

An Overview of Solid Organ Transplantation

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The era of solid organ transplantation was inaugurated in 1954 with the performance of the first successful kidney transplantation. This success was followed by a series of technical achievements that expanded the field to heart, liver, pancreas, and lung transplantation. The introduction of cyclosporine in the early 1980s revolutionized immunosuppressive strategies and further propelled the field forward. Once a medical curiosity, solid organ transplantation is now a commonplace occurrence, with more than 27,000 procedures performed in the United States in 2004 alone [1]. This article offers an overview of the various solid organ transplant procedures to provide a context within which subsequent articles on pulmonary complications can be viewed.

Heart transplantation

Status of heart transplantation in the United States

Heart transplantation remains the treatment of choice for younger patients who have intractable heart failure despite maximal medical and device therapy who are otherwise healthy. In the United States for the 365-day period ending June 30, 2004, 1997 cardiac transplants were performed. On that

same date, 3494 patients were on the waiting list for cardiac transplantation [2]. Since 1993, the number of patients being listed for transplant has been decreasing gradually because of improved medical and surgical management of advanced heart failure that has led to a 1-year survival approaching that of transplantation [3]. In addition, a new status system has shifted the distribution of donor organs to sicker patients, making early listing less imperative [4]. The annual mortality rate for patients listed and awaiting cardiac transplantation is approximately 18%. This statistic may be underestimated, because 2.6% of listed patients are removed from the list because of deterioration before death. The median time from initial listing to cardiac transplantation in adults is about 9.4 months [2]. The times can vary significantly depending on the urgency status of the patient (1A, 1B, or 2), blood group, body size, and geographic location [5]. As an example, for blood group O recipients the median waiting time in the United States was 290 days; blood group AB patients waited a median of 47 days [1]. Patients who are listed as status 1A had a median time to transplantation of 49 days; those listed as status 2 waited a median of 392 days [1].

Indications and contraindications

The primary indications for cardiac transplantation include refractory heart failure despite maximal medical support, refractory ventricular arrhythmias,

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and refractory angina [6]. The 1-year survival of patients after transplantation is about 86%; therefore, patients listed for transplantation should have an estimated 1-year risk of mortality without transplantation of greater than 15% [2]. Several risk models have been proposed to help risk stratify patients who have heart failure using both invasive and noninvasive methods [6]. The most potent predictor of outcome in ambulatory patients who have heart failure is a symptom-limited metabolic stress test to calculate peak oxygen consumption (VO_2). Several studies have indicated that a peak VO_2 of less than 10 mL/kg/min indicates a poor prognosis with a survival that is less than that of transplantation. Patients who have a peak VO_2 of less than 12 mL/kg/min and refractory symptoms of heart failure also have been shown to have an improved quality of life after transplantation [6]. Nonambulatory patients who require continuous intravenous administration of inotropes and who cannot be weaned or who require mechanical support to maintain an adequate cardiac index are also considered potential candidates for cardiac transplantation. In rare instances, refractory ventricular arrhythmias or refractory angina that persist despite maximal medical and surgical therapies are also indications for transplantation [7].

The contraindications for cardiac transplantation include any medical condition that would be expected to limit life expectancy after transplantation. Recent or active malignancies, active infections, or other chronic life-threatening diseases typically exclude a patient from being considered for transplantation. In addition, evidence of end-organ damage, including advanced pulmonary disease, renal insufficiency, hepatic insufficiency, or severe vascular disease, also precludes transplantation. Age greater than 65 years has become a relative contraindication, because patients above this age have been shown to have worse outcomes [4,6]. Psychosocial factors, including inability to follow a rigorous medical regimen after transplantation, can also be contraindications. Pulmonary hypertension with a pulmonary vascular resistance of greater than 4 Wood units that cannot be reduced by medical means or through the placement of a ventricular-assist device is considered an absolute contraindication for isolated cardiac transplantation. In the setting of fixed pulmonary hypertension, the donor right ventricle often fails, leading to a high risk of perioperative mortality [6].

