Chapter 74

Anesthesia for Abdominal Organ Transplantation

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Key Points

- Survival after abdominal organ transplantation continues to improve.
- The imbalance between organ supply and demand is increasing.
- To increase the supply of organs, living donors and extended criteria deceased donors are being used more frequently.
- Knowledge of the pathophysiologic changes associated with end-stage disease is required to provide optimal care for patients undergoing transplant surgery.
- The kidney is the most frequently transplanted organ.
- Kidney transplant recipients are older and are more likely to have chronic illnesses than in the past.
- The perioperative and long-term risk of cardiovascular disease is increased in patients with end-stage renal disease.
- Maintenance of renal perfusion pressure in the perioperative period is critical for graft function.
- Liver transplant recipients are older in age and have more comorbidities than in the past.
- The Model for End-stage Liver Disease (MELD) score prioritizes candidates for organ allocation.
- The pathophysiologic changes associated with liver disease affect nearly every organ system.
- Intraoperative care requires preparation for massive transfusion, management of coagulation abnormalities, and hemodynamic instability.
- Pancreatic transplantation is definitive treatment for diabetes mellitus.
- Pancreatic transplants are performed simultaneously with kidney transplantation (SPK), after kidney transplantation (PAK), or alone (PTA).
- Patients who are younger than 50 years with diabetes and end-stage renal disease benefit from simultaneous kidney and pancreas transplantation.
- Frequent monitoring of blood glucose concentrations is required during the perioperative period.
- Diabetic patients are at significant risk for cardiovascular disease.

Abdominal Organ Transplantation

The success of transplantation over the past decade corresponds to improved survival for recipients. Three-year posttransplant recipient survival is 80% for livers and 90% for patients receiving kidneys (Fig. 74-1). Three-year survival for liver transplantation matches that of heart transplantation. Increasingly, indications for transplantation have broadened. Patients with conditions previously considered contraindications, such as advanced age and some types of cardiopulmonary disease, are no longer precluded from transplantation.

Among the various organs, the kidney is the most transplanted organ. In 2011, more than 17,000 kidney transplants were performed. In the same year, liver was the second most commonly transplanted organ, with more than 6300 transplants performed. The heart is third, with more than 2000 transplants.

As of mid-year 2011, there are over 275,000 patients living with functioning transplants in the United States.
This number has nearly doubled in the past 8 years. The majority of these patients are kidney recipients (180,000), followed by liver (62,000), heart (25,000) and lung (10,000) recipients. Thoracic organ transplantation is reviewed elsewhere (see Chapters 66 and 67). Approximately 1000 intestinal recipients are living with functioning grafts.

Despite these successes, the number of patients who could benefit from transplantation far exceeds those who receive an organ. The imbalance between supply and demand is highlighted by the size of the waitlists for each organ, which is approximately threefold the number of annual transplants for kidney (more than 54,000) and double the number of annual transplants (more than 12,000) for liver. In 2011, for every two patients who undergo liver transplantation, one patient dies on the liver waitlist. For every three patients who undergo kidney transplantation, one patient dies while waiting for a kidney.1

Solutions to organ shortage include living donor transplantation, which is used more commonly for kidney transplants (one third of kidney transplants in 2011) than liver transplantation (less than 5% of liver transplants in 2011). Other strategies include the use of extended criteria donors, which is discussed in detail elsewhere (see Chapter 75).

The evaluation of patients for transplantation varies among transplant centers, but the goals are similar. These include ascertaining that: (1) transplantation is indicated for the management of the prospective recipient, (2) comorbidities do not preclude transplantation, and (3) emotional and social resources permit a major surgery and its associated rehabilitation, including compliance with long-term immunosuppression therapy. The center’s transplant selection committee typically consists of physicians (nephrologist and hepatologist for kidney and liver transplantation, respectively), transplant surgeon, psychiatrist, dietitian, social worker, and additional consultants as indicated. Anesthesiologists consult for patients with high operative risk, such as pulmonary hypertension, coronary artery disease (CAD), or patients with prior anesthetic complications.

Reasons to deny transplantation vary among transplant centers. Critically ill patients receiving life support, vasopressors, or dialysis have decreased posttransplant survival.2 Additional comorbidities can exacerbate the risk to a level that may be unacceptable to some centers. Medical reasons include comorbidities such as significant CAD, moderate or severe pulmonary hypertension, metastatic disease, uncontrolled intracranial hypertension, and untreated sepsis. Psychosocial contraindications include alcohol or recreational drug use, and the lack of social support, which might preclude compliance with immunosuppression regimens, follow-up care, or both. Age alone is generally not a contraindication.

The success of organ transplantation relies heavily on a highly specialized team approach that includes the organ procurement organization, transplant coordinators, nurses, physicians, and allied health care providers. With the exception of kidney transplantation, most abdominal organ transplants are performed at tertiary medical centers with extensive resources available to support the program. Many of these centers have specialized anesthesia teams, particularly for liver transplantation.

This chapter reviews the anesthetic considerations for kidney, liver, pancreas, and intestinal transplantation in adults. The overall care of pediatric patients is described in Chapter 93. The management of heart and lung, but not renal, is described in Chapter 94. In Chapter 95, the intensive care clinical care is described in pediatric patients who are receiving a kidney transplant.

**KIDNEY TRANSPLANTATION**

The first kidney transplantations were performed in the 1950s; however, renal transplantation did not become widespread until the development of effective immunosuppression in the 1960s. Since then, kidney transplantation has become the most common organ transplant surgery performed. Kidney transplants have steadily increased over the past 40 years worldwide, with the growth of kidney transplant programs throughout Europe, North America, and Asia, as well as in many developing countries. There are differences in the distribution of living versus cadaveric donor organs between regions; many countries in Africa and Asia rely exclusively on living donation, whereas many countries in Europe perform mainly cadaveric renal transplants.3 During the past decade in the United States, there has been a steady increase in the number of patients on the kidney transplant waitlist (Fig. 74-2). The demographics of patients on the waitlist have changed; patients are older (more than half are older than age 50) and are more likely to have developed end-stage renal disease (ESRD) secondary to chronic hypertension and advanced diabetes. The incidence of chronic kidney disease (CKD) among individuals older than 65 years continues to increase in the United States (Fig. 74-3). Although it is not known how many patients with CKD progress to ESRD, the prevalence of ESRD in the United States has steadily increased over the past 30 years. At the end of 2009, nearly 900,000 people in the United States were being treated for ESRD.4 The waiting time for kidney transplantation has increased in the United States as well, reflecting that the need for organs outstrips

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**Figure 74-1.** Patient survival 1, 3, and 5 years after transplant, by organ. Data are for U.S. transplants performed during 1997 to 2004. (From http://optn.transplant.hrsa.gov/latestData/rptStrat.asp. Accessed December 2012)
the organ supply. Recent data showed that there were more than 80,000 patients on the waitlist in the United States (active and inactive), and approximately 16,000 kidney transplants were performed in 1 year. More than 5000 patients were removed from the waitlist in the same year because of death, whereas almost 2000 were removed after becoming too ill for transplantation. These national trends reflect a kidney transplant population that is older and more likely to suffer from chronic diseases, which has significant implications regarding perioperative risk during kidney transplant. Nevertheless, current 3-year posttransplant survival for adults is 96% for living donor transplants and 90% for deceased-donor transplants.

Paired kidney donations have increased from fewer than 100 per year in 2006 to more than 400 per year in 2011. Paired donation consists of two incompatible donor-recipient pairs exchanging kidneys to create two compatible pairs. With the development of donor chain transplants and establishment of a national system for paired donation, these techniques are expected to become more common.

**INDICATIONS FOR KIDNEY TRANSPLANTATION**

Kidney transplantation is indicated in patients with ESRD caused by any one of a variety of underlying conditions. Glomerular disease, congenital diseases, and polycystic kidney disease are common indications in younger patients. Nephropathies associated with hypertension and diabetes are now the most common indications for kidney transplantation in the United States. Renal graft failure is an increasingly common indication for transplantation in the United States as well.

**PATHOPHYSIOLOGY OF END-STAGE RENAL DISEASE**

End-stage renal disease refers to the final progression of CKD, when renal function is irreversibly impaired and the development of uremia is imminent. Essential functions of the kidney include regulation of the ionic composition of the plasma, maintenance of fluid volumes, elimination of nitrogenous wastes and drugs, synthesis of erythropoietin, and adjustment of plasma pH. Significant declines in glomerular filtration rate (GFR) and urine production occur when these critical functions are significantly damaged, resulting in the clinical manifestations of uremia. After the development of ESRD, renal replacement therapy is required. ESRD has an effect on nearly every organ system, and it has a major impact on patient mortality despite chronic therapy including hemodialysis.

ESRD results in abnormalities of fluid balance and electrolytes. With the onset of uremia and oliguria, expansion of the extracellular fluid volume ensues, presenting with edema, hypertension, and signs and symptoms of volume overload. Disorders of sodium, calcium, magnesium, and phosphate can result in chronic changes in bone metabolism, hyperparathyroidism, and vascular calcifications. The development of hyperkalemia, with its effects on the myocardium, is the most critical electrolyte abnormality. Failure of the renal elimination of organic acids results in the development of an anion-gap metabolic acidosis.

ESRD has a significant effect on the cardiovascular system. Cardiovascular disease is the most common cause of morbidity and mortality in patients with ESRD, accounting for 35% to 40% of all deaths in patients receiving hemodialysis. As GFR decreases, the risk of cardiac mortality increases. Following successful kidney transplantation, cardiovascular disease remains the most common cause of death. Kidney transplant recipients are at increased risk for the development of myocardial infarction (MI), congestive heart failure, and atrial fibrillation. ESRD increases the development of atherosclerosis and is a major risk factor for the development of ischemic vascular disease, which can affect the coronary, cerebrovascular, and peripheral vascular systems. The likelihood of CAD, which
can present as angina, MI, arrhythmia, or sudden cardiac death, is even greater in patients with ESRD, hypertension, and diabetes. Hypertension may be the etiology of ESRD in nearly 30% of patients, or conversely, hypertension may result from hyperreninemia, hypervolemia, and renal vasculature changes associated with ESRD. Concentric left ventricular hypertrophy and diastolic dysfunction occur in the early stages of CKD, and are the two most common echocardiographic abnormalities in patients with ESRD.14 Patients with ESRD are at particular risk for diastolic congestive heart failure, especially in the setting of excessive intravascular volume. Heart failure owing to dilated cardiomyopathy with decreased systolic function can occur in patients with ESRD as well. The cardiorenal syndrome is defined by an interconnection between the renal and cardiac systems, where the decline of one organ influences the decline of the other. There is evidence that correction of renal function by renal transplantation can improve systolic dysfunction and reverse left ventricular dilation and hypertension.15 A variety of arrhythmias can occur in ESRD because of progression of cardiac disease, myocardial ischemia, or electrolyte disturbances. Atrial fibrillation occurs in 13% to 27% of patients on hemodialysis, and it is associated with a significant risk of stroke.16 Pericardial disease is common in patients with uremia, manifesting as pericarditis or pericardial effusion.

Characteristic hematologic and hemostatic abnormalities occur with ESRD. Normochromic, normocytic anemia secondary to lack of erythropoietin is common and may be exacerbated by iron deficiency, chronic inflammation, and bone marrow fibrosis. Anemia decreases quality of life in ESRD and is associated with adverse cardiac outcomes. Erythropoiesis-stimulating drugs and iron are commonly prescribed for the treatment of uremic anemia, and hemoglobin levels of 11 to 12 g/dL are typically achieved17 (see Chapters 61 and 63). ESRD is associated with abnormal hemostasis because of a broad spectrum of platelet function abnormalities, including decreased platelet activity, aggregation, and adhesiveness. Production of von Willebrand factor and factor VIII is decreased. Historically, renal failure increases the likelihood of bleeding; however, ESRD is also associated with a hypercoagulable state owing to complex abnormalities involving increased coagulation and endothelial activation.18 These hematologic changes of hypercoagulability resolve in patients with ESRD after successful kidney transplantation.19

Gastrointestinal signs and symptoms including nausea, vomiting, abdominal pain, and abnormal gastric motility occur in ESRD patients. Using electrogastrography, impairments in gastric myoelectrical activity exist in patients with symptomatic ESRD as compared to patients with normal renal function.20 Patients with ESRD have delayed gastric emptying, regardless of the timing of their last oral intake. The presence of diabetes, obesity, or both can further impair gastric emptying.

Central nervous system and neuromuscular abnormalities can occur in ESRD secondary to uncleared nitrogenous molecules. These abnormalities can range from mild changes in memory or attention to signs and symptoms of neuromuscular irritability. Severe neurologic manifestations of uremia with asterixis, seizures, and decreased mental status are rare with regular dialysis. Autonomic and peripheral neuropathies can occur in patients with ESRD and are possibly reversible with kidney transplantation.

ANESTHESIA FOR KIDNEY TRANSPLANTATION: PREOPERATIVE EVALUATION

Before kidney transplantation, patients typically undergo a prolonged and intense pretransplant evaluation by a multidisciplinary transplant committee to determine their candidacy for transplantation. In general, the preoperative evaluation of patients for kidney transplant should focus on the multiorgan manifestations of ESRD, with the goals of risk stratification and optimization of the medical status of the patient before transplant (see Chapter 39). Cadaveric kidney transplantation is an urgent procedure, because harvested organs tolerate a finite duration of cold ischemia, usually less than 24 hours. Living donor kidney transplants are scheduled well in advance, allowing for a more thorough preoperative assessment before surgery.

Before surgery, patients receiving hemodialysis should be maintained on their regular dialysis schedules, whether hemodialysis or peritoneal dialysis. Ideally, dialysis should be performed before surgery, especially in patients with excessive intravascular volume or with documented hyperkalemia or acidosis. A comprehensive laboratory panel that includes electrolytes, complete blood count, and platelet count is appropriate before surgery. A type and screen or type and cross for packed red blood cells should be obtained (see Chapter 61). Although major blood loss during routine kidney transplantation is not common, the surgery involves major vascular structures with the potential for rapid bleeding. Documentation of an increased potassium level immediately before surgery, especially with electrocardiogram (ECG) changes consistent with hyperkalemia, should prompt consideration of immediate dialysis to correct potassium levels before surgery. Preoperative vital signs should be closely assessed, especially heart rate and arterial blood pressure trends in hospitalized patients. Preoperative intravascular volume status should be assessed. Comparing the patient’s current weight to their known euvolemic weight, or “dry weight,” may be helpful. Patients undergoing surgery immediately after dialysis may be significantly hypovolemic and prone to intraoperative hypotension. Orthostatic assessments and the presence of resting hypotension and increased heart rate may identify significant hypovolemia. Preoperative volume resuscitation with non–potassium-containing saline solutions or colloids can prevent hypotension on induction of anesthesia. Conversely, patients who have preoperative body weights heavier than their euvolemic weight may have an excessive intravascular volume, and they may be prone to congestive heart failure during kidney transplantation. A thorough cardiopulmonary examination is indicated in all patients, and findings of significant excessive intravascular volume may be an indication for immediate preoperative dialysis before surgery.

