolate mofetil, so as to provide steroid-free immunosuppression regimes. A well-known side effect of sirolimus, impaired wound healing, may limit use of this agent in the immediate postoperative period. The antiproliferative effect of sirolimus has also been used in conjunction with coronary stents to prevent restenosis in coronary arteries following balloon angioplasty. These antiproliferative actions have also led to the study of this drug for its antitumor properties.
Mycophenolate Mofetil

The antiproliferative agent mycophenolate mofetil (CellCept) is frequently given as part of a double- or triple-drug regimen. It is used interchangeably with azathioprine and has a similar side-effect profile. The primary benefit of an antiproliferative agent in conjunction with a calcineurin inhibitor is an increase in the overall level of immunosuppression. Use of these agents may allow lower dosing of the calcineurin inhibitor, thus minimizing nephrotoxicity and preserving long-term renal function. The primary side effects of mycophenolate mofetil include gastrointestinal distress, which can manifest as nausea or loose stools, and bone marrow suppression, resulting in neutropenia and anemia.

### Common Prophylactics

- **Ganciclovir/valganciclovir**: Antiviral medication used to treat/prevent CMV infections
  - Bone marrow suppression
- **Fluconazole**: Antifungal used to treat/prevent opportunistic fungal infections
  - Hepatotoxicity, drug interactions
- **Aspirin**: Antiplatelet agent used to prevent graft thrombosis
  - Bleeding, ulcers
- **Trimethoprim/sulfamethoxazole**: Antibiotic used to treat/prevent PCP
  - Bone marrow suppression, hepatotoxicity
- **Lamivudine**: Inhibit both types (1 and 2) of HIV reverse transcriptase and also reverse transcriptase of hepatitis B
  - No major side effects (extremely well tolerated)
Azathioprine

The antiproliferative agent azathioprine (Imuran) is a DNA synthesis inhibitor through its action as a purine analog. This drug is one of the oldest known immunosuppressive agents and acts by inhibiting the proliferation of leukocytes (as well as all fast-growing cells). Azathioprine was used in conjunction with steroids as the immunosuppressive regimen first used in kidney and liver transplantation. This dual therapy was the standard in antirejection therapy until the introduction of calcineurin inhibitors in the late 1970s. Azathioprine is also used in patients with certain autoimmune diseases.

Azathioprine is generally well tolerated, with its primary side effect being bone marrow suppression. These effects are reversible with lower doses or with stopping the medication. Many centers use either azathioprine or mycophenolate mofetil in LT patients to permit a lower dosing of the nephrotoxic calcineurin inhibitors.

Prednisone

Prednisone is a synthetic corticosteroid that results in a broad suppression of the immune response and is used in the treatment of a wide variety of disease processes. Prednisone has been an important component of immunosuppression in organ transplantation since its inception. Prednisone taken orally is converted in the liver to prednisolone, an active steroid. This drug suppresses the adrenal glands and results in a variety of side effects, including high blood glucose levels, weight gain, poor tissue healing, osteoporosis, glaucoma, and Cushing syndrome.

Induction Therapy

The use of induction therapy with antilymphocyte monoclonal or polyclonal antibody preparations is now a frequent practice at many LT centers. The most commonly used induction agents are rabbit antithymocyte globulin (rATG), alemtuzumab, basiliximab, and daclizumab. Modifications in the initiation of the immunosuppressive regimen, including induction therapy, have more recently translated into decreased episodes of acute cellular rejection in the immediate post-transplant period. This benefit, then, results in improved short-term patient and graft survival. Liver allografts do not routinely undergo human leukocyte antigen matching and may be transplanted into highly sensitized patients; thus, the initial induction may protect against early rejection or early antibody-mediated graft injury. An initial theory regarding immunosuppression induction was that this therapy would promote tolerance by providing a significant post-transplant window for the regrowth of the immune system. With the native immune system being depleted and, in essence, reset in the presence of the transplant graft, there was a hope for the development of tolerance with replenishment of immune cells. These induction agents have not produced tolerance to this point, but it is believed that they do permit a reduction in the required maintenance immunosuppression.

Rabbit Antithymocyte Globulin

The agent rATG (thymoglobulin) is prepared by immunizing rabbits with cells derived from fragments of the human thymus gland. Unlike monoclonal preparations directed against specific T-cell antigens, rATG is a polyclonal preparation containing antibodies to a variety of T- and B-cell antigens. Studies have shown that the human thymus, in addition to containing thymocytes that usually express T-cell antigens, also contains 5% to 10% plasma cells. Therefore, the rabbit inoculation results in a preparation that contains antibodies against plasma cell/B-cell antigens, as well as the expected T-cell antigens. In addition to T-cell and B-cell depletion, studies have shown a possible protective effect against reperfusion injury when rATG is administered before reperfusion of solid organs. Several mechanisms have been proposed to explain this finding, including a blockade of adhesion molecules and decreased cell surface expression of beta-integrins as well as endothelial inflammatory cells.