Allocation system

In January of 1999, the United Network for Organ Sharing (UNOS) implemented an acuity status

system for patients awaiting cardiac transplantation in the United States. Under this system, donor hearts are to be allocated to the sickest patients first to maximize waiting list survival. The current acuity system includes three levels. Patients who are at the greatest risk of death are listed as status 1A; patients who are status 2 are considered to have a lower risk. Within an ABO blood group and recipient size range, donor organs are offered first to the highest priority patients and then to the lower risk groups until the organs are matched with a recipient. Hearts are offered geographically using the location of the donor. Hearts are offered first to local transplant centers and then to centers outside the region in a series of concentric circles of 500 miles in diameter until an organ is matched [8]. The ischemic time of approximately 4 hours limits the distance from which a heart can be harvested.

For each acuity status, a number of objective criteria must be met. The criteria for being listed as status 1A include

- Mechanical circulatory support (intra-aortic balloon pump, total artificial heart, or extracorporeal membrane oxygenation)
- Implantation of a ventricular-assist device (for 30 days once the center has determined the patient is stable)
- Complications involving a ventricular-assist device including mechanical failure or infection, or
- High-dose or multiple inotropes (dobutamine, dopamine, or milrinone) with an indwelling pulmonary artery catheter

IA status can also be obtained through an exception review process in each region. This system is used when the patient has a high risk of death within 1 to 2 weeks without transplantation but does not fit any of the established criteria [8]. The 30-day period of 1A time after placement of a ventricular-assist device can be applied at any time after transplantation. This provision allows the patient to recover from the initial surgery as well as from heart failure. Several studies have indicated that waiting several weeks for end-organ function to normalize after ventricular-assist device surgery improves cardiac transplantation outcomes. Therefore, many centers wait to activate the 30 days of 1A time at 2 to 6 weeks after implantation [9].

1B status is for patients who are being treated with a single inotrope that does not meet the criteria of high dose. Patients can be ambulatory and in the community or hospitalized. 1B status can also be

obtained either before or after the 30-day period after placement of a ventricular-assist device. Status 2 patients are those who meet the indications for transplantation and have an expected 1-year mortality risk of more than 15% but are not taking continuous inotropes or do not have a mechanical support device [8].

Pretransplantation care

Patients awaiting cardiac transplantation are managed with a variety of heart failure therapies including neurohormonal blocking agents (angiotensin-converting enzyme inhibitors, beta blockers, aldosterone antagonists, angiotensin receptor blockers) and diuretics. In addition, eligible patients may receive a biventricular pacemaker, and almost all these patients have an implantable defibrillator to protect against sudden cardiac death before transplantation [10]. It is important that clinicians re-evaluate patients being considered for cardiac transplantation, because several of the newer therapies can promote positive remodeling of the ventricle over time, precluding or at least delaying the need for transplantation.

Intravenous inotropic therapy is often initiated for patients who remain in a low cardiac output state or who have refractory symptoms of congestion despite maximal medical support and, if appropriate, biventricular pacing. The most commonly used chronic inotropes include milrinone and dobutamine. Inotropes can significantly improve cardiac index, decrease symptoms, and improve end-organ perfusion. Inotropes also significantly increase the risk of arrhythmias, including potentially fatal ventricular arrhythmias. In the past, patients receiving continuous inotropes remained hospitalized until a suitable organ became available. Recent studies have shown that with the use of an implantable defibrillator to treat dangerous ventricular arrhythmias, patients awaiting transplantation can be managed safely as outpatients [11].

Patients who have acute hemodynamic compromise or have a chronic low cardiac output state despite inotropic support may be candidates for placement of a ventricular-assist device. These devices can supplement or replace the cardiac output from the right, left, or both ventricles. Ventricular-assist devices have been used to bridge patients to transplantation, and there is evidence that in the appropriate population these devices can reverse end-organ dysfunction and allow improved outcomes after transplantation [9]. Certain ventricular-assist devices allow patients to be managed successfully as outpatients while awaiting transplantation.