As discussed previously, the current demographic of kidney transplant patients has a frequent association with cardiac disease, which has a major effect on
posttransplant outcome. As a result, preoperative cardiac evaluation is of critical importance in this patient group (see Chapter 39). Compared with the routine preoperative evaluation of noncardiac surgery patients, which focuses on the perioperative period, the renal transplant patient should be assessed to consider both short- and long-term cardiac outcomes. The goal of the preoperative cardiac evaluation is ultimately to decrease the morbidity and mortality associated with cardiovascular disease in kidney transplant candidates. Although decisions regarding candidacy in high-risk patients are usually made well before surgery, the anesthesiologist should be involved in the routine cardiac risk assessment of the kidney transplant patient before surgery. The main focus of the preoperative cardiovascular assessment in kidney transplant patients is to identify occult ischemic heart disease in an asymptomatic patient.

The 2007 American College of Cardiology Foundation/American Heart Association (ACC/AHA) Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery suggests a preoperative algorithm designed to assist in the risk stratification of surgical patients. The algorithm identifies active cardiac conditions that are associated with major risk (unstable coronary syndromes, decompensated heart failure, significant arrhythmia, and severe valvular disease) and then stratifies patients based on functional capacity. No further testing is recommended when functional status is adequate (more than four metabolic equivalent tasks [METs]). If functional status is less than four METs, further ischemia testing is then determined by the type of surgery (low, intermediate, or high risk) and by the presence of further risk factors (history of ischemic heart disease, heart failure, diabetes, renal insufficiency, and cerebrovascular disease).21 Kidney transplantation is considered an intermediate-risk procedure in the ACC/AHA Guidelines. The utility of the 2007 ACC/AHA Guidelines to detect patients with ischemic heart disease has been called into question in the kidney transplant population.22 Silent myocardial ischemia can occur more frequently in patients with ESRD than in the general population, making the detection of unstable coronary syndromes more difficult. One study reported that chest pain presenting at the time of acute MI was less common in patients with ESRD requiring dialysis compared with patients not using dialysis (44% versus 68%).23 Decreased functional status might not be a specific or sensitive indicator of cardiovascular risk in kidney transplant candidates. One study of 204 kidney transplant candidates examined the effectiveness of various guidelines to detect asymptomatic CAD. Of the 204 patients, 178 underwent noninvasive ischemia testing; 17 patients with ischemia were identified. The authors determined that if the ACC/AHA guidelines had been strictly applied to this group of patients, only 39 of the 178 candidates would have undergone noninvasive testing, and only 4 of the 17 patients with ischemia would have been detected.24 Finally, renal insufficiency is itself a risk factor. The unique characteristics of ESRD patients, along with discrepancies among guidelines, has called into question the applicability of available recommendations regarding cardiac testing in the kidney transplant population.22

Noninvasive testing methods for CAD have been well studied in the kidney transplant population. In studies that compared either dobutamine stress echocardiography (DSE) or myocardial perfusion studies with angiography in patients with renal failure, both methods had decreased accuracy compared to their accuracy in nonrenal failure patients. DSE had sensitivities of 0.44 to 0.89 and specificities of 0.71 to 0.94. Myocardial perfusion studies had sensitivities of 0.29 to 0.92 and specificities of 0.67 to 0.89.22 Although noninvasive testing has variable sensitivity and specificity for CAD in transplant cohorts, abnormal noninvasive test results correlate with adverse cardiac events and mortality in patients with ESRD. A meta-analysis of studies using either DSE or myocardial perfusion studies in patients with ESRD demonstrated that patients with inducible ischemia or fixed defects had a significantly increased risk of cardiac death compared to patients with normal studies.22

Before 2010, several guidelines and consensus-based recommendations regarding preoperative cardiac risk assessment in kidney transplant candidates had been published. The risk assessment of asymptomatic kidney transplant candidates is of prime importance.26,27 Likewise, surveys of practice patterns in the United States demonstrate a spectrum of approaches for the screening of asymptomatic kidney transplant candidates.28,29 Although preoperative cardiac evaluation recommendations have not been standardized for kidney transplant candidates, a stepwise process including a comprehensive cardiovascular history and assessment of signs and symptoms of advanced cardiac disease, assessment of functional status, and identification of risk factors should be assessed.

A baseline ECG is an appropriate initial screening test in most kidney transplant patients, especially in patients older than 40 years. ECG abnormalities associated with cardiac disease are common in patients with ESRD. A preoperative ECG should be obtained in patients with known CAD, peripheral vascular disease, and cardiac symptoms.22 Noninvasive testing may be considered in asymptomatic patients with multiple risk factors for CAD. Using a revised list of risk factors, one study demonstrated an improvement in the sensitivity and specificity for the detection of occult CAD in transplant candidates compared to using the established ACC/AHA risk factors.24 Based on this study’s results, risk factors associated with an increased risk of CAD in renal transplant candidates include diabetes, history of cardiovascular disease, more than 1 year of dialysis, left ventricular hypertrophy, age older than 60 years old, smoking, hypertension, and dyslipidemia.22 Preoperative assessment of left and right ventricular function by echocardiography is an appropriate test in most kidney transplant candidates.22 The likelihood of structural cardiac abnormalities and the potential for left ventricular dysfunction in ESRD is significant, and transthoracic echocardiography provides detailed information regarding resting cardiac function and structure with few testing risks.

An increased prevalence of occult pulmonary hypertension occurs in patients with ESRD receiving dialysis. A 40% incidence of pulmonary hypertension existed in a series of 58 ESRD patients receiving chronic
hemodialysis. The mechanism involves both uremia-induced pulmonary vasoconstriction and increased cardiac output secondary to an arteriovenous fistula. Pulmonary hypertension may be reversible after kidney transplantation. The identification of pulmonary hypertension is important because its presence in patients with ESRD is associated with decreased survival. A screening ECG can identify patients with pulmonary hypertension (see Chapter 47). In addition, right heart catheterization is likely indicated in patients with evidence of significant pulmonary hypertension by echocardiography.

Patients with cardiac conditions may remain on transplant lists for a long duration (i.e., many months or even years) before undergoing transplantation. During this time, cardiac disease can progress. Although routine periodic noninvasive screening in asymptomatic patients awaiting transplant is not warranted, patients with known cardiac disease should undergo regular repeat cardiac assessments; however, the ideal frequency of assessments is not known.

A detailed list of the patient’s cardiovascular medications should be obtained, and the patient should be clearly advised which medications should be taken before surgery. In general, most patients with ESRD receive multiple medications for the chronic treatment of hypertension; however, the ideal combination of drugs is not clear. Strategies for the perioperative administration of antihypertensive blood pressure medications are important; however, the urgency of donor kidney transplantation often allows only the immediate preoperative administration of antihypertensive medications. Perioperative β-adrenergic blocker therapy apparently decreases the incidence of perioperative MI and mortality in high-risk and intermediate-risk surgical patients, but perioperative β-adrenergic blockade has not been effective in other studies with low-cardiac risk patients and with patients with diabetes. One study demonstrated that perioperative β-adrenergic blockade decreased short- and long-term mortality in renal failure patients undergoing vascular surgery. To clarify this issue, there are unfortunately no randomized, prospective trials that have investigated perioperative β-adrenergic blockade in kidney transplant patients. The ACC/AHA 2007 Guidelines recommend that patients previously receiving β-adrenergic blockers should continue to receive them. Based on recommendations for nontransplant surgical patients, perioperative β-adrenergic blockade may be initiated in renal transplant candidates with known CAD, with CAD risk factors (diabetes, heart failure, and atherosclerosis), and with myocardial ischemia that occurs during preoperative noninvasive stress testing.

In asymptomatic kidney transplant patients not previously receiving β-adrenergic blockers without two or more CAD risk factors, perioperative β-adrenergic blockade should not be initiated because of the risk of perioperative bradycardia and hypotension observed in nontransplant cohorts.

Patients with ESRD are at risk for atherosclerosis and may be receiving lipid-lowering medications at the time of surgery. Although there are no studies that definitively show that hyperlipidemia therapy improves outcomes in ESRD, lipid-lowering medications probably should be continued during the perioperative period in patients previously receiving them.

As mentioned previously, there is an increasing prevalence of diabetes in the kidney transplant population. There have been many studies assessing the risks and benefits of glycemic control with intravenous insulin therapy in surgical patients. A recent meta-analysis found that the use of perioperative insulin infusions is associated with episodes of hypoglycemia, although overall mortality may be reduced. A multinational randomized trial in intensive care unit (ICU) patients comparing “tight” glucose control with intensive insulin therapy (target glucose levels ranging 81 to 108 mg/dL) to conventional insulin therapy (target glucose levels < 180 mg/dL) demonstrated a more frequent 90-day mortality with tight glucose control. Perioperative glycemic therapy should be started in patients with diabetes who are undergoing kidney transplant, yet a benefit from strict blood glucose control in the kidney transplant population has not been demonstrated in the literature. On the morning of surgery, blood glucose levels should be measured, and insulin therapy may be initiated in patients before surgery for significant hyperglycemia, with appropriate serial blood glucose measurements during the perioperative period. As in all types of surgery, orally administered antihyperglycemic medications should be withheld on the morning of surgery in patients with non–insulin-dependent diabetes (see Chapter 39).

ANESTHESIA FOR KIDNEY TRANSPLANT: INTRAOPERATIVE MANAGEMENT

General anesthesia with endotracheal intubation is the preferred anesthetic method for kidney transplantation in most kidney transplant centers. The goals of anesthesia are to facilitate an adequate depth of anesthesia while maintaining hemodynamic stability and to provide appropriate muscle relaxation to facilitate surgical conditions. As mentioned previously, patients with ESRD are considered a risk for aspiration of gastric contents secondary to the presence of uremic gastropathy and other conditions, such as obesity (see Chapter 71) and diabetes. An oral nonparticulate antacid and intravenous administration of an H-2 blocker, such as ranitidine, probably should be given before induction of anesthesia. A rapid-sequence induction of anesthesia with continuous cricoid pressure is the preferred method of induction for general anesthesia. Succinylcholine can be used safely in standard doses in patients with ESRD when potassium levels are within normal limits (usually <5.5 mEq/L). Potassium transiently increases 0.5 to 1.0 mEq/L for 10 to 15 minutes before returning to baseline levels in patients with ESRD and those with normal renal function. A modified rapid sequence induction using rocuronium 0.8 to 1.2 mg/kg intravenously is an appropriate substitute for succinylcholine when hyperkalemia or other contraindications to succinylcholine exist. A meta-analysis of 26 studies that compared the intubation conditions produced by succinylcholine and rocuronium found that intubation conditions were clinically similar when propofol was used as the induction anesthetic. The hemodynamic response to laryngoscopy may be accelerated in patients with ESRD with underlying chronic hypertension. Tachycardia and hypertension can be attenuated with supplemental...
opioids, esmolol, lidocaine, or nitroglycerin titrated to effect. Following the stress of tracheal intubation kidney transplant patients may develop hypotension before surgical incision, especially in patients who have been rendered hypovolemic from recent dialysis or in patients receiving renin-angiotensin blocking drugs.

Intraoperative monitoring may be limited to standard noninvasive monitors in younger, healthier transplant recipients and in select living donor recipients. Intraarterial blood pressure monitoring can be beneficial, especially in patients with uncontrolled hypertension, CAD, or heart failure. Pulmonary artery catheter or transesophageal echocardiographic monitoring may be considered in patients with advanced CAD, left or right ventricular dysfunction, and pulmonary hypertension. Central venous pressure monitoring is a standard monitoring technique in some centers; however, central venous pressure is not a reliable monitor of fluid status or responsiveness. The insertion of a central line provides reliable venous access for intra-vascular fluid resuscitation and transfusion, and access for administration of immunosuppression drugs and vasoactive infusions. Large-bore venous access is necessary for appropriate intravascular volume administration in the perioperative period. Intravenous access can be challenging in some kidney transplant patients, because intravenous sites may be limited by the presence of an upper extremity arteriovenous fistula. Conversely, central venous access may be difficult to accomplish in patients with ESRD who have undergone multiple previous central venous dialysis catheter placements, especially if central venous thrombosis has been documented.

Maintenance of anesthesia is typically performed using a combination of intravenous and inhaled anesthetics. Volatile inhaled anesthetics are titrated to the level of surgical stimulation, which varies during the phases of the procedure. Desflurane and isoflurane are not associated with nephrotoxicity. Although sevoflurane has potential nephrotoxic effects from the metabolites compound A and fluoride ion, detrimental effects on renal function have not been demonstrated in patients with renal insufficiency (see Chapter 26). A study of 200 renal transplant recipients retrospectively compared outcomes in recipients that received anesthetics using sevoflurane versus isoflurane. There was no difference between patient groups in postoperative creatinine levels, the need for dialysis, or graft rejection up to 6 months after transplantation. Although large prospective studies are lacking in kidney transplant patients, the use of sevoflurane during kidney transplantation appears to be a reasonable anesthetic choice.

Analgesia during the intraoperative period can be provided with the synthetic opioids fentanyl, sufentanil, alfentanil, and remifentanil, because their pharmacokinetics and pharmacodynamics are not affected by renal insufficiency. Morphine, oxycodone, and meperidine should be used sparingly in patients with renal failure, because these drugs have active metabolites that accumulate in these patients (see Chapter 30).

Appropriate neuromuscular blockade during kidney transplantation is important for optimizing surgical conditions (see Chapters 34 and 35); however, recovery from neuromuscular blockade may be variable in patients with ESRD, regardless of the drug used. Both vecuronium and rocuronium have prolonged durations of action in renal failure patients, because their clearances rely both on renal and hepatic metabolism. Pancuronium is likely the muscle relaxant of choice in patients with ESRD, because it undergoes organ-independent clearance. Pancuronium is primarily eliminated by the kidneys, and probably should be avoided in patients with renal failure. For patients with ESRD who are undergoing kidney transplantation, judicious use of neuromuscular blocking drugs is a necessity. Titration to surgical conditions and close monitoring of the level of neuromuscular blockade are crucial (see Chapter 53).