A primary benefit of rATG induction is effective early immunosuppression without renal toxicity. Targeting cell surface antigens using monoclonal and polyclonal antibodies represents an attractive therapy in the prevention of acute rejection after solid organ transplantation while minimizing initial high doses of tacrolimus (and its side effect of nephrotoxicity). Use of rATG to induce immunosuppression in other transplanted organs allows a delay in the introduction of calcineurin inhibitors, which may spare renal function in the immediate post-transplant period. Although tacrolimus therapy is initiated immediately after LT, rATG may provide adequate early immunosuppression in case of poor absorption of tacrolimus, or it allows a slower climb to the desired trough levels, thus minimizing nephrotoxicity. An important side effect of rATG is a significant septic-type reaction with administration of the agent; this reaction manifests as hypoxia and pulmonary edema, tachycardia, fever, and shaking chills. Early reports of rATG in clinical transplantation have included excellent patient and graft survival.

Alemtuzumab

Alemtuzumab (Campath-1H) is a recombinant DNA-derived humanized monoclonal antibody directed against CD52 that has increased in popularity as an induction agent in transplantation over the past decade. Administration of this antibody results in a large depletion of lymphocytes, as well as natural killer cells, monocytes, and thymocytes. This broad depletion of immune cells provides an opportunity to reset the immune system on exposure to the transplanted organ. However, alemtuzumab differs from rATG in that alemtuzumab does not appear to deplete plasma cells or memory lymphocytes. These cells are not depleted; therefore, it appears that there is a lower incidence of post-transplant infectious risk, because these immunocompetent cells remain active. Alemtuzumab has been associated with infusion-related events similar to those seen with rATG, which include instability of blood pressure, rigors, fever, hypoxia, and bronchospasm. Alemtuzumab has been used primarily for induction immunosuppression in intestinal transplantation, and experience in LT is limited.

Alemtuzumab is also known as Campath. This name is historical in that early mouse antibodies against human leukocytes were developed at Cambridge University in the pathology department. The initial mouse-derived agent (Campath-1) was not appropriate for human infusion because of the mouse component of the antibody. A portion of the antibody, specific to CD52, was engrafted on a human antibody (humanized) and became known as Campath-1H.

Daclizumab

Daclizumab (Zenapax) is a humanized monoclonal antibody with high affinity to the T-cell IL-2 receptor. Daclizumab binding is highly specific for an IL-2 receptor subunit that is expressed on activated lymphocytes but not seen on inactive lymphocytes. Therefore, this agent specifically inhibits IL-2–mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection. With saturation of the T-cell IL-2 receptors as well as prevention of T-cell activation and signaling, B-cell activation may also be impeded. Daclizumab has primarily been studied in kidney transplantation but is now being used more with other transplanted organs. Daclizumab is similar to basiliximab (Simulect) in that both agents are monoclonal antibodies against the IL-2 receptor of T cells. Both have been shown to be clinically effective immunosuppressive medications. Daclizumab has been described as an induction agent and may allow the delayed introduction of calcineurin inhibitors in the early post-transplant period.
Unlike rATG and alemtuzumab, administration-related reactions to daclizumab are infrequent and mild, although anaphylactic reaction has been reported.

Post-transplant Prophylaxis and Treatment of Infections

LT patients may require a plethora of additional medications immediately after transplantation, but many of these can be stopped with time. Trimethoprim/sulfamethoxazole (Bactrim, Septura) is a combination drug given to immunosuppressed patients for Pneumocystis carinii prophylaxis. Patients generally take this for a minimum of 1 year following transplantation but may take the drug indefinitely. Side effects of this medication include bone marrow suppression and hepatotoxicity. This medication is frequently stopped if liver function enzymes are elevated in a transplant patient to determine if there is some other etiology of the abnormality.

Ganciclovir (Cytovene), valganciclovir (Valcyte), and acyclovir (Zovirax) are given for CMV prophylaxis. The choice of antiviral agent depends on the patient's risk category for invasive CMV disease. The lowest-risk group is the donor CMV-negative and recipient CMV-negative group, and the highest-risk group is the donor CMV-positive and recipient CMV-negative group. These drugs can also result in bone marrow suppression, and severe thrombocytopenia often is a reason for stopping them.

Fluconazole (Diflucan) is used as antifungal prophylaxis for both topical and systemic disease. It is well known to be hepatotoxic, and if there is an unexpected elevation in the patient's liver function enzymes, the drug frequently must be stopped.

Lamivudine (Epivir) is used for the treatment of chronic hepatitis B and is also used in the prophylaxis of hepatitis B in patients who receive liver allografts from donors who have been exposed to HBV.

Aspirin is given to most transplant patients as an antiplatelet agent to prevent thrombosis of the transplanted graft.

Suggested Readings


Demetris AJ, Eghtesad B, Marcos A, et al. Recurrent hepatitis C in liver allografts from donors who have been exposed to HBV.