Surgical techniques

Three surgical techniques are commonly in use for cardiac transplantation: the standard, bicaval, or total technique [12]. In the standard or biatrial technique, cuffs of the recipient atria, including the orifices of the pulmonary veins, are left intact and then are sewn to the donor atria. Advantages of this technique include a shorter surgical time and no need to re-implant the pulmonary veins. During the past several years, the bicaval approach has gained favor, because it has reduced atrial arrhythmias, sino-atrial nodal dysfunction, and tricuspid regurgitation. In this technique, the recipient pulmonary veins are excised in a cuff of left atrium and then are attached to the donor left atrium. The entire recipient right atrium is removed. The superior and inferior vena cavae are attached, as are the aorta and pulmonary arteries. Several studies have shown that this technique, although it adds ischemic time, has led to improved short- and long-term outcomes. The total technique involves removal of the entire recipient heart with the exception of two small “buttons” of left atrial tissue containing the four pulmonary veins. The remainder of the anastomoses are identical to the bicaval technique, except that there are two anastomoses in the left atrium. Limited studies have suggested that this technique adds significant ischemic time but does not lead to improved outcomes [6,12].

Cardiac transplantation outcomes

The outcomes in cardiac transplantation have improved over time, with the 1-year survival rate for patients undergoing transplantation from January 1, 2001 through June 30, 2003 being 86.7%. The 3-year survival rate is 78.6% [2]. At 1 year, 90% of surviving patients report no functional limitations, and approximately 36% return to work [13]. In the first year, the most common cause of death includes graft dysfunction. After the first year, infections and graft dysfunction are the most common causes. Late causes of death include graft vasculopathy and malignancies [13].

Graft vasculopathy is one of the major limitations to long-term survival after cardiac transplantation. Several donor and recipient factors can influence the development of vasculopathy and lead to graft dysfunction and death. Graft vasculopathy differs from typical coronary disease in that it is diffuse in nature and can affect the small vessels first, making it difficult to detect with coronary angiography. Intravascular ultrasound has become the criterion standard for detecting and monitoring graft coronary disease

but is not available routinely outside research protocols. Most researchers agree that this form of vasculopathy is immune mediated, and several small studies have shown regression with newer or augmented immunosuppression. The routine use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in all cardiac transplant recipients, regardless of lipid profile, has become the standard of care because of evidence suggesting that the anti-inflammatory property of statins may help prevent or delay vasculopathy [14].

Liver transplantation

Background

The first successful human liver transplantation was performed in 1967 by Starzl and colleagues [15]. As of November 30, 2004, more than 68,000 liver transplantations have been performed in 142 institutions across the United States; 5670 liver transplants were performed in 2003 alone [1]. More than 16,000 patients await liver transplantation each year, and median times on the waiting list range from 210 to 1243 days, depending on blood type. Because of the shortage of suitable donor organs, 1818 patients died in 2002 while awaiting liver transplantation [16].

Indications for liver transplantation

Orthotopic liver transplantation may be indicated for acute or chronic liver failure from any cause [17]. In the United States, alcohol-induced liver disease and chronic hepatitis C infection are the most common indications for liver transplantation [15,18,19].

Hepatic decompensation is associated with high short-term morbidity and mortality. Two-year survival in patients who have cirrhosis complicated by ascites is only 50% [20]. Similarly, patients who have cirrhosis and are admitted with variceal hemorrhage have an inpatient mortality of 30% to 50% [21,22]. Renal failure, which is common in patients who have fulminant hepatic failure (FHF) or advanced cirrhosis, is associated with increased short- and long-term pretransplantation mortality [23]. Patients who have type 1 hepatorenal syndrome (HRS) have a 2-week mortality of 80%, and only 10% of these patients survive longer than 3 months [24]. Hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatopulmonary syndrome are other late manifestations of chronic liver disease that are associated with significant morbidity and should

prompt referral to a liver transplant center [25]. Hepatocellular carcinoma is common in patients who have cirrhosis but also may be found in patients who have chronic replicative hepatitis B infection in the absence of significant fibrosis. Patients who have a single, isolated hepatocellular carcinoma measuring between 2 and 5 cm in diameter or patients who have fewer than three lesions, each less than 3 cm in diameter, should be referred for liver transplantation.