The surgical procedure involves placement of the renal allograft in the left or right extraperitoneal fossa, although the right side is usually preferred (Fig. 74-4). A vertical curvilinear incision 20 to 25 cm long is typically made, extending from the pubis symphysis to above the anterior inferior iliac spine. The abdominal musculature is divided, and the peritoneum is entered and retracted. During the initial incision and dissection, surgical stimulation is increased and hemodynamic responses may be exaggerated in some patients. Adequate analgesia, depth of anesthesia, and muscle relaxation should be appropriately titrated to effect. The external iliac vein and artery are identified and mobilized. Occasionally, different vascular structures are chosen for the renal anastomoses. Heparin may be administered before clamping of the vessels. The external iliac vein is clamped first, and the renal vein anastomosis is performed. Next, the external iliac artery is clamped and the renal artery anastomosis is performed. During the anastomoses of the renal vessels, expansion of intravascular volume with normal saline should be initiated. Furosemide and mannitol are administered before reperfusion to stimulate diuresis. Mannitol, along with adequate intravascular volume resuscitation, decreases the likelihood of acute tubular necrosis in renal transplantation. Adequate intravascular volume expansion with crystalloid or colloids increases renal blood flow, which improves immediate graft function. At the time of removal of the vascular clamps, additional intravascular volume expansion may be required to stabilize hemodynamics. On rare occasions, removal of vascular clamps may be associated with acute bleeding requiring further resuscitation and transfusion. Hypotension following reperfusion will result in hypoperfusion of the graft. Hypotension may precipitate renal injury owing to ischemia and can contribute to vascular thrombosis of the graft. Appropriate decreases in the depth of volatile anesthetic and volume expansion will maintain adequate renal perfusion pressures in most patients. In the event of hypotension, adrenergic vasopressors are typically avoided because of renal vasoconstrictive effects. Hypotension unresponsive to volume expansion may require interventions to increase cardiac output, especially in high-risk patients. Invasive hemodynamic monitoring is invaluable in this situation. Dopamine is typically the first vasoactive infusion used in kidney transplant patients; however, this is controversial. In an
proven to prevent graft complications. After completion of the vascular anastomoses, the donor graft ureter is implanted into the recipient bladder. The bladder is filled with antibiotic saline irrigation solution by way of a three-way Foley catheter, allowing for implantation of the donor ureter. A temporary ureteral stent may be placed as well. After completion of the bladder anastomosis, the wound is closed in layers. Neuromuscular blockade should be maintained until the fascial layer has been closed to prevent straining or coughing that could potentially disrupt the graft position or vascular connections. During emergence, exaggerated hemodynamic responses are common, especially in patients with poorly controlled hypertension. Appropriate titration of short-acting drugs to attenuate these responses upon emergence is helpful, especially in patients at risk for CAD. Careful neuromuscular blockade monitoring and appropriate administration of reversal agents are central to avoiding postoperative pulmonary complications (see Chapters 34 and 35). Likewise, ESRD patients may demonstrate delayed emergence from anesthesia and have exaggerated responses to opioids and sedative-hypnotics. Exubation of the trachea should occur after the patient demonstrates the ability to protect the airway, because kidney transplant patients are still considered a risk for aspiration of gastric contents at the completion of surgery.

**Figure 74-4.** Renal transplantation. A, Renal artery anastomosis performed end-to-side to the external iliac artery. B, Renal vein anastomosis performed end-to-side to the external iliac vein. C, Ureteral anastomosis to the bladder mucosa. (From Hardy J: Hardy’s Textbook of Surgery, ed 2. Philadelphia, 1988, JB Lippincott.)

**Organ Matching and Allocation**

Organ matching for kidney transplantation involves several steps to determine compatibility between donor and recipient. Initially, matching of the major ABO blood group is determined for all donors and recipients. Before the transplant surgery, a crossmatch is performed by mixing recipient blood with donor blood cells. This crossmatch is performed to identify any recipient antibodies that are reactive against donor antigens. Histocompatibility matching is an important part of the matching process, in which the human lymphocyte antigen (HLA) profile of the recipient is determined and compared with the HLA.

ANESTHESIA FOR KIDNEY TRANSPLANT: POSTOPERATIVE MANAGEMENT

After extubation of the trachea, the kidney transplant recipient requires careful monitoring in the postanesthesia care unit. Close monitoring of urine output in the initial postoperative period is important. Acute decreases in urine output should initiate a rapid evaluation of the etiology and appropriate treatment. A pretransplant etiology should be treated with aggressive intravascular volume resuscitation. In some patients, additional invasive hemodynamic monitoring may be required. Postrenal etiologies owing to technical problems with the ureteral anastomosis may require early surgical re-exploration. Postoperative complications include vascular thromboses (1% to 2%), wound hematomas (1% to 2%), and infection. High-risk patients with advanced cardiac and pulmonary disease may require further postoperative monitoring in the intensive care setting. Variable rates of admission to ICUs have been reported by different centers, but in general, postoperative intensive care admissions for kidney transplant recipients are much less common than for liver and kidney-pancreas transplant recipients. One single-center study of 1015 consecutive kidney transplants over a 10-year period found an ICU admission rate of 6%. The mortality rate in patients that required intensive care admission may be more frequent (40%) than in other nontransplant ICU patients (20%). Most patients were admitted for sepsis and required ventilator support. Postoperative pain control is usually provided with synthetic opioid analgesics without active metabolites (see Chapter 98). Pain after kidney transplant is highly variable; in some patients, pain may be severe and challenging to treat effectively. Patient-controlled opioid analgesia is commonly initiated in the postanesthesia care unit. Regional anesthesia for kidney transplantation is controversial. One report demonstrated effective postoperative analgesia in kidney transplant recipients with epidural analgesia. However, the concern for uremic coagulopathy and the potential for hypotension with epidural analgesia has limited its use in kidney transplant recipients. One pilot study in kidney transplant recipients demonstrated that a supplemental transversus abdominis plane block before incision improved postoperative pain scores and decreased opioid requirements compared with control patients who received standard opioid therapy and acetaminophen.
profile of the donor. Organ rejection by the recipient’s immune system is mediated by the recognition of mismatched (non-self) HLAs located on the surface of donor cells. Many standard HLAs are compared between potential donors and recipients before transplantation. In general, survival rates are worse with HLA-mismatched grafts. Although better immunosuppression has improved the overall survival rates for kidney transplants during the past 3 decades, the graft loss rate for HLA-mismatched kidneys has remained twice as frequent as HLA-matched grafts.49 For all potential recipients awaiting a deceased donor, their HLA profile is compared to the donor profile, and an appropriate donor-recipient pairing is made based on the best match. For living donors, HLA matching is performed well in advance of the surgery.

Currently, deceased-donor kidneys in the United States, unlike other organs, are allocated primarily based upon the recipient’s accrued time on the waitlist. With improvements in immunosuppression, HLA matching is not as prominently weighted in the kidney allocation process as previously. Despite the increase in living donor transplants within the past 20 years, efforts have been made to revise the current deceased-donor kidney allocation system in the United States to allocate organs to the highest acuity patients, similar to liver graft allocation. Ideally, a new allocation system would decrease the number of recipient deaths before transplant while matching donor and recipient characteristics to maximize post-transplant recipient survival.

ANESTHESIA FOR PATIENTS AFTER KIDNEY TRANSPLANTATION

After successful kidney transplantation, most patients are classified as having National Kidney Foundation stage 2 or 3 CKD with usual GFRs more than 30 mL/min. GFR typically deteriorates by 1.4 to 2.4 mL/min/yr in renal transplant recipients.50 Posttransplant mortality increases as renal graft function deteriorates. Renal function is followed closely within the first few years after transplant to assess for rejection, which is identified by worsening organ function. In post-kidney transplant patients undergoing nontransplant surgery, renal function should be assessed before surgery. Most patients will be under the care of a nephrologist within the first years of a kidney transplant; assessment of the patient’s medical records or renal function tests should be obtained preoperatively. Rejection should be ruled out before nontransplant surgery, as surgery during an episode of rejection can increase morbidity.51 Cardiovascular disease is the most common cause of death in kidney transplant patients. As described previously, cardiovascular disease is involved in the pathogenesis of renal failure and is a consequence of kidney disease. Ischemic heart disease, cerebrovascular disease, and peripheral vascular disease significantly affect the survival of kidney transplant patients. Progression of preexisting CAD can occur in the posttransplant patient, as immunosuppression contributes to the development of de novo hyperlipidemia, hypertension, and diabetes. The incidences of hypertension (80%), hyperlipidemia (60% to 80%), and new-onset diabetes (25%) are increased in kidney transplant recipients.50 Obesity and the development of metabolic syndrome are common after kidney transplant (see Chapter 71). More than 60% of renal transplant patients received a diagnosis of metabolic syndrome within 6 years following kidney transplant in one study.52 Because long-term studies on cardiac outcomes following nontransplant surgery in kidney transplant recipients are lacking, specific recommendations for regular cardiovascular testing are lacking as well. For previous kidney transplant patients undergoing nontransplant surgery, the ACC/AHA guidelines for the preoperative evaluation for noncardiac surgery should be used to guide preoperative cardiovascular testing21 (see Chapter 38).

Other disease processes related to kidney disease and immunosuppression should be sought. Kidney transplant patients are at increased risk for posttransplant malignancies, anemia, and osteodystrophy. Infection is a constant concern in kidney transplant recipients, because they are at risk for both opportunistic and community-acquired infections. Cytomegalovirus (CMV) infection is the most common infection in kidney transplant patients, and it is rarely acquired by transfusion (see Chapter 61). CMV-negative blood should be used when transfusions are required in patients who are CMV negative.

Anesthesia for nontransplant surgery can be accomplished safely with general, regional, and local sedation techniques. Most anesthetic drugs are safe in post-transplant patients, assuming the presence of adequate hepatic and renal function.51 Although preoperative creatinine may be near normal in kidney transplant recipients, GFR in these patients is usually reduced, resulting in prolongation of the activity of drugs cleared by the kidneys. Obviously, drugs that cause nephrotoxicity should be avoided.

PANCREAS TRANSPLANTATION

Surgical treatment for diabetes includes pancreas transplant alone (PTA) and, in patients with diabetes and ESRD, pancreas after kidney transplant (PAK) and simultaneous pancreas-kidney transplant (SPK). Usually, whole pancreas is transplanted from deceased donors. Less commonly, the distal pancreas is transplanted from a living donor. In 2008, there were 432 pancreas transplants performed in the United States (223 PTAs and 209 PAKs), and 826 SPKs. The total number of pancreas transplants performed in the United States for all three groups has decreased annually over the past several years (Fig. 74-5). The reasons for this decline are not well understood.53 The 5-year patient survival for pancreas transplant is 90% for PTA, 86% for PAK, and 88% for SPK. The 5-year graft survival for pancreas transplant is 73% for SPK, 52% for PTA, and 55% for PAK.5

INDICATIONS FOR PANCREAS AND KIDNEY-PANCREAS TRANSPLANTATION

Pancreas transplantation provides patients with insulin-dependent diabetes mellitus a permanent source of endogenous insulin, thus restoring normoglycemia. SPK and PAK transplants are indicated in patients with diabetes
and ESRD who are deemed appropriate candidates for kidney transplantation or who have already undergone kidney transplantation. PTA is indicated in patients with diabetes without indications for kidney transplantation and who have a history of severe frequent metabolic complications, or who have a history of problems maintain- ing insulin therapy that result in intractable diabetic complications.54 Most patients who undergo pancreas transplant have type 1 diabetes mellitus. Rare indications for pancreas transplant include select cases of type 2 diabetes mellitus, chronic pancreatitis that has developed endocrine deficiency, cystic fibrosis with endocrine deficiency, and prior total pancreatectomy.

For patients with diabetes and ESRD, those younger than 50 years have better survival than older patients when undergoing pancreas transplantation at the time of kidney transplantation.55 The survival benefit in SPK may be due to long-term decreases in CAD complications.56 For patients with normal renal function who undergo PTA, long-term survival appears to be the same as in patients receiving chronic insulin therapy57; however, pancreas transplant has a favorable effect on the progression of retinopathy. The progression of retinopathy is decreased or reversed in a significant percentage of PTA patients compared to diabetic patients treated with conventional insulin therapy.58

**PATHOPHYSIOLOGY OF PANCREATIC INSUFFICIENCY**

Type 1 diabetes mellitus occurs secondary to destruction of pancreatic islet cells resulting in a permanent functional loss of the endogenous production of insulin, necessitating life-long exogenous insulin therapy. The underlying cause of type 1 diabetes mellitus remains unknown. Type 2 diabetes mellitus results from peripheral resistance to the effects of insulin. Both diseases produce chronic increases of blood glucose concentrations resulting in the multiorgan manifestations of diabetes.

The chronic complications of diabetes that have the greatest effect on patient morbidity and survival are those that affect the cardiovascular system. CAD, cerebrovascular disease, and peripheral vascular disease occur in patients with diabetes owing to acceleration of atherosclerosis. Both macrovascular and microvascular disease occurs. Patients with diabetes develop CAD earlier, are more likely to have atypical symptoms, and have a higher mortality rate from MI than nondiabetics.59 Peripheral and autonomic neuropathies develop in diabetes, resulting in gastroparesis, lower extremity paresthesia, ulcerations, orthostatic hypotension, and labile heart rate and arterial blood pressure. Patients with diabetes have a high cumulative prevalence of blindness (10%), renal failure (22%), lower extremity amputation (12%), MI (21%), and stroke (10%)60 (see Chapter 39).

Acute complications of type 1 diabetes mellitus typically involve conditions associated with severe hyperglycemia, such as diabetic ketoacidosis and hyperglycemic hyperosmolar nonketoetic coma. Hypoglycemia is a direct result of exogenous insulin administration. Patients with type 1 diabetes are prone to large fluctuations in blood glucose levels. Hypoglycemic episodes contribute to acute morbidity and mortality in diabetic patients.

**ANESTHESIA FOR PANCREAS TRANSPLANTATION: PREOPERATIVE EVALUATION**

The preoperative evaluation for the patient undergoing pancreas transplantation involves an assessment of all of the potential acute and chronic complications of type 1 diabetes. Pancreas transplant centers pursue a comprehensive, multi-disciplinary evaluation and selection process before listing candidates. This evaluation should address the organ systems most affected by long-standing diabetes, including the cardiovascular, renal, and neurologic systems. Assessment for the presence and severity of CAD should be undertaken in all candidates, including noninvasive ischemia testing, evaluation of ventricular function, and coronary angiography in select patients. Previously, patients considered for pancreas transplantation were younger than 40 years and had a lower risk for the cardiac and vascular sequelae of diabetes. Older patients are now considered for pancreas transplantation, but have a significantly higher risk for CAD and vascular disease.61 Strategies to reduce cardiac complications, such as maintenance of β-adrenergic blockade and continu- ation of drugs that decrease blood lipid concentrations during the perioperative period, should be applied when appropriate.61

In most cases, pancreas transplantation involves a deceased-donor organ with a 24-hour maximum cold ischemia time; therefore, pancreas transplantation is considered an urgent procedure. Preoperative evaluation by the anesthesiologist should focus on any acute changes in the patient’s medical status, especially those involving acute diabetic complications such as ketoacidosis and hypoglycemia. Blood glucose measurements should be assessed closely before surgery, and recent insulin administration should be noted. Evaluation of renal function in

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**Figure 74-5.** Pancreas transplant rates per 100 waitlist years. The pancreas transplantation rate is decreasing. PTA, Pancreas transplant alone; SPK, simultaneous pancreas-kidney transplant; PAK, pancreas transplant after kidney transplant. (OPTN & SRTR Annual Data Report 2011. U.S. Department of Health and Human Services Health Resources and Services Administration, p 7, Figure PA 1.4)
all candidates is important before surgery. Most patients with diabetes listed for pancreas transplant have ESRD as well and will undergo SPK. A full evaluation of electrolytes, including creatinine and potassium, should be obtained before surgery. Serial trends in heart rates and arterial blood pressures in hospitalized patients should be assessed, as most patients will have a history of hypertension requiring multiple medications, especially patients with renal failure. Preoperative assessment of intravascular volume status is especially important in patients with ESRD on hemodialysis (see Chapter 38). Finally, a directed physical examination focusing on the airway and cardiopulmonary system should be performed. The incidence of difficult tracheal intubations in patients with long-standing diabetes was thought to be more frequent because of anatomic changes of the upper airway; however, two recent reports did not concur. Nevertheless, attention to anatomic signs of a potentially difficult airway is important in patients with diabetes, especially those with cervical arthritis and significant obesity.