Patients hospitalized for FHF resulting from viral or autoimmune hepatitis, Wilson's disease, acute Budd-Chiari syndrome, or drug hepatotoxicity should be referred to a transplant center for expedited transplant evaluation. Patients who have FHF are listed separately from those with chronic liver disease. In response to the severity of acute liver injury, patients who have FHF are given status 1 priority, which places them at the top of the waiting list.

Last, liver transplantation may be indicated in patients who have intractable pruritus, metabolic bone disease, recurrent bacterial cholangitis, or progressive malnutrition. Although these patients may not have decompensated cirrhosis or FHF, transplantation should be considered to treat the extremely poor quality of life associated with these conditions.

Listing criteria and organ allocation

Although a topic of recent debate, there are no minimal listing criteria for liver transplantation at this time [26]. Donor livers are allocated based on ABO blood type, and acutely ill patients who are listed as status 1 are transplanted first. After status 1, livers are allocated by the modified Model for End-stage Liver Disease (MELD) score, which is used in patients who have chronic liver disease. The MELD score originally was developed to predict outcomes in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt [27]. The MELD score (range: 6–40) is derived from three widely available and easily repeatable laboratory values: total bilirubin, creatinine, and international normalized ratio. Studies have found the MELD score to be highly predictive of 3-month mortality in hospitalized patients who have cirrhosis. MELD scores between 20 and 35 are associated with 10% to 60% 3-month mortality, whereas MELD scores greater than 35 are associated with 80% mortality at 3 months [28,29]. At present, MELD exception points are conferred to patients who have stage 2 hepatocellular carcinoma or hepatopulmonary syndrome [1,26]. When two or more patients of the same blood group have the same MELD score, patients who have the longest waiting-list time are given priority.

Contraindications

Problems that absolutely preclude liver transplantation include active extrahepatic infections, poor social support, untreated psychiatric disorders, significant coronary artery disease, advanced chronic obstructive or restrictive pulmonary disease, and active alcohol or drug abuse [15]. Untreated HIV infection has been considered an absolute contraindication. Patients who have well-controlled HIV, however, should be considered for clinical trials that will assess the role of transplantation in stable patients receiving highly active antiretroviral therapy. Other contraindications to orthotopic liver transplantation include extrahepatic malignancies, cholangiocarcinoma, and anatomic abnormalities that make transplantation unfeasible.

Advanced age is a negative risk factor, because patients older than 65 years have worse outcomes than patients who are 60 to 65 years of age or younger [30]. Despite these findings, advanced age alone should not exclude patients from transplantation but should necessitate a thorough pretransplantation evaluation. Although patients who have diabetes are at higher risk for adverse outcomes after transplantation, liver transplantation is not contraindicated in patients who have well-controlled diabetes [31,32].

Renal failure, irrespective of its cause, does not exclude patients from liver transplantation. As mentioned previously, type 1 HRS is an indication for transplantation. Patients who have HRS of prolonged duration (likely type 2 HRS) or with chronic renal failure from other causes should be evaluated by a transplant nephrologist and considered for combined liver-kidney transplantation.

Deceased-donor versus living-donor liver transplantation

Most transplanted livers come from deceased donors. In 2003, 5348 deceased-donor liver transplants (DDLT) were performed, whereas only 322 living-donor liver transplants (LDLT) were done during the same period [1]. The concept of LDLT originated from renal transplantation, and LDLT was found to be particularly applicable to pediatric patients because left lateral segment transplants could provide sufficient hepatic mass for small children. Because of the increasing demand for donor organs and a static deceased-donor pool, LDLT has been increasingly recognized as a viable option for patients in need of transplantation. Unlike the pediatric patient, an adult recipient requires a larger liver volume, which

may include a right hepatic lobe resection or a full left graft in smaller adult recipients [33–35].

Despite the usefulness of LDLT, the risk to the donor is significant. Nine percent to 19% of donors may develop complications [36]. Complications include wound infection, small-bowel obstruction, and incisional hernias. Approximately 10% of donors develop bile leaks and neurapraxia. Although morbidity is possible, donors have demonstrated general acceptance of the procedure and have had favorable outcomes [36].

Surgical procedure

The technical aspects of surgery involving DDLT and LDLT are beyond the scope of this article. The three major phases of surgery include native liver dissection (1 to 2 hours), the anhepatic phase (1.5 to 3 hours), and revascularization of the liver [15]. The most commonly used surgical technique was described by Starzl and colleagues in 1963 [37]. Earlier operations included removal of the retrohepatic vena cava causing decreased venous return to the heart and hemodynamic instability [38]. One of the major modifications in transplant surgery has included preservation of the retrohepatic vena cava to maintain venous return to the heart, minimizing hemodynamic instability and eliminating the need for venovenous bypass [39]. This “piggyback” technique is now commonly used in most transplant centers and has been found to be safe and associated with few surgical complications [15,38].

Certain perioperative factors are of potential consequence in the posttransplantation period. Prolonged cold-ischemia time is associated with primary non-function and hepatic artery thrombosis [15]. Cold-ischemia times longer than 15 hours are significantly associated with higher rates of acute cellular rejection [40].

Immediate postoperative complications

Many of the immediate complications after transplantation are related to the surgical procedure. The most common postoperative surgical complication is intra-abdominal bleeding, which may occur in 10% to 15% of patients [41]. Although a picture of ischemic liver injury is common immediately after transplantation, the liver-associated enzymes usually normalize by 2 to 3 days after transplantation. Evidence of cholestasis after this time requires further investigation. It is appropriate to begin with an ultrasound examination to evaluate for biliary ductal dilation, which may signal a biliary stricture. Simultaneous

Doppler imaging should be obtained to evaluate for hepatic artery thrombosis, portal and hepatic vein thrombosis, or inferior vena cava obstruction. If a stricture is found, or if the ultrasound is unrevealing, endoscopic retrograde cholangiopancreatography should be considered the criterion standard to evaluate the biliary tree. Biliary stents may be required for strictures or leaks. Liver biopsy is recommended for patients who have persistently abnormal liver-associated enzymes to evaluate for acute cellular rejection or other causes of hepatic injury and dysfunction, such as drug-induced hepatotoxicity or infection.

Outcomes

Patient survival rates among DDLT recipients are 88% at 1 year and 74% at 5 years after transplantation [16]. Virtually identical patient survival rates are associated with LDLT [16]. Graft survival rates, however, seem to be somewhat lower for LDLT (64.4% for LDLT versus 73.3% for DDLT at 2 years) [42]. Nonetheless, LDLT is a reasonable option for patients who are unlikely to receive DDLT in a timely fashion.

Kidney transplantation

Background and history

Chronic kidney disease is associated with debilitating consequences and a reduction in life expectancy. Chronic kidney disease commonly progresses to end-stage renal disease (ESRD), in which renal replacement therapy is required to prevent death from uremic complications. Dialysis and transplantation are the two treatment options for ESRD. Compared with dialysis, transplantation is associated with significant improvement in quality of life and in overall longevity [43]. At the same time, annualized per patient costs of transplant-related care of around \$17,000 pale in comparison with the \$53,000 for dialysis [44].