**ANESTHESIA FOR PANCREAS TRANSPLANTATION: INTRAOPERATIVE MANAGEMENT**

General anesthesia with endotracheal intubation is required for all types of pancreas transplantation. The surgical procedure is typically prolonged, and an adequate depth of anesthesia and muscle relaxation is required for optimal surgical conditions. Diabetic patients and those with ESRD have a high likelihood of gastropathy and may have an increased risk for aspiration of gastric contents. Administration of an oral nonparticulate antacid preoperatively should be considered. A rapid-sequence induction of anesthesia with continuous cricoid pressure is the safest approach to securing the airway. Patients with diabetes, ESRD, cardiovascular disease, and autonomic neuropathy may be prone to wide fluctuations in heart rate and arterial blood pressure. Vital signs should be closely monitored, and maintenance of hemodynamic stability should be a primary anesthetic goal, especially during and immediately following anesthetic induction. Invasive monitoring is standard for pancreas transplantation. Arterial monitoring allows for beat-to-beat arterial blood pressure measurements, as well as access for analysis of arterial blood gases and blood glucose monitoring. Central venous access may be indicated for central administration of vasoactive infusions and immunosuppression drugs. Central venous pressure monitoring is used in some centers; however, the usefulness of this practice has been questioned, as central venous pressure might not be a reliable indicator of intravascular fluid responsiveness.40 Arterial line placement before induction of anesthesia may be considered, especially in patients with severe hypertension or CAD. Anesthesia is typically maintained with a balanced technique using volatile anesthetics, opioids, and muscle relaxants. In patients with renal failure, medications should be chosen that are not dependent on the kidneys for elimination. All the caveats for the anesthetic management of patients undergoing kidney transplantation should be applied for patients undergoing SPK.

A midline surgical incision is made for both pancreas and kidney-pancreas transplant surgeries. Extensive retraction necessitates adequate muscle relaxation. Prolonged exposure of the abdominal viscera results in significant third-space losses; adequate volume expansion with crystalloid or colloids is often required. The pancreas graft is usually placed in the iliac fossa. The arterial vascular supply to the pancreas graft is usually provided by an anastomosis to the iliac artery. Venous drainage from the pancreas graft can be delivered to either the iliac vein or the native portal vein. Usually the venous outflow from the pancreas is delivered to the iliac vein, which is associated with a lower rate of venous thrombosis. Alternatively, venous outflow may be directed to the native portal vein, which is the physiologically normal pattern of pancreatic venous efflux. There appears to be no significant advantage to portal venous drainage over systemic venous drainage for pancreas transplantation.56

Pancreatic exocrine drainage can be delivered to either the bladder or the intestine (Fig. 74-6). Although enteric pancreatic drainage is physiologically normal, this method is associated with surgical complications that can result in graft dysfunction, thrombosis, and early rejection. Exocrine drainage to the bladder allows for measurement of urinary amylase levels, which can be used to diagnose early rejection episodes before blood glucose levels are affected. Exocrine bladder drainage is associated with urologic complications and metabolic acidosis. Currently, most pancreas transplants utilize enteric drainage as there is no difference in graft or patient survival compared to bladder drainage.64,65

Prior to completion of the vascular anastomoses during pancreas transplantation, blood glucose levels should be assessed at least hourly as levels frequently fluctuate in brittle diabetic patients. Blood glucose should be maintained at less than 200 mg/dL, using intravenous insulin and dextrose infusions if necessary. Sliding scale insulin infusion protocols may be applied. Dextrose prevents the development of ketoacidosis during the early stages of the procedure. Before unclamping of the vascular anastomoses, adequate volume resuscitation should be initiated. Adequate cardiac preload and normal arterial blood pressures should be the hemodynamic goals before unclamping.

After unclamping of the vascular connections, adequate perfusion pressure to the graft is critical. Hypotension should be corrected rapidly, and intravascular volume status should be optimized. If hypotension occurs because of myocardial dysfunction, intracardiac pressure monitoring or transthoracic echocardiography can assist in the diagnosis and may help to guide therapy. Blood transfusions, colloids, and vasoactive medications may be required for the treatment of hypotension after reperfusion of the pancreatic graft. Therapy should also be guided by frequent arterial blood gas analyses with assessment of electrolytes and hemoglobin.

One of the most important intraoperative care points for pancreas transplantation is the management of blood glucose following pancreas reperfusion. After unclamping, the pancreas may release insulin into the circulation within several minutes. Blood glucose should be measured approximately every 30 minutes for the remainder
of the procedure. After successful transplantation, insulin requirements rapidly decline, and patients may be at risk for hypoglycemia. Delayed graft function can be identified by the presence of hyperglycemia. In this event, insulin infusion should be titrated to maintain blood glucose levels less than 200 mg/dL.

ANESTHETIC MANAGEMENT OF PANCREAS TRANSPLANTATION: POSTOPERATIVE MANAGEMENT

After the completion of surgery, complete reversal of neuromuscular blockade, hemodynamic stability, normothermia, and the ability of the patient to protect the airway will facilitate tracheal extubation. Pancreas transplant patients should be monitored closely in the postanesthesia care unit and ICU. Regular blood glucose measurements should be continued in the postoperative period to avoid hypoglycemia. Electrolytes, complete blood count, and analysis of arterial blood gas should be obtained immediately postoperatively, because acid-base disturbances, anemia, and electrolyte imbalances are common. Euvolemia should be maintained. Depending on the patient’s age and underlying risk for CAD, serial troponins and ECG may be assessed for the presence of myocardial ischemia or infarction, because cardiac symptoms may be lacking in this population. Postoperative pain can be severe, given the extensive surgical wound and duration of surgery. Postoperative pain usually is managed with opioids in the perioperative period with transition to patient controlled analgesia in the early postoperative period (see Chapter 98). Epidural analgesia may be appropriate for pancreas transplant recipients, although the possibility of hypotension in the early postoperative period can be problematic.

For SPK, the usual postoperative strategies for kidney transplant patients including close monitoring of urine output should be applied.

Surgical complications occur in 7% to 9% of all pancreas transplants and usually require reoperation. Technical complications are associated with the potential for graft loss and patient morbidity.66 Graft thrombosis is the most important early complication and requires emergent surgical exploration. Intra-abdominal bleeding can occur secondary to coagulopathy induced by anticoagulation for the treatment of graft thrombosis. Late complications include bladder or enteric leaks, intra-abdominal sepsis, and rejection.

ORGAN MATCHING AND ALLOCATION

The organ matching process for pancreas transplantation is similar to that for kidney transplant organ matching. Blood group and HLA matching are initially performed to match the donor and recipient, followed by a cross-match at the time of surgery. There has been a trend over the past decade toward less stringent HLA matching for all forms of pancreas transplantation. Despite this trend, pancreas transplant graft survival rates continue to improve, likely because of enhancements in surgical techniques and immunosuppression.66,67

Most organs allocated for pancreas transplantation are for diabetic recipients younger than 40 years. However, over the past decade, the average transplant recipient’s age has become older because of the allocation of more organs for patients with type 2 diabetes.61 In the United States, pancreas allocation is regulated initially for local distribution, followed by regional and national distribution. Unlike kidney transplantation, technical complications are the most common cause of pancreas transplant...
grant failure. Donor risk factors that affect pancreas graft survival include donor age older than 45 years, donor body mass index (BMI) greater than 30 kg/m², and cerebrovascular or nontraumatic cause of death. These factors have a significant effect on donor organ selection.

ANESTHESIA FOR PATIENTS AFTER PANCREAS TRANSPLANTATION

After successful pancreas transplantation, long-term normoglycemia is expected. For patients with a history of previous pancreas transplant presenting for surgery, a comprehensive posttransplant history of any episodes of surgical complications and episodes of rejection should be obtained. Blood glucose concentrations should be measured on the day of surgery. A detailed history and review of medical records focusing on CAD, renal disease, and vascular disease is critical, because pancreas transplant patients have a high prevalence of these conditions. Furthermore, disease progression can occur despite successful pancreas transplantation. There are no studies of cardiac outcomes in pancreas recipients undergoing nontransplant surgery; therefore, a stepwise approach to the preoperative cardiac evaluation, guided by the 2007 ACC/AHA Guidelines, is a reasonable approach for pancreas recipients undergoing subsequent nontransplant surgery.21

LIVER TRANSPLANTATION

In 1963, shortly after the effectiveness of azathioprine and prednisone was established for renal transplantation, Dr. Thomas Starzl performed the first human liver transplant.69 The recipient, a 3-year-old child with biliary atresia, died in the operating room from massive hemorrhage caused by venous collaterals and uncontrollable coagulopathy. Four years later, Starzl performed the first successful transplant in an 18-month-old infant with hepatocellular carcinoma. The advent of cyclosporine in 1979, followed by the 1983 pronouncement of the National Institutes of Health Consensus Conference that liver transplantation was no longer experimental, ushered in the era of liver transplantation. Over the ensuing decades, liver transplantation centers were established around the world, and the field matured following continued improvements in surgical technique, immunosuppression, and the management of coagulopathy and infections.

The number of disciplines that have contributed to the advances in liver transplantation illustrates the team approach involved in the care of the liver transplant recipient. Hepatologists, surgeons, nephrologists, specialists in critical care medicine and infectious disease, anesthesiologists, pediatricians, radiologists, and pathologists have important roles. Key team members extend beyond physicians and include transplant coordinators, nurses, blood bank personnel, and procurement organizations.

Liver transplantation is unique among abdominal organ transplants in that a dedicated team is typically involved because of the unique challenges encountered during liver transplant surgery. The United Network of Organ Sharing (UNOS), which manages the U.S. organ transplant system under contract with the U.S. Department of Health and Human Services, recognizes the important role of anesthesiologists in the perioperative care of liver transplant candidates. In 2011, UNOS instituted a requirement that U.S. liver transplant programs designate a Director of Liver Transplant Anesthesia who meets qualifications based on experience and training. These qualifications parallel similar requirements for the transplant surgeon and physician (hepatologist). In addition, UNOS delineated the clinical responsibilities of the Director of Liver Transplant Anesthesia, which include preoperative assessment of transplant candidates, participation in candidate selection, intraoperative management, postoperative visits, and participation in mortality and morbidity conferences.70 Lastly, the director is expected to maintain current knowledge in the field of transplant anesthesia by participating in continuing medical education activities related to transplantation.

INDICATIONS FOR LIVER TRANSPLANTATION

Liver transplantation is the only definitive treatment for decompensated cirrhosis, unresectable primary hepatic malignancies, acute liver failure, and metabolic disease. Of these indications, decompensated cirrhosis accounted for 75% of adult liver transplants performed in the United States in 2011, followed by malignancy in 21%, acute liver failure in 4%, and metabolic disease in 2%.1

Cirrhosis is further categorized into hepatitis C viral disease (23% of the total transplants performed in 2011 in the United States), alcoholic liver disease (18%), cholestatic disease (9%), and a miscellaneous category (22%) that includes nonalcoholic steatohepatitis (NASH), autoimmune disease, and others (Fig. 74-7).

Advances in the treatment of chronic liver disease, particularly antiviral therapy and transjugular intrahepatic portosystemic shunt (TIPS) placement, have led to improvements in survival over the past decade.71 In selected patients with advanced cirrhosis and active
variceal bleeding, early placement of TIPS improved 1-year survival to 86% compared with 61% in a group randomized to similar therapy without early TIPS. However, when life-threatening complications of liver failure such as encephalopathy, ascites, gastrointestinal bleeding or uremia develop, survival is improved by liver transplantation (90% 1-year survival) compared with medical therapy (Table 74-1). Referral for liver transplantation is appropriate in the presence of an index complication of cirrhosis.

Chronic liver disease and cirrhosis is the fifth leading cause of death in the United States for individuals aged 45 to 64 years; it is surpassed only by cancer, heart disease, accidents (unintentional injury), and chronic respiratory diseases. Among all age groups, liver disease accounted for more than 33,000 deaths in 2011, making it the twelfth leading cause of death.

**TRENDS IN LIVER TRANSPLANTATION**

Over the past decade, the proportion of transplants performed for malignancy and cirrhosis owing to NASH is increasing. Malignancy accounted for just 4% of liver transplants in 2001, whereas it accounted for 21% in 2011. Currently NASH is the third most common indication for transplantation, and by 2025 it is expected to overtake cirrhosis owing to hepatitis C as the single most frequent indication for liver transplantation. The number of transplants performed for hepatitis C has decreased from 31% to 23% of liver transplants over the past decade (2001 to 2011).

The total number of liver transplants performed in the United States increased from 3900 in 1998 to 6000 in 2006. The number has since stabilized at approximately 6000 per year. European transplant centers perform a similar number of transplants per year (approximately 6000) for similar indications. During the past decade, the number of patients (adult and pediatric) living with hepatitis C who are waitlisted for organ allocation has increased by 50%, although fewer females undergo liver transplant compared to males, the gender gap is narrowing. Finally, the trend toward combined organ transplantation, particularly liver-kidney transplant, has continued and in 2011 represented approximately 7% of transplants.

The primary limitation to liver transplantation is the continuing organ shortage, which has resulted in the death of approximately 12% of waitlisted transplant candidates each year for the past decade. This number has plateaued, but the number of patients removed from the waitlist because they are too sick to undergo transplant has doubled over the past 3 years. Responses to these concerns have resulted in the use of expanded-criteria donors, including grafts donated after cardiac death, which increased from less than 2% of liver transplants in 2001 to 6% in 2011. Living donation has decreased over the past 10 years, particularly for adult recipients. In 2001, more than 400 living donor grafts were transplanted into adult recipients. In 2011, fewer than 200 adults received living donor grafts. This change highlights the concern over postoperative complications in living donors, particularly those providing a larger liver mass, as is the case with right lobe donation. Two living donor deaths were reported in 2010, further illustrating the risk to living donors.

The recurrence of hepatitis C after successful liver transplantation has been increasingly recognized as a challenge. Because hepatitis C is the most common indication for transplantation, recurrent infection and graft failure represents a formidable issue. The deleterious effects of immunosuppression on viral replication have led many centers to attempt to withdraw steroids in selected patients with viral infections.