The first kidney transplantation was successfully performed by Joseph Murray and colleagues in Boston in 1954, between a pair of identical twins receiving no immunosuppression [45]. After these pioneering efforts, kidney transplantation expanded globally, and Murray received the Nobel Prize in Medicine in 1990. Currently, there are around 350,000 ESRD patients in the United States, although with population aging and the escalation of diabetes

and hypertension, this number is projected to exceed 650,000 by the end of the decade [46]. The increased success of transplantation and mounting ESRD rates have culminated in a greater demand–supply disparity and a surge in the number of patients waitlisted for a kidney. Although 200,000 kidney transplantations have been performed in the United States since 1988, nearly 65,000 patients remain on the national waiting list for a kidney, more than double the number a decade ago [1].

Indications for kidney transplantation

Any patient whose quality of life or lifespan is likely to be improved after transplantation should be considered a potential candidate. The remarkably few contraindications to kidney transplantation alone are related mostly to excessive comorbidity, when the risks of sustaining harm with surgery and immunosuppression outweigh the benefits of transplantation. Such conditions include advanced liver or lung disease, intractable or advanced infection, or unremitting malignancy. Cardiovascular disease, for which kidney disease is a major risk factor, is the leading cause of mortality in ESRD patients [47,48]. Special emphasis therefore is placed on evaluation of cardiovascular disease in kidney candidates, but its presence does not preclude transplantation unless it is active and not amenable to any intervention. It is recommended that waitlisted kidney candidates be periodically rescreened for cardiovascular disease until they receive a transplant [49].

Types of kidney transplants

Both living and deceased donors are used as sources of kidneys for renal transplantation. Living donors are either genetically related (parent, child, sibling) or unrelated (friend, spouse, altruistic donor) to the recipient. Living donation avoids ischemia-reperfusion injury associated with procurement, storage, transportation, and implantation of kidneys from deceased donors; moreover, living donors are healthy at the time of donation. For all these reasons, living-donor kidneys are typically superior in quality and function. In particular, the best outcomes are observed with kidneys transplanted between human leukocyte antigen (HLA)-identical siblings. Survival rates for all types of non-HLA-identical living-donor transplants are similar regardless of the donor–recipient genetic relationship and, importantly, exceed results with even the best-matched deceased-donor kidneys. Living-donor kidney transplantation can also be performed on an elective basis and can be

timed to minimize or even avoid the need for any dialysis in the recipient.

With the burgeoning waiting list and increasingly poor quality of available deceased-donor kidneys, the emphasis on living donation has magnified during the past decade. Coupled with the advent of laparoscopic nephrectomy technology and the observed outcome benefits of living-kidney donation alluded to previously, living donation in the United States has expanded from about 2500 in 1992 to more than 6000 in 2001 [50]. During this same time, the deceased-donor count changed only from 4500 to 5500 per year [50]. Because two recipients can receive kidneys from each deceased donor, there still are more deceased-donor transplantations performed overall each year. For the living donor, living with one remaining kidney has no effect on life expectancy or lifestyle, childbearing potential, or access to medical care or insurability.

Timing of waitlist placement and transplantation

Current UNOS policy mandates that patients can be waitlisted for a transplant only when their glomerular filtration rate is less than 20 mL/min. Once listed, median waiting times range between 3 and 4 years, although this time varies regionally and according to patient blood type [50]. Professional guidelines recommend referral of patients for transplantation well in advance of their needing dialysis, to help identify potential living donors and to also gain lead-time on the waitlist [51]. Because dialysis duration before transplantation is related inversely to survival after transplantation, transplantation before starting dialysis is desirable [52,53]. Because of lengthening waiting times, however, transplantation before dialysis seldom occurs in patients who do not have living donors.

Human leukocyte antigen matching and allocation

Acute rejection occurs with increasing degree of HLA mismatch [54]. Because zero-mismatched kidneys experience the lowest rates of acute rejection, a national policy for sharing of such organs from deceased donors has been developed and refined during the past 2 decades [55]. At present, 17% of deceased-donor kidneys are shared nationally by this policy, although there is evidence that the benefits of optimal HLA matching may be mitigated by increased ischemia-reperfusion injury associated with shipment of such organs [56].

Another enormous challenge facing the kidney transplant community is the growing pool of patients

who have acquired anti-HLA antibodies because of sensitization from prior blood transfusions or transplants or through pregnancy. In many cases, the high levels of sensitization render it almost impossible to find suitable donors for affected individuals. There is growing interest in the use of pretransplantation immunosuppressive protocols to lower or eliminate anti-HLA antibodies in such patients to facilitate future transplantation. Similar experimental strategies also are being investigated for the transplantation of kidneys across ABO-incompatible barriers. Preliminary results with these novel regimens are encouraging, although their longer-term safety and efficacy remain unknown [44,57].

Kidney transplant surgery and the perioperative period

The transplanted kidney is placed extraperitoneally in the right or left lower abdominal quadrant. The transplant renal artery and veins generally are anastomosed to the external iliac artery and vein, respectively. The transplanted ureter usually is reimplanted to the recipient bladder using a technique to prevent urine reflux. Although immediate function of the transplanted kidney is desirable, it often does not occur. Many transplant centers obtain imaging studies (ultrasound with Doppler; nuclear isotope flow scan) of the kidney in the immediate postoperative period to assess blood flow and allograft function. Technical factors related to vascular anastomoses or immunologic catastrophes such as hyperacute rejection may, rarely, result in immediate graft failure within hours of transplantation and the need for transplant nephrectomy. More commonly, most deceased-donor and some live-donor recipients experience early transient graft dysfunction. The term "delayed graft function" is defined as the requirement for dialysis within the first week after transplantation. Although this term does not capture patients who have early graft dysfunction who do not require dialysis and includes patients who have immediate function who are dialyzed for an indication such as hyperkalemia, it has persisted as a universal standard for clinical trial purposes. Delayed graft function usually is caused by acute tubular necrosis; the reported frequency ranges from 2% to 50% [58]. Factors such as deceased-donor source, procurement injury, ischemia-reperfusion injury, drug nephrotoxicity, volume depletion, and acute rejection all predispose to delayed graft function [58]. Although functional recovery is the rule, long-term graft survival may be compromised. Strategies to mitigate delayed graft function include trimming ischemic

times by expediting the transplantation, aggressive perioperative volume expansion, and avoiding or minimizing calcineurin inhibitors and other nephrotoxic agents in the peritransplantation setting. When delayed graft function persists despite these strategies, kidney transplant biopsy is commonly performed within the first 2 to 3 weeks after transplantation to optimize therapy.

Outcomes after kidney transplantation

One-year patient survival rates exceed 95%, whereas 1-year graft survival rates are now over 91% overall [50]. Current 5-year patient and graft survival rates are 92% and 79% for living-donor and 86% and 65% for deceased-donor recipients, respectively [50]. Long-term, graft half-life beyond the first year after transplantation has improved only marginally, with graft loss in this setting caused mainly by chronic allograft nephropathy, a process characterized by an inexorable decline in kidney function resulting from progressive scarring [59]. Both immunologic (eg, acute rejection, HLA mismatching) and nonimmunologic factors (eg, ischemia-reperfusion injury, hypertension, calcineurin-inhibitor toxicity) have been implicated in predisposing to chronic allograft nephropathy. With an improving immunosuppressive arsenal, chronic allograft nephropathy now is being replaced by death, most commonly in the setting of cardiovascular disease, as the leading cause of chronic graft failure [48,59].

Lung transplantation

Background/current status

Human lung transplantation was attempted first in 1963, but it was not until 2 decades later that extended survival was achieved. After the initial technical successes of the 1980s, the field of lung transplantation realized dramatic growth in both the number of procedures performed and the number of candidates placed on waiting lists for organs. Since the latter part of the 1990s, however, lung transplant activity has leveled to an approximate rate of 1000 procedures annually in the United States, representing one half the volume of heart transplants and one fifth the volume of liver transplants performed [16]. The constraints on lung transplantation reflect in large part the severe scarcity of suitable allografts; only approximately 15% of cadaveric donors capable of donating at least one solid organ have

lungs suitable for transplantation. There has been a modest increase in the number of lung donors in the past several years, but this increase has been offset by a growing trend favoring bilateral over single-lung transplantation [16]. Because of the current constraints, the number of registered candidates awaiting lung transplantation in the United States now exceeds the annual number of procedures by almost fourfold. Additionally, the median waiting time has escalated to approximately 3 years, although it is anticipated that this waiting period will change with implementation of the new allocations system (discussed later).