The number of pediatric liver transplants in the United States has been stable at 500 to 600 per year over the past decade (2002 to 2011; see Chapter 93). During the same period, approximately 10% to 15% of pediatric recipients in the United States received grafts from living donors, down from 20% to 25% in the prior decade. The most common indication for transplant in pediatric recipients is cholestatic disease (47%), followed by malignancy (14%), metabolic disease (13%), and acute hepatic necrosis (11%). The European Liver Transplant Registry (ELTR) reports similar numbers of pediatric recipients, approximately 10% of the total number of liver recipients.

**PATHOPHYSIOLOGY OF END-STAGE LIVER DISEASE**

Cirrhosis is the end product of chronic parenchymal inflammation and necrosis, which results in fibrosis and disruption of hepatic architecture. Resistance to blood flow leads to portal hypertension and the formation of vascular shunts between portal and systemic veins.
When the pressure gradient between the portal and hepatic veins exceeds 10 to 12 mm Hg, portal hypertension is severe, and complications such as ascites, esophageal variceal bleeding, encephalopathy, and hepatorenal syndrome occur. Decompensated cirrhosis affects nearly every other organ system.80 The preoperative assessment of liver transplant candidates requires a knowledge of the pathophysiological changes associated with decompensated cirrhosis.

Cardiovascular Complications

Hyperdynamic circulation—characterized by a high cardiac output, low arterial blood pressure, and low systemic vascular resistance—is the hallmark of end-stage liver disease. Patients appear well perfused despite systolic arterial pressures less than 100 mm Hg. Pulmonary arterial pressures may be mildly elevated because of increased flow; however, the pulmonary vascular resistance (PVR) is usually within the normal range. These patients have an elevated intravascular volume that is sequestered into a dilated splanchnic vascular bed. The effective circulating volume is typically reduced.

Hyperdynamic circulation is the result of portal hypertension-induced production of vasodilators such as natriuretic peptides, vasoactive intestinal peptide, endothelin, glucagon, and particularly nitric oxide.81 Elevated production of nitric oxide has been observed to precede the formation of the hyperdynamic circulation in cirrhosis. The overproduction of vasodilators is responsible for reduced circulatory responsiveness to sympathetic stimulation.82 Clinically, this frequently results in a need for increased doses of vasopressors.

In addition, patients with cirrhosis can have other cardiac functional abnormalities that are not immediately apparent in the baseline state. These abnormalities define a condition termed cirrhotic cardiomyopathy and include systolic and diastolic dysfunction, cardiac resistance to β-adrenergic stimulation, and electrophysiologic abnormalities. Systolic incompetence is revealed by physiologic or pharmacologic stress and is manifested by an inability to increase cardiac output in response to exercise, and an inability to increase ejection fraction despite an increase in end-diastolic volume. The severity of cardiac dysfunction seems to be correlated directly with the severity of liver disease.83 Diastolic dysfunction has been described in patients with cirrhosis as well, on the basis of diagnostic echocardiographic findings of abnormalities in transmural flow during diastole. These abnormalities consist of a decrement or reversal of the E/A wave ratio and prolongation of E wave deceleration time, reflecting ventricular resistance to diastolic filling. Diastolic dysfunction manifests as sensitivity to changes in cardiac filling and results in vulnerability to heart failure.

Autonomic dysfunction is present in a significant proportion of cirrhotic patients. It presents as chronotropic and hemodynamic incompetence in response to hemodynamic challenges. Prolonged QTc interval is also observed in patients with cirrhosis, and care should be taken when treating these patients with drugs known to prolong the QT interval.84

Risk factors for CAD in patients with cirrhosis are similar to those of other patient populations: hypertension, dyslipidemia, age, gender, and obesity. However, NASH has been recognized as an increasingly important cause for transplantation and carries with it the risks of obesity, diabetes, and chronic inflammatory state. The optimal test for identifying cirrhotic patients with significant CAD is unclear. Because many of these patients cannot exercise, pharmacologic stress testing is most commonly used. Unfortunately, studies investigating the predictive value of noninvasive functional testing, particularly dobutamine stress echocardiography, have generally shown poor sensitivity and varying negative predictive value (75% to 89%).85 Thus, among liver transplantation candidates, consideration should be given to proceeding with coronary angiography if the patient is judged to have a high likelihood of CAD.86 For less complex surgeries, however, this may not be warranted. There is evidence that patients with treated CAD have posttransplant survival similar to patients without angiographic evidence of CAD.87

Pulmonary Complications

As many as 50% to 70% of patients with chronic liver disease complain of shortness of breath.88 The differential diagnosis includes ventilation-perfusion abnormalities associated with underlying obstructive airways disease, fluid retention, pleural effusion, and decreased lung capacities secondary to large volume ascites. Alpha-1 antitrypsin deficiency has both lung and liver manifestations, as does cystic fibrosis. In addition, there are two types of vascular abnormalities unique to the setting of portal hypertension, and they have significant morbidity and mortality. These abnormalities, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN), are unique entities that have discrete implications on liver transplant candidacy.

HPS is present in up to 20% of patients who present for liver transplantation.89 The diagnostic criteria for HPS include portal hypertension, PaO₂ less than 80 mm Hg on room air (or alveolar-arterial oxygen gradient greater than 15 mm Hg), and evidence of intrapulmonary vascular dilation (IPVD).90 Demonstration of IPVD can be made by contrast-enhanced echocardiography or by perfusion lung scanning using technetium-labeled macroaggregated albumin. In the absence of HPS, microbubbles and albumin macroaggregates injected into the venous circulation are trapped by the pulmonary capillary bed. The delayed (more than three cardiac cycles) appearance of microbubbles in the left atrium (on echocardiography) or increased (>5%) extrapulmonary uptake of technetium-labeled macroaggregated albumin suggests the presence of IPVD, which results in a massive increase in pulmonary capillary diameter, from between 8 to 15 μm to 50 to 500 μm. This increase, together with the usually hyperdynamic circulation of the cirrhotic patient, allows insufficient time for oxygen diffusion through the entire stream of capillary blood. As a result, the central stream of poorly oxygenated blood is functionally shunted. This lesion is typically correctable with the administration of oxygen. Because IPVDs predominate in the bases of the lungs, standing worsens hypoxemia compared with the supine position (orthodoxia).
The natural history of HPS is usually one of progressive hypoxemia. Liver transplantation can be expected to correct hypoxemia in greater than 85% of patients, although it may take up to 1 year to do so. In patients with HPS, survival with transplantation is considerably more frequent than without transplantation. Previously, PaO₂ ≤ 50 mm Hg was considered a predictor of increased mortality with or without transplantation. However, in the largest single-center series of liver transplantation for HPS, the overall 5-year survival was 76%, comparable to transplantation in patients without HPS. These findings suggest that timely transplantation in patients with HPS results in good outcomes. Accordingly, allocation exception points have been assigned to patients with HPS and room air PaO₂ ≤ 60 mm Hg.

PPHTN is defined as pulmonary hypertension in the presence of portal hypertension in a patient without other predisposing factors. The European Respiratory Society Task Force on Hepatopulmonary Disease diagnostic criteria are: (1) clinical evidence of portal hypertension with or without hepatic disease; (2) mean pulmonary artery pressure of 25 mm Hg at rest or 30 mm Hg during exercise; (3) mean pulmonary artery occlusion pressure less than 15 mm Hg or transpulmonary gradient (mean PA pressure minus wedge pressure) greater than 12 mm Hg; and (4) PVR greater than 240 dyn·s·cm⁻⁵ or 3 Wood Units. The requirement for calculation of the PVR is a reflection of the fact that many patients with cirrhosis have mildly elevated mean pulmonary artery pressure based simply on an elevated cardiac output (Table 74-2). Mild, moderate, and severe PPHTN are defined by mean PA pressure less than 35 mm Hg, 35 to 50 mm Hg, and greater than 50 mm Hg, respectively.

The prevalence of PPHTN is 2% in a population of patients with known portal hypertension, as compared with 0.13% in an unselected population. The prevalence is 4% to 6% among liver transplant candidates. The occurrence of PPHTN is unrelated to the severity of the underlying liver disease. Similar to HPS, the symptoms of PPHTN are nonspecific, commonly consisting of dyspnea, generalized weakness, and decreased exercise tolerance.

The single best screening study for PPHTN is two-dimensional transthoracic echocardiography, which estimates right ventricular systolic pressure using the velocity of the tricuspid regurgitant jet. In the absence of pulmonary valvular stenosis, right ventricular systolic pressure is a good estimate of pulmonary arterial systolic pressure. Transthoracic echocardiography screening has a sensitivity of 97% and a specificity of 77% in diagnosing moderate to severe PPHTN in patients undergoing pretransplantation workup. Right-sided cardiac catheterization is necessary, however, to confirm elevated pressures and to measure PVR.

Moderate and severe PPHTN are associated with increased mortality during liver transplantation. In a multicenter study of 36 patients with PPHTN who underwent liver transplantation, more than one third of the patients died during the hospitalization (within 3 weeks of surgery). Nonsurvivors (12 of 13 patients) had mean PA pressures greater than 35 mm Hg. In addition to elevated mortality, the effect of successful liver transplantation on the natural course of PPHTN is unpredictable. Some patients experience a resolution with transplant, some continue to require medical therapy, and in some cases PPHTN worsens. This suggests that patients with moderate or severe PPHTN should undergo treatment for PPHTN before liver transplantation.

Vasodilator therapy consists of prostanoids (epoprostenol), phosphodiesterase inhibitors (sildenafil), and endothelin antagonists (bosentan). Calcium channel blockers, often used in noncirrhotic patients with pulmonary hypertension, are contraindicated in patients with cirrhosis because the associated mesenteric vasodilation worsens portal hypertension. Patients who respond to treatment sufficiently to reduce their mean PA pressure below 35 mm Hg and PVR below 400 dyn·s·cm⁻⁵ should be considered suitable transplant candidates.

### Renal Dysfunction

Renal dysfunction in patients with cirrhosis is the result of renal hypoperfusion and avid retention of sodium. Hepatorenal syndrome (HRS) is a prerenal abnormality caused by circulatory derangements of advanced cirrhosis. It is considered a functional disorder, based on successful transplantation of kidneys from patients with HRS. Renal function is an important risk factor for mortality, a fact that is emphasized by its presence as one of only three variables used in calculating the Model for End-Stage Liver Disease (MELD) score.

In addition to HRS, patients with cirrhosis are also at risk for other causes of renal dysfunction, such as parenchymal renal disease, sepsis, nephrotoxicity, and hypovolemia. HRS is a diagnosis of exclusion, and other treatable causes must

| Table 74-2 | RIGHT HEART CATHETERIZATION DATA FROM FOUR REPRESENTATIVE PATIENTS WITH CIRRHOSIS AND SIMILAR ELEVATIONS IN MEAN PULMONARY ARTERY PRESSURE |
|---|---|---|---|---|---|
| Patient | Mean PA Pressure (mm Hg) | Pulmonary Capillary Wedge Pressure (mm Hg) | Cardiac Output (L/min) | Pulmonary Vascular Resistance (dynes·sec·cm⁻⁵) | Diagnosis |
| 1 | 35 | 10 | 5 | 400 | Primary pulmonary hypertension |
| 2 | 35 | 10 | 10 | 200 | Hyperdynamic circulation |
| 3 | 35 | 25 | 5 | 160 | Fluid overload |
| 4 | 35 | 25 | 10 | 80 | Fluid overload in a patient w/ hyperdynamic circulation |

PA, Pulmonary artery.

*Note that only the first patient has primary pulmonary hypertension, as evidenced by elevated pulmonary vascular resistance.*
be fourth of the cases of acute kidney injury in hospitalized cirrhotic patients. In patients with cirrhosis and ascites, the incidence of HRS is nearly 40% at 5 years.

HRS is caused by the local production of vasodilators, particularly nitric oxide, in patients with portal hypertension. Splanchnic vasodilation leads to a decrease in the effective circulating blood volume and a decrease in arterial blood pressure, which activates the sympathetic, renin-angiotensin-aldosterone, and vasopressin systems. The net result is a severe reduction in renal perfusion and glomerular filtration.

Type I HRS is characterized by rapidly progressive renal failure and a doubling of serum creatinine over 2 weeks after a precipitating cause such as spontaneous bacterial peritonitis, sepsis, gastrointestinal bleeding, or surgical stress. Patients with type I HRS have a median survival of 2 to 4 weeks without therapy. Patients with type II HRS have a median survival of about 6 months.

Although renal vasoconstriction is the proximate cause of HRS, therapy aimed at directly increasing renal perfusion by the use of prostaglandins, dopamine agonists, or endothelin antagonists has not proven to be successful. Vasoconstrictor therapy targeting the underlying splanchnic vasodilation is more effective.

These therapies include arginine vasopressin, somatostatin, and α-agonists such as norepinephrine and midodrine, combined with volume expansion. Terlipressin, the most studied vasopressor for HRS, is not available in the United States.

Placement of a TIPS lowers portal pressures and can decompress the splanchnic circulation. Pilot studies have shown that a TIPS is capable of reversing both types of HRS, but because of extensive exclusionary criteria in trials and the risk of worsening hepatic encephalopathy, a TIPS might not be suitable for all patients with HRS.

Liver transplantation is the definitive therapy for HRS. For patients with HRS who are transplant candidates, renal replacement therapy is the typical bridge to transplantation. Although renal recovery is anticipated, 35% of patients with pretransplant HRS will continue to require support in the immediate postoperative period, compared with 5% of patients without pretransplant HRS. During the First International Liver Transplantation Society Expert Panel Consensus on Renal Insufficiency in Liver Transplantation, it was recommended that patients who received dialysis at least twice weekly for more than 6 weeks before liver transplantation be considered for combined liver-kidney transplantation.

**Hepatic Encephalopathy**

Hepatic encephalopathy (HE) is a serious, albeit reversible neuropsychiatric complication that is a feature of both chronic and acute liver disease. Manifestations range from subtle, subclinical abnormalities to overt neurologic and behavioral derangements that are readily apparent at the bedside.

HE has been attributed to hyperammonemia, but the severity of HE does not necessarily correlate with ammonia levels. A number of other factors and mechanisms also contribute to HE, including other gut-derived neurotoxins, γ-aminobutyric acid (GABA) and other endogenous GABA-receptor agonists, oxidative stress, inflammatory mediators, hyponatremia, and abnormal serotonin and histamine neurotransmission.

The initial step in evaluating the patient with liver disease who presents with encephalopathy is to rule out causes other than HE. The differential diagnosis includes other metabolic causes such as uremia, sepsis, glucose and electrolyte abnormalities, and endocrinopathies. Structural and vascular central nervous system lesions or infections should also be considered. Because cirrhotic patients are exquisitely sensitive to sedative medications and have impaired hepatic (and often renal) metabolism, a careful search for possible drug-related encephalopathy should be undertaken. Once other potential causes have been eliminated, the next step should be a systematic search for an underlying cause or precipitating factor, such as infections (e.g., spontaneous bacterial peritonitis, sepsis) or gastrointestinal bleeding.

Therapy to reduce ammonia levels consists of the nonabsorbable disaccharide lactulose and nonabsorbable antibiotics such as neomycin, metronidazole, and rifaximin. Nonabsorbable antibiotics appear to be equally effective to nonabsorbable disaccharides, but concerns about toxicity associated with long-term administration limit their use.

**Ascites**

Ascites is the most common complication of cirrhosis leading to hospitalization. Patients have ascites should be referred for liver transplantation evaluation in the absence of contraindications. Nonhepatic causes account for 15% of ascites and include malignancy, cardiac failure, renal disease, pancreatitis, and tuberculosis. Paracentesis is an important aid in diagnosis. A serum-ascites albumin gradient greater than 1.1 mg/dL indicates portal hypertension with 97% accuracy. Rapid correction of hyponatremia is undesirable because patients with cirrhosis are at risk for central pontine myelinolysis, a potentially devastating neurologic complication. Observations in liver transplant recipients suggest limiting correction to less than 16 mEq/L during the intraoperative period.

Once ascites becomes refractory to maximum standard medical therapy, therapeutic options are limited and include serial paracentesis, liver transplantation, TIPS placement, and peritoneovenous shunt.

Risk factors for development of spontaneous bacterial peritonitis include a prior episode of this acute infection, gastrointestinal bleeding, and an ascites albumin level of less than 1.5 g/dL. Long-term antibiotic prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole is recommended for patients who have survived an episode of spontaneous bacterial peritonitis.

**Varices**

Cirrhosis increases portal pressure as a result of chronic inflammation. Fibrosis and regenerative nodules cause resistance to splanchnic flow and lead to formation of portosystemic collaterals. Progression of portal hypertension leads to increased local production of nitric oxide and exacerbates splanchnic vasodilation. Rupture of the
high-pressure collaterals that are formed is a highly lethal and feared complication of portal hypertension.

Portal hypertension is diagnosed by measurement of the wedged hepatic venous pressure (WHVP). Although this is not a direct measure of portal pressure, WHVP has been demonstrated to correlate well with it. This measurement is taken by advancing a catheter into a hepatic vein to the wedge position. To correct for the contribution of increased intra-abdominal pressure from ascites, a free hepatic venous pressure or an inferior vena cava (IVC) pressure should be subtracted from the measured WHVP to give the hepatic venous pressure gradient (HVPG). A normal HVPG is 3 to 5 mm Hg. Patients with varices have HVPGs of 10 to 12 mm Hg or greater.

Esophagogastroduodenoscopy is the gold-standard procedure for diagnosing varices. Risk for variceal bleeding correlates with size of varices, presence of red wale marks, and variceal pressure (i.e., HVPG). Therapeutic decisions are based on these observations and measurements. Nonselective β-adrenergic blockers reduce portal pressure by two mechanisms: a decrease in cardiac output (β1) and splanchnic vasoconstriction (β2). For patients who cannot tolerate β-adrenergic blockers or in whom they are contraindicated, another option for primary prophylaxis of variceal bleeding is endoscopic ligation. The TIPS procedure had been considered a backup procedure for variceal bleeding, but recently has been advocated for early treatment in select patients. However, TIPS is associated with a higher incidence of encephalopathy; despite this, TIPS may decrease mortality in select patients.

Acute variceal bleeding should be managed with a combination of intravascular volume resuscitation, correction of severe coagulopathy, pharmacologic manipulation of portal pressure, and endoscopic variceal ligation. Aggressive intravascular volume replacement can lead to resistant or recurrent bleeding because bleeding is a pressure-related phenomenon. Elective intubation of the trachea for airway protection is often warranted. Medications to reduce portal pressure include vasopressin and somatostatin. Although β-adrenergic blockers can reduce portal pressures, their effect on systemic pressures makes them undesirable in this setting. Early endoscopic variceal ligation in combination with pharmacotherapy is the preferred treatment for acute variceal bleeding. Balloon tamponade can be effective for resistant variceal bleeding, but is associated with significant complications, including esophageal rupture and aspiration. It is recommended as a bridge to more definitive therapy such as surgical shunt, TIPS, or liver transplantation.

**Hemostasis**

Hemostasis is a dynamic process that is the product of interaction between coagulation, platelets, and fibrinolysis, resulting in the formation and revision of clot (see Chapter 62). Liver disease affects all of these components, both quantitatively and qualitatively. The liver is the site of synthesis for all procoagulant and anticoagulant factors, with the exception of tissue thromboplastin (III), calcium (IV), and von Willebrand factor (VIII). It is also the site for clearance of activated factors.

Patients with cirrhosis are customarily considered to have a bleeding diathesis based on abnormal results in conventional tests of coagulation, such as prothrombin time (PT) and partial thromboplastin time (PTT). However, such tests reflect the activity of only a portion of the procoagulant factors, and do not consider the concomitant decrease in anticoagulant factors, which are not assessed. It is the balance of procoagulant and anticoagulant forces, not the isolated measurement of either portion of the coagulation system, that indicates the effective generation of thrombin. Not surprisingly, PT and PTT abnormalities correlate poorly with bleeding complications following invasive procedures, such as liver biopsy. There is evidence that decreased levels of protein C in cirrhotic patients balance the decreased levels of procoagulants, which can leave thrombin generation in vivo unaltered.

If procoagulants predominate because of disproportionate reductions of anticoagulants (protein S and C, antithrombin III), accompanied by an increase in procoagulants (FVIII), a hypercoagulable state results. This possibility is supported by studies reporting venous thromboembolism associated with cirrhotic and noncirrhotic liver disease.

Thrombocytopenia is a well-known feature of cirrhosis. The primary cause is splenic sequestration in the setting of portal hypertension. Elevated levels of von Willebrand factor compensate for decreased platelets counts, augmenting the platelet-endothelial cell interaction on vessel walls.

The fibrinolytic system in cirrhotic patients has many abnormalities, which may account for accelerated fibrinolysis. The liver is the site of tissue plasminogen activator clearance, and elevated tissue plasminogen activator levels have been noted in patients with cirrhosis. The liver is also the site of synthesis for plasmin inhibitors, such as plasmin activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI). A balance of factors that promote and inhibit fibrinolysis is desired. Commonly used studies for assessing the presence and severity of accelerated fibrinolysis include euglobulin clot lysis time and thromboelastography.

Disseminated intravascular coagulation (DIC) is primarily a thrombotic diathesis, followed by widespread secondary fibrinolyis. As factors are consumed, DIC becomes a bleeding diathesis of factor and platelet deficiency. Whether or not DIC is a feature of stable chronic liver disease is controversial. Standard laboratory tests cannot distinguish between consumption and decreased synthesis, and so have little utility. Instead, assays to assess for excessive thrombin production are used. These assays include the cleaved by-products of coagulation factor activation such as prothrombin fragment F1+2, fibrinopeptide A, and thrombin-antithrombin complexes. These assays suggest that overt DIC is not a feature of stable chronic liver disease; however, accelerated intravascular coagulation and fibrinolysis has been described, which is a low-grade consumptive process. Patients who exhibit accelerated intravascular coagulation and fibrinolysis are at increased risk of DIC in the presence of a known stimulus, such as sepsis or spontaneous bacterial peritonitis.
Surgical Procedure

Preoperative Considerations

In 2011, the median time to transplant in the United States was 12.6 months (interquartile range, 1.6 to 72 months). As a result, a transplant candidate can be months removed from their initial evaluation when a suitable donor graft is identified. Therefore, the prospective recipient’s evaluation should be reviewed while arrangements are made for donation. Candidates undergo an extensive preoperative assessment by multiple teams that typically include the surgical team, hepatologists, cardiologists, pulmonologists, psychiatrists, and social workers. In the event of unique comorbidities, additional consultants are involved as needed. Of particular interest to the anesthesiologist are interim changes in health status, hospitalizations (the possibility of infection should be considered with new-onset encephalopathy, variceal bleed, ascites, or hemodynamic deterioration), details of the initial and any subsequent cardiopulmonary evaluation (assess for the presence of coronary disease, heart failure, pulmonary hypertension, or arrhythmia), and renal status (acute kidney injury).

Patients predicted to have decreased survival 1-year after transplant represent a high-risk group and include patients undergoing retransplantation or those supported by mechanical ventilation, infusions of vasopressors, and renal replacement therapy (Fig. 74-8). Patients with oliguria, acidemia, or dependent on renal replacement therapy may benefit from intraoperative renal replacement therapy.

A protocol should be in place to notify the blood bank of the pending transplant, which results in the setup of red blood cells and plasma in a volume according to institutional protocol. If any delay is anticipated in the availability of blood products, for instance in the event of antibodies, the blood bank personnel should notify the transplant coordinator and anesthesiologist. In the presence of red cell antibodies, our institutional policy is to set up compatible red cells for the start and completion of the transplant, and to use compatibility-unknown red cells in the event of large transfusion requirements (see Chapter 61).

The surgical procedure is divided into three distinct stages. During the prehepatic or dissection stage, the liver is mobilized and vascular structures (suprahepatic and infraportal venae cavae, portal vein, and hepatic artery) are identified. The anhepatic phase begins with clamping of these vessels and hepatectomy of the native liver and continues during the implantation of graft. Reperfusion, usually via the portal vein, starts the nehepatic phase, which continues through completion of the remaining vascular anastomosis (usually the hepatic artery), anastomosis of the bile duct, hemostasis, and abdominal closure.

Intraoperative Management

Intraoperative personnel and monitoring vary among liver transplant services based on institutional practice, caseload, and resources. Most centers allocate two anesthesia providers to liver transplants; however, the qualifications of these providers vary. A typical arrangement in an academic setting consists of an attending anesthesiologist experienced in liver transplantation and a senior resident. In private practice settings, the second provider may be a second anesthesiologist, a certified nurse anesthetist, a licensed health care provider such as a perfusionist, or some combination of these.
Anesthesia typically begins with a rapid sequence induction because of the emergent nature of the surgery, preoperative administration of oral immunosuppressants/bowel decontamination antibiotics, and the presence of ascites. An arterial catheter is placed either before induction of anesthesia or, more commonly, immediately thereafter. Large-bore intravenous access is obtained. Either a triple-lumen 9-French introducer is placed centrally, or in the event of significant concern over blood loss (as is the case for retransplantation or in patients with extensive prior abdominal surgery) two double-lumen 9-French introducers are placed in a central vein. Sites designated for venovenous bypass are avoided, if possible. A pulmonary artery catheter is commonly used in adult patients; however, if the recipient has had a recent negative evaluation for pulmonary arterial hypertension, a pulmonary artery catheter may be avoided. Transesophageal echocardiography is increasingly used during the procedure. In a survey of high-volume liver transplant centers, more than 85% of respondent anesthesiologists (n = 217) reported using transesophageal echocardiography to some degree.132 Most performed a limited-scene examination, and only 12% were board certified in echocardiography. Transesophageal echocardiography appears to be associated with a low likelihood of hemorrhagic complications, even in the presence of esophageal varices.133 Some liver transplant centers avoid pulmonary artery catheter insertion in the event that transesophageal echocardiography is used, although a pulmonary artery catheter may be necessary when continuous intraoperative monitoring of pulmonary artery pressures is desired or for postoperative hemodynamic and fluid management in the ICU. New technologies, including arterial pressure waveform analysis and three-dimensional echocardiography, do not correlate with thermodilution-derived parameters and are not currently advocated for routine use intraoperatively.134,135

A rapid infusion system capable of high transfusion flow rates (>500 mL/min) is typically used. Such systems incorporate a reservoir, pump, filters, heat exchanger, and safety features designed to avoid and monitor for the presence of blood or air embolism, hypothermia, and line occlusion. Rapid infusion systems facilitate volume replacement and transfusion management.

The effects of the anesthetic technique on patient outcome are unknown. At the authors’ center, a balanced anesthetic is used; this typically consists of a volatile anesthetic in low to moderate concentrations (0.5 to 1.0 minimum alveolar concentration, [MAC]) to ensure unconsciousness, whereas an opioid, usually fentanyl, is chosen to blunt the sympathetic response to stimulation and to provide a smooth transition for postoperative analgesia. In recipients with fulminant hepatic failure and cerebral edema, volatile anesthetics are avoided or used cautiously in low concentrations, in many cases with intracranial pressure monitoring (see later). In either case, periods of hypotension during the surgery may require temporary discontinuation of the volatile anesthetic. Midazolam, with minimal hemodynamic effects, can be used for its amnestic effects during these hypotensive periods. Historically, the volatile anesthetic of choice has been isoflurane, which preserves splanchnic blood flow better than previously used volatile drugs.136 Studies in healthy humans have confirmed the vasodilator effects of isoflurane on the hepatic circulation, compared with the vasoconstrictor effects of halothane.137 This beneficial effect on hepatic oxygen supply can be advantageous to the newly reperfused graft. The effects of desflurane on hepatic blood flow have been evaluated with conflicting results. In animals, desflurane decreased total hepatic blood flow in a dose-dependent fashion at concentrations up to 1.0 MAC; however, in a human study that excluded patients with liver disease, liver blood flow was slightly more rapid with desflurane than with isoflurane, although this effect was not statistically significant.138 Another study compared the effects of sevoflurane and desflurane on hepatic blood flow and hepatocellular integrity in older patients139 (see Chapter 80). Both anesthetics resulted in decreases in gastric mucosal pH and increases in cytosolic liver enzymes. The authors conclude that hepatocyte function is well preserved (lidocaine metabolism to monoethylglycinexylidide was unaffected by either agent), but disturbances of hepatocellular integrity and gastric tonometry suggest that splanchnic perfusion and oxygen delivery to the liver are decreased. Whether the increased metabolism of sevoflurane (100-fold that of desflurane) is detrimental to the liver is unknown, but it seems unlikely that the metabolites of sevoflurane cause liver damage.140 Compound A, a breakdown product of sevoflurane found to be nephrotoxic in animals, has not been shown to cause renal toxicities in humans, even during low-flow sevoflurane administration141 (see Chapter 26).

Cisatracurium is an attractive choice for neuromuscular blockade in patients undergoing liver transplantation because of its organ-independent elimination and diminished histamine release142 (see Chapter 34). In patients with end-stage liver disease, the volume of distribution of cisatracurium is larger than that in healthy control patients. Hepatic clearance is also increased in patients with liver disease; this results in similar elimination half times and similar duration of action (time to 25% recovery). Other reports have suggested the use of rocuronium during liver transplantation, because the duration of the neuromuscular block appears to be a useful predictor of primary allograft function. All patients whose recovery time was longer than 150 minutes experienced primary graft dysfunction.143

Premephatic Stage

The preanhepatic stage begins with surgical incision and ends with vascular exclusion and heptectomy of the native liver. Using conventional caval interposition technique, vascular exclusion of the liver is accomplished by cross-clamping the portal vein, the suprahepatic IVC, the infrahepatic IVC, and the hepatic artery (Fig. 74-9). If a piggyback technique is used, the native retrohepatic IVC cava is preserved (Fig. 74-10).

The preanhepatic phase involves dissection and mobilization of the liver and identification of the porta hepatis. With abdominal incision and drainage of ascites, hypovolemia can occur. This should be treated in an anticipatory fashion with colloid-containing fluid to minimize changes in preload. In the presence of preexisting
coagulopathy, fresh frozen plasma is indicated soon after incision, although some authors have challenged the need for fresh frozen plasma during orthotopic liver transplantation (OLT). In Europe, prothrombin complex concentrates (PCCs), which contain vitamin K–dependent factors (II, VII, IX, and X), are increasingly used as an alternative to plasma transfusion to avoid the risk of transfusion-related acute lung injury and transfusion-associated circulatory overload (see Chapter 61). The so-called four-factor PCCs available in Europe contain therapeutic levels of factor VII in addition to Protein C and S, and differ from the three-factor PCCs available in the United States. The primary concern related to PCC administration is thromboembolic complications, which vary according to the patient’s underlying disease, dosing, and the constituents in each of the commercially available PCC products. Another product, recombinant activated factor VII, was evaluated during liver transplantation and was found to improve coagulation study results, but did not result in a decrease in transfusion requirements. Recombinant factor VIIa has been linked to an increased risk of arterial, but not venous, thromboembolic events. Thromboelastography or standard laboratory tests (prothrombin time, fibrinogen, and platelet count) are used to guide the correction of coagulopathy. Some authors disagree with the premise that coagulation monitoring is associated with blood product transfusion requirements during OLT. However, in coagulopathic cardiac surgery patients, therapy guided by point-of-care testing using thromboelastometry resulted in fewer transfusions of red blood cells and plasma and improved 6-month survival. Considerable institutional variation exists in transfusion practices for OLT, as do variations in patient acuity as evidenced by MELD scores. However, these differences in transfusion requirements might not be accounted for by variations in blood loss during the procedure. Fibrinolysis is unusual during the prehepatic phase of the surgery; therefore, cryoprecipitate administration is typically unnecessary. Hyponatremia should not be corrected rapidly. A perioperative increase of 21 to 32 mEq/L in the serum sodium level was associated with central pontine myelinolysis in one report, whereas an increase of less than 16 mEq/L was not. Citrate intoxication (ionized hypocalcemia resulting from the infusion of citrate-rich blood products in the absence
of hepatic function) is avoided by the administration of calcium chloride (see Chapter 61). Ionized hypomagnesemia also results from citrate infusion, but values of ionized magnesium gradually return to normal after graft reperfusion. The clinical significance of this remains speculative, but cardiovascular function may be affected. Aggressive treatment of hypokalemia is best avoided, particularly in preparation for reperfusion and the associated increase in serum potassium. Hyperkalemia should be avoided by the administration of diuretics and insulin accompanied by glucose or, in the event these are ineffective, by intraoperative dialysis. In the absence of insulin administration, supplemental glucose is usually not required except in pediatric patients or those with severe disease, such as fulminant hepatic failure. Hyperglycemia should be avoided, because glucose levels greater than 180 mg/dL are associated with an increase in surgical site infections in liver transplant recipients. Blood gases, electrolytes, glucose, ionized calcium, and hemoglobin levels should be assessed regularly, and as frequently as hourly in the event of massive blood loss or preexisting abnormalities. Point-of-care testing facilitates rapid turnaround times for laboratory values. Coagulation studies are typically assessed at the beginning of the surgery, after correction of specific deficiencies, after reperfusion, and in the presence of microvascular bleeding. The maintenance of urine output is desirable; however, the use of low-dose dopamine for this reason is unproven. Hypothermia should be avoided. Core temperature control can be aided with heated venovenous bypass during the anhepatic phase. Regardless of whether bypass is used, forced-air warming blankets should be positioned beneath the patient and over the lower and upper body (see Chapter 54). Bleeding during this phase of surgery is related to the degree of preexisting coagulopathy, the presence and severity of portal hypertension, and the duration and complexity of the surgical procedure, which is adversely affected by prior abdominal surgery and adhesions.

**Anhepatic Stage**

The anhepatic stage begins with the occlusion of vascular inflow to the liver, and it ends with graft reperfusion. Cross-clamping of the suprahepatic and infrahepatic IVC decreases venous return by as much as 50%. Venovenous bypass (VVB) diverts IVC and portal venous flow to the superior vena cava via the axillary vein, attenuates the decrease in preload, improves renal perfusion pressure, lessens splanchnic congestion, and can delay the development of metabolic acidosis. However, the use of VVB is not without risk. Air embolism, thromboembolism, and inadvertent decannulation can be fatal or result in significant morbidity. VVB is not uniformly used at all centers. A recent meta-analysis of three trials failed to reveal any difference in the incidence of renal failure or blood transfusion requirements between patients randomized to VVB compared with patients in whom the technique was not used. The use of the “piggyback” technique, with IVC preservation, decreases the need for VVB.

Hepatectomy is followed by hemostasis and vascular anastomoses of the suprahepatic and infrahepatic IVC and the portal vein. Despite the absence of hepatic clotting factor production during the anhepatic stage, blood loss is usually limited by vascular clamping of the inflow vessels to the liver. However, fibrinolysis may begin during this stage because of an absence of liver-produced plasminogen activator inhibitor, which results in the unopposed action of tissue plasminogen activator. The use of antifibrinolytics varies among centers (discussed later).

**Neohepatic Stage**

Reperfusion of the graft through the portal vein begins the neohepatic stage. Reperfusion is associated with abrupt increases in potassium and hydrogen ion concentrations, an increase in preload, and a decrease in systemic vascular resistance and blood pressure. Hypothermia, monitored through a centrally placed catheter, is a marker for the presence of graft outflow into the central circulation. Life-threatening hyperkalemia, clinically detectable by changes in the EKG, requires prompt treatment. Calcium chloride and sodium bicarbonate are the drugs of choice for the acute treatment of hyperkalemia. If time permits, albuterol and insulin are also effective. Intraoperative dialysis should be considered early in the procedure for patients with oliguria with elevated potassium levels.

The hallmark of the postreperfusion syndrome (PRS) is systemic hypotension and pulmonary hypertension occurring within the first 5 minutes after reperfusion of the graft. Approximately one in three patients undergoing OLT have profound hypotension after reperfusion. The cause is uncertain, but a number of factors have been implicated, such as hyperkalemia, acidosis, hypothermia, emboli (air or thrombotic), and vasoactive substances. Risk factors for hyperkalemia in the early postreperfusion period are elevated preanhepatic potassium levels and the use of donated-after-cardiac-death donor organs. A retrospective study of 321 patients identified suboptimal grafts (higher degree of steatosis) and graft cold ischemia time as risk factors for PRS. In this study all cases of PRS, defined as mean blood pressure less than 60 mm Hg, occurred in suboptimal donors with graft cold ischemia times longer than 6 hours. The authors defined suboptimal grafts as those from donors older than 50 years, those with a history of cardiac arrest, hypotension, need for high-dose inotropic drugs, ICU stay longer than 5 days, or elevated liver fat content. The PRS group had higher postreperfusion K+ levels (at 1 and 5 minutes), and lower postreperfusion temperature (at 1 minute) than in the group without PRS.

In addition, other critical events such as severe, acute bleeding resulting in hemodynamic compromise and necessitating massive transfusion can occur at any point during the surgery. Arrhythmias and intracardiac thromboembolism can also occur at any time intraoperatively, but are more likely after reperfusion. Hepatic arterial anastomosis and biliary reconstruction are generally performed after venous reperfusion, although in pediatric patients the arterial anastomosis may be completed before reperfusion. Signs of graft function that might be observed in the operating room and early postoperative period include decreased calcium requirements, improvement in acidosis, increased urine
output, a rise in core temperature, and bile output from the graft.\textsuperscript{71,173}

**Antifibrinolytics**

Fibrinolysis is most severe after reperfusion and is caused by abrupt increases in tissue plasminogen activator from graft endothelial cell release. Antifibrinolytic drugs and cryoprecipitate may be required. In studies before 1997, the benefits of antifibrinolytic drugs for OLT, typically defined as a decrease in blood loss or transfusion requirements, were not present in prospective, randomized, blinded studies. Nearly all these studies evaluated aprotinin. In contrast, tranexamic acid and e-aminocaproic acid have not been studied extensively. In 2001, a randomized, blinded study from the Mayo Clinic showed a decrease in erythrocyte requirements (median of 5 units versus 7 units) with aprotinin compared with placebo.\textsuperscript{174} The European Multicenter Study of Aprotinin in Liver Transplant (EMSALT) also showed a decrease in red blood cell usage with both large dose \(2 \times 10^6\) kallikrein inhibiting units [KIU] loading dose followed by \(1 \times 10^6\) KIU/h and regular dose \(2 \times 10^6\) KIU loading dose followed by \(0.5 \times 10^6\) KIU/h aprotinin compared with placebo (red blood cell requirements of 1500, 1750, and 2450 mL, respectively).\textsuperscript{175} The authors report no difference in the prevalence of thromboembolic events in the aprotinin groups compared with control group. It was noted that the three patients who developed hepatic artery thromboses were in the control group. These three events may have been related to surgical technical issues, whereas the thrombotic events in the aprotinin group (pulmonary emboli, right coronary occlusion) were less likely attributable to the surgery. It is unclear whether antifibrinolytic drugs increase the risk of thrombotic events.\textsuperscript{176} Fibrinolysis is an unpredictable event, and the risks of thrombosis are unknown. Aprotinin intensifies the likelihood of increases in creatinine levels in the first week after liver transplantation, but not with an increased need for renal replacement therapy.\textsuperscript{177} Aprotinin was withdrawn from world markets in 2008 because of higher mortality in patients who received aminocaproic acid during cardiac surgery.\textsuperscript{178}

**Postoperative Care**

The goals of the immediate postoperative period are to ensure a smooth transition from anesthesia and surgery (maintain hemodynamic stability, metabolic homeostasis, adequate analgesia), monitor graft function (transaminase levels, prothrombin time, bilirubin levels, bile and urine output, acid-base status), and maintain surveillance for known complications (bleeding, bile leaks, vascular thrombosis, primary nonfunction). The use of steroids leads to hyperglycemia, which can require insulin infusion. (See Chapters 95 and 102.)

The lack of bile output, accompanied by hemodynamic instability, suggests primary nonfunction of the graft, which may require urgent retransplantation. Conversely, a functioning liver graft facilitates early neurologic recovery, cardiovascular stability, and improved renal function, signs that can occur within hours of the completion of surgery.

Hepatic artery thrombosis can lead to graft necrosis, necessitating retransplantation. Within the first 2 to 3 postoperative days, markedly abnormal transaminase levels are common because of graft ischemia or injury during procurement, preservation, and reperfusion. After this period, hepatic enzyme and bilirubin levels that do not trend downward suggest the possibility of hepatic artery thrombosis, which should lead to prompt evaluation via Doppler ultrasonography.

Postoperative pain control is generally achieved with opioids, including patient-controlled analgesia (see Chapter 98). Analgesic requirements may be decreased compared with other major abdominal surgery.\textsuperscript{179,180} Epidural analgesia is contraindicated because of coagulopathy, which usually preexists, or develops during the perioperative period.

The timing of tracheal extubation and termination of postoperative mechanical ventilation is not clear.\textsuperscript{181,182} Early extubation of the trachea, including endotracheal tube removal in the operating room, is feasible in select patients. However, the benefits of immediate extubation appear limited to the potential of decreased resource utilization, which might not be fully realized in centers that direct posttransplant patients to ICUs regardless of their need for ventilatory support. As a result, many centers prefer to see clear signs of graft function before extubation.

**ACUTE LIVER FAILURE**

Acute liver failure (ALF; previously termed **fulminant hepatic failure**) is defined as the appearance of encephalopathy together with coagulopathy (international normalized ratio \(\geq 1.5\)) in a patient without previous liver disease who has an illness of less than 26 weeks in duration. ALF is a rare entity with an incidence of approximately 2000 cases per year in the United States. Drug-related toxicity, primarily acetaminophen, accounts for more than half of the cases of ALF in the United States. Other causes include idiopathic, acute viral hepatitis, autoimmune, and ischemic. In the United States, approximately 45% of patients recover spontaneously, 25% undergo liver transplantation, and 30% die.\textsuperscript{183} Etiology has a significant bearing on outcome; patients with acetaminophen toxicity, ischemic injury, or hepatitis A have the most favorable prognosis, whereas those with non-acetaminophen drug-induced liver injury, acute hepatitis B, Wilson’s disease, or autoimmune hepatitis have poor prognoses in the absence of transplantation.\textsuperscript{184} Evidence of portal hypertension and cirrhosis is absent because of the rapid progression of disease. Acute decompensation of chronic liver disease, termed **acute on chronic liver disease**, is a separate condition with different etiologies, therapy, and prognostic indicators.

Although various etiologies of ALF exist, there are manifestations that are common to all patients with massive hepatic necrosis. The most serious, and lethal, is acute cerebral edema and intracranial hypertension. Effects on other organ systems include coagulopathy, circulatory dysfunction and hypotension, acute kidney injury, and metabolic derangements.
General measures to reduce cerebral edema include maintaining the patient in a 30-degree, head-up position, and making sure the head is in neutral position so as not to impede venous return. Once a patient is intubated, muscle relaxants should be considered to minimize rises in intracranial pressure from coughing, bucking, and shivering. Mannitol can be used to induce an osmotic diuresis, but may have limited utility in the patient with compromised renal function. Another option may be hypertonic saline, ideally targeting a serum sodium of 145 to 155 mEq/L. Current recommendations are to maintain normocarbia and to reserve hyperventilation for response to acute rises in intracranial pressure. Barbiturates can be used to decrease cerebral metabolism; however, their use may be limited by hypotension.

Monitoring techniques for cerebral edema and intracranial hypertension are controversial (also see Chapter 70). Serial head computed tomography (CT) images are not sensitive indicators of intracranial hypertension. CT can, however, provide information on structural abnormalities such as intracranial hemorrhage. Although many centers place an intracranial pressure (ICP) monitor to guide therapy in patients with stage III-IV coma, there are no randomized controlled studies to support this practice. Furthermore, ICP monitor placement is not a benign procedure, frequently entailing aggressive correction of coagulopathy and transport to and from the operating room for a critically ill, fragile patient. Nonetheless, ICP monitors are invaluable for guiding acute therapy, and for helping to determine who might no longer be a viable candidate for transplantation. In addition to measuring ICP, these monitors allow calculation of cerebral perfusion pressure ([CPP] = mean arterial pressure [MAP] – intracranial pressure [ICP]), which should be kept between 50 and 80 mm Hg. In one case series, a sustained CPP less than 40 mm Hg for greater than 2 hours was associated with a poor neurologic outcome. An effective protocol for managing intracranial hypertension in patients with stage III or IV encephalopathy has been described and resulted in a 95% response to treatment in episodes of ICP greater than 20 mm Hg. Furthermore, in this prospective series, ICP was monitored in all patients, and no patients died of isolated cerebral edema. The authors used a protocol that included activated recombinant factor VII (rFVIIa) to correct coagulopathy before ICP placement. Significant bleeding complications from ICP monitoring were not encountered.185

The decision regarding which patients should receive a transplant, based on who might recover spontaneously or who is unlikely to benefit from transplantation, is one of the most difficult decisions encountered during the management of patients with liver disease. The two most widely used prognostic models are the Clichy or Paul Brousse Hospital criteria and the King’s College Hospital criteria. The Clichy criteria recommend transplantation for patients in stage III or IV coma, based on age and factor V levels.186 There is no distinction made for etiology of ALF, which is considered a weakness of these criteria. The King’s College Hospital criteria are superior for predicting outcomes in patients with ALF based on acetaminophen toxicity. However, the negative predictive value is less than 50% in patients who have not used acetaminophen.187 Thus, patients who fail to fulfill these criteria include a number of patients who will die without proper consideration for transplantation.

In patients with ALF who are undergoing an invasive procedure, correction of thrombocytopenia to 50,000 platelets/mm$^3$ or greater and international normalized ratio (INR) to 1.5 or less is suggested.184,188 Treatment thresholds are less clear for patients who are not bleeding, but prophylactic therapy is advised for severe abnormalities (e.g., platelet count \( \leq 10,000/mm^3 \), INR > 7, and fibrinogen < 100 mg/dL).184 Use of rFVIIa is reserved for rapid correction in patients who cannot tolerate a large volume of plasma. This agent may carry a thrombotic risk and is contraindicated in hypercoagulable conditions, which include pregnancy and Budd-Chiari syndrome. Hypotensive patients with ALF should undergo intravascular volume status and cardiac function assessment before consideration of inotropes or vasopressors. Vasopressors can be used to treat either systemic hypotension or to maintain an adequate CPP. Based on recommendations for septic patients, norepinephrine should be used. The use of vasopressin is controversial because there is evidence that its use is associated with increases in ICP.189 However, another study in which terlipressin was used did not reveal similar increases in ICP.190

**LIVING DONOR LIVER TRANSPLANTATION**

See Chapter 75.

**PEDIATRIC LIVER TRANSPLANTATION**

See Chapters 94 and 95.

**ORGAN MATCHING AND ALLOCATION**

The primary criteria used to match donor liver grafts with recipients are ABO blood type and graft size. ABO-incompatible transplantation (ILT) is generally limited to emergent situations, and as many as half of the adult recipients in early reports required retransplantation. Subsequent reports have identified patient populations with more favorable outcomes after ILT. Recipients with blood type O and pediatric patients tolerate ILT better than others.191 Nonetheless, ILT remains a technique reserved for emergent situations.

In the United States, a national registry maintained by UNOS allocates organs to transplant candidates. In Europe, organs are allocated to transplant centers that subsequently identify the most suitable candidate from their waitlist. UNOS considers only disease severity, and no longer uses waiting time, when allocating deceased-donor liver grafts. Older systems used the Child-Turcotte-Pugh (CTP) score to determine disease severity (Table 74-3). Beginning in 2002, the MELD score replaced the CTP score. The MELD score is a mathematical formula that incorporates the serum bilirubin, creatinine level, and INR. It is considered more objective because there is no reliance on subjective physical examination to determine the presence and severity of findings, such as ascites or encephalopathy. The MELD score is a continuous scale,
UNOS policy grants exception points to patients with HPS before manifesting changes in the MELD score.\textsuperscript{193} Waitlisted patients with HPS also receive fewer points than those without HCC; therefore, additional adjustments may be needed. Patients with HCC appear to be advantaged compared with those without HCC; therefore, additional adjustments may be needed.\textsuperscript{193}

Waitlisted patients with HPS also receive exception points. UNOS policy does not specify the number of points allocated, but instead indicates that the exception should provide a chance of transplantation within 3 months. Evidence suggests that as a group, patients with HPS may have accrued a survival advantage compared with nonexception status candidates as a result of this policy; however, more analysis is needed before modifications are made.\textsuperscript{194}

Most liver transplant candidates have MELD scores less than 25; only 2% of the waitlist has a MELD score greater than 25.\textsuperscript{1} Candidates with MELD scores less than 15 have better survival without transplantation.\textsuperscript{195} However, when the qualities of the donor graft are taken into account using the donor risk index, candidates with MELD scores of 12 to 14 benefit from liver transplant in the event that a favorable (low donor risk index) graft is transplanted.\textsuperscript{196}

### ANESTHESIA FOR PATIENTS AFTER LIVER TRANSPLANTATION

Liver transplant recipients with functioning grafts typically metabolize drugs in a normal fashion, but graft function must be assessed rather than assumed. The prothrombin time (or INR) is an excellent marker of synthetic function. In patients with grafts with impaired synthetic function, clotting abnormalities can be corrected with vitamin K or fresh frozen plasma; ascites managed with diuretics, albumin administration, or paracentesis; and the risk of encephalopathy minimized with lactulose administration and careful use of sedatives.

Careful adherence to sterile technique is required to prevent infectious complications in this immunosuppressed population. A stress dose of corticosteroids is required for patients receiving chronic supplementation. Renal function should be assessed and managed carefully to avoid an exacerbation of immunosuppressant-associated renal impairment. Hypertension is a common finding in patients whose condition is managed with calcineurin inhibitors such as cyclosporine. Drugs known to decrease hepatic blood flow, such as propranolol, should be avoided. Regional anesthesia is an option in patients with acceptable clotting status.

### INTESTINAL TRANSPLANTATION

Intestinal transplantation is indicated in patients with irreversible intestinal failure and an inability to continue total parenteral nutrition.\textsuperscript{197} Impending liver failure, lack of central vein access, frequent line infections or recurrent episodes of dehydration despite intravenous fluid supplementation can lead to intolerance to total parenteral nutrition. Intestinal failure is the inability to maintain adequate nutrition via the alimentary tract, commonly because of surgical removal or congenital absence of more than 70% of the small bowel (short-gut syndrome).

Approximately 130 intestinal transplants were performed in the United States in 2011.\textsuperscript{1} The number of small bowel transplant candidates has declined since 2006, most likely because of improved medical management. In 2011, nearly 60% of waitlisted candidates were younger than 18 years (>40% were younger than 5 years). Almost half of intestinal grafts were transplanted with another organ in 2011; the remainder were transplanted as isolated intestinal transplants (Fig. 74-12). In the past, the most common accompanying organ was the liver; in 2011, it was the pancreas. The median time to transplant...
in 2011 was 15 months for patients younger than 18 years of age, and 3 months for those aged 18 years or older. Patient survival after intestinal transplantation is improving. One-year survival is approximately 80%, and 5-year survival approaches 50%.

Intestinal transplant candidates should undergo an age-appropriate cardiovascular evaluation, with particular attention to vascular access. Because of the need for chronic indwelling vascular access, thrombosis and obstruction of central veins is common (vanishing vein syndrome) in patients presenting for intestinal transplantation. Doppler ultrasonography, contrast venography or magnetic resonance angiography, or all three, are indicated before surgery.198

Intraoperative blood loss varies based on whether other organs are transplanted simultaneously and on the extent of abdominal adhesions present from prior surgeries. Rapid infusion devices should be available. Patients are frequently hypercoagulable; care should be taken to avoid therapies that can increase the risk of thromboembolism.

Repeat hospitalization is common after transplantation, occurring in 85% by 6 months after transplant and in nearly all recipients by 4 years. Infection is responsible for 50% of mortality.199 Other complications include acute rejection (fever, bloody stools), chronic rejection, graft-versus-host disease in 6%, and lymphoproliferative disease in 7% to 8%.200

**MULTIVISCERAL TRANSPLANTATION**

Multivisceral transplant includes the small intestine, stomach, liver, spleen, and the duodeno-pancreatic complex. Modified multivisceral transplant includes the visceral organs without the liver.200 The indications for multivisceral transplant have been widened because of
the technically advantageous nature of the procedure, which involves a decreased number of anastomoses compared to combined liver-intestinal transplant. This is particularly favorable for infants. When the liver is included, the risk of stenosis or thrombosis of the portal anastomosis is avoided.201

**POSTABDOMINAL TRANSPLANTATION COMPLICATIONS**

**Surgical Complications**

Early postoperative surgical complications include postoperative bleeding, drainage leaks (bile, urine, pancreatic secretions), and vascular thrombosis. The risk of bleeding and thrombosis is lessened when a balance is maintained between procoagulants and anticoagulants (protein S and C, antithrombin). Because standard laboratory tests monitor only coagulation, this balance may be difficult to assess in the absence of viscoelastic tests, which evaluate whole blood cloting.

Complications vary based on donor graft qualities and recipient characteristics. For instance, hepatic artery thrombosis is more common in pediatric recipients because of the small caliber of the vessel, and bile leaks are more common after liver transplantation using grafts from cardiac death donors (see Chapter 75).202

**Infection**

After the immediate postoperative period, infection is the primary cause of death. Immunosuppressive medications, used to prevent rejection, are largely responsible for this risk. Bacterial infections predominate during the early postoperative period. Surgical site infections, intra-abdominal abscesses, and infected hematomas are common. In this immunosuppressed population, multi-drug-resistant organisms are common. In liver transplant recipients, bacterial translocation or bile leaks can result in peritonitis, cholangitis, and perihepatic abscesses. In a recent study of liver transplant recipients, 47% of ICU patients had bloodstream infections, 35% had intra-abdominal abscesses, and 17% had ventilator-associated pneumonia.203 Prompt diagnosis and treatment with minimally invasive drainage techniques should be considered over early laparotomy. When this approach fails, laparotomy is indicated.

Prolonged endotracheal intubation and indwelling central venous and urinary catheters are a common source of infection. These devices should be removed as early as possible in the postoperative period. In the meantime, strict aseptic technique is required when accessing indwelling catheters and tubes.

Comorbidities, such as diabetes and renal dysfunction, can increase the risk of infection. Viral and fungal infections are more likely after the first postoperative week. Risk factors for fungal infection in liver transplant patients include preexisting viral hepatitis, diabetes mellitus, multiple organ system failure, prolonged parenteral nutrition, long-term mechanical ventilation, and increased antibiotic use.204 Common sites of fungal infection include oral, esophageal, pulmonary, and intracerebral. Invasive fungal infections, despite prolonged treatment with amphotericin or itraconazole, are associated with a poor prognosis.

**Immunosuppression**

Acute rejection is an important cause of graft dysfunction at 1 week and beyond, occurring in as many as one quarter of liver recipients.205 The goals of immunosuppression are to prevent graft loss and to avoid the adverse consequences of antirejection regimens.205 Immunosuppression for solid organ transplant is divided into initial (induction) and maintenance phases. Calcineurin inhibitors cyclosporine and tacrolimus (formerly FK506) are the foundation for the majority of induction and maintenance regimens. Both agents inhibit transcription of interleukin (IL)-2 and other cytokines, primarily in helper T lymphocytes. Both manifest renal toxicity, which is caused by afferent arteriolar vasoconstriction and a reduction in GFR. The resulting azotemia is reversible with a reduction of dosage. Hypertension is due to vasoconstriction and sodium retention, and typically appears within the first weeks of treatment. Neurologic toxicity includes tremors, headaches, seizures, and even focal neurologic abnormalities. Mycophenolate mofetil therapy is a beneficial adjunct by allowing a reduction in the doses of calcineurin inhibitors.

In addition to tacrolimus, the most widely used drug, there are many other drugs available.206 Sirolimus, an inhibitor of the protein mTOR, is used for calcineurin-sparing effects and in patients transplanted for hepatocellular carcinoma to reduce recurrence.207 Basiliximab, a monoclonal antibody to CD25, has been used as an alternative to steroids for the induction of immunosuppression in liver transplantation.208

New immunosuppressive drugs are typically introduced for use in renal transplantation before they are applied in liver transplantation. Of note, recipients of liver grafts require less immunosuppression than do recipients of other organs, and liver grafts confer protection on other organs transplanted from the same donor. This effect is an example of the privileged immune status of the liver.205

The diagnosis of rejection requires a biopsy. The threshold for performing a biopsy should be low, albeit with an awareness that other conditions can mimic the histologic changes seen with rejection. For instance, diffuse lymphocytic infiltration of the kidney can be seen with rejection or lymphoproliferative disorder, and recurrent hepatitis C in the liver can resemble rejection.

**Malignancy**

Immunosuppressant drugs increase the susceptibility of transplant recipients to malignancy.209 This effect is primarily related to the level of immunosuppression, but production of transforming growth factor-β may also be responsible.

The spectrum of malignancy is wide ranging and includes cancers seen with HIV-infection, a condition also associated with immunosuppression. Lymphoma regression occurs if the immunosuppressive agent is discontinued early.

In a retrospective study of more than 250,000 solid organ transplant recipients, Hodgkin lymphoma risk factors included male sex, young age, and Epstein-Barr
virus (EBV) seronegativity at the time of transplant. In a study of 175,000 solid organ recipients (primarily kidney and liver recipients), malignancy was identified in more than 10,000 patients, a standardized incidence ratio (SIR) of greater than 2 compared with the general population. The cancer sites with the highest relative risk included Kaposi sarcoma (SIR = 61), lip (SIR = 17), skin, nonmelanoma (SIR = 14), liver (SIR = 12), vulva (SIR = 8), and non-Hodgkin lymphoma (SIR = 8).

Posttransplant lymphoproliferative disorder (PTLD) is associated with a proliferation of B cells after transplantation in response to infection with EBV. Clinical presentation varies from a mononucleosis-like syndrome to malignant lymphoma. Pediatric patients are at increased risk due to a lower likelihood of prior exposure to EBV. Diagnosis is made by biopsy of the affected area, which can include the graft. Treatment consists of a reduction of immunosuppression levels and antiviral therapy against EBV, primarily ganciclovir. Individuals at high risk, such as patients who are seronegative for EBV or who receive a graft from a seropositive donor, should be maintained on antiviral prophylaxis.

The mean latency period for all cancers is 3 to 5 years after transplant, although specific malignancies exhibited unique time intervals. Cancer sites vary depending on the organ transplanted; for example, renal transplant recipients have a 100-fold greater than expected risk of developing carcinoma in the native kidney. The reasons are unclear, but prolonged dialysis before transplantation may be a risk factor. The use of specific immunosuppressive drugs also affects the relative risk of various cancers. For example, OKT3, which contains antibodies directed against T lymphocytes, is associated with an increased incidence of PTLD. Antibodies directed against B lymphocytes (rituximab) can reduce the incidence of PTLD. Sirolimus is not associated with cancer risk, and in fact may have antitumor effects.

Long-Term Survival

Long-term survival is affected by common diseases, such as hypertension, hyperlipidemia, and diabetes mellitus. Three years after liver transplantation, cardiovascular disease and de novo malignancy are the major causes of mortality. Recurrent rejection and hepatitis C account for most of the hepatic causes of mortality.

CONCLUSIONS

Abdominal organ transplantation has matured over the past 30 years. From its beginning as an experimental procedure, it has become the best hope for survival in the case of liver transplantation, and the best option for an independent life without morbidity in the case of renal and pancreatic transplantation. Challenges for the future include a solution to the organ shortage, methods to minimize the likelihood of disease recurrence, and pharmacologic advances aimed at limiting the side effects of immunosuppression.

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