Candidate selection

Lung transplantation is a therapeutic option for a broad spectrum of chronic, debilitating pulmonary disorders of the airways, parenchyma, and vasculature [60]. Chronic obstructive pulmonary disease (COPD) is the leading indication for lung transplantation, accounting for approximately half of all procedures performed worldwide [61]. Other leading indications include idiopathic pulmonary fibrosis (17% of cases) and cystic fibrosis (16% of cases). Once a common indication for transplantation, primary pulmonary hypertension now accounts for less than 5% of procedures, reflecting major advances in the medical management of these patients [16,61]. Transplantation of patients who have lung involvement caused by collagen vascular disease (eg, scleroderma) remains controversial because of concerns that extrapulmonary manifestations of the systemic disease could compromise the posttransplantation course. Nonetheless, short-term functional outcomes and survival after transplantation are comparable with other patient populations, and most centers are willing to offer transplantation to carefully selected patients who do not have significant extrapulmonary organ dysfunction [62]. In contrast, lung transplantation for bronchoalveolar carcinoma, a subtype of lung cancer that tends to remain localized to the lung parenchyma, largely has been abandoned because of an unacceptably high rate of cancer recurrence [63].

Listing for transplantation is considered when the lung disease is deemed to pose a high risk of death within several years. Disease-specific guidelines for timely referral and listing of patients, based on available predictive indices, have been published [64]. The imprecise nature of these predictive indices must be acknowledged, particularly with respect to COPD and Eisenmenger's syndrome, which tend to follow highly variable and often protracted courses even in the advanced stages. The patient's perception of

an unacceptably poor quality of life is an important additional factor to consider but should not serve as the sole justification for referral of a patient whose disease is not deemed to be at a life-threatening stage.

The scarcity of organs and the somewhat inferior outcomes achieved with increasing age have prompted the establishment of recommended age cutoffs: 55 years for heart-lung, 60 years for bilateral lung, and 65 years for single-lung transplantation. Candidates should be functionally disabled (New York Heart Association class III or IV) but still ambulatory. Many programs screen for and exclude profoundly debilitated patients by requiring a minimum distance on a standard 6-minute walk test, most frequently 600 feet [65]. The presence of significant renal, hepatic, or left ventricular dysfunction precludes isolated lung transplantation, but multiorgan transplantation can be considered in highly select patients. Other absolute contraindications include active infection with HIV, hepatitis B virus, or hepatitis C virus with histologic evidence of significant liver damage; active or recent cigarette smoking, drug or alcohol abuse; recent malignancy (other than non-melanotic skin cancers); and extremes of weight. The risk posed by other chronic medical conditions such as diabetes mellitus, osteoporosis, gastroesophageal reflux, and limited coronary artery disease should be assessed individually based on severity of disease, presence of end-organ damage, and ease of control with standard therapies. Among candidates who have cystic fibrosis, airways colonization with *Burkholderia cepacia* is considered a strong contraindication to lung transplantation by the majority of centers, because of the demonstrated propensity of this organism to cause lethal infections after transplantation [65,66]. Transplantation of patients receiving mechanical ventilation is associated with an increased risk of mortality at 1 year and therefore is not commonly performed [61,65].

Allocation system

From 1990 to 2005, lung allocation in the United States was based on a seniority system that prioritized candidates by the amount of time they had accrued on the waiting list, without regard to severity of illness. This system ultimately was called into question because it failed to accommodate patients who have a more rapidly progressive course, who often could not tolerate the prolonged waiting times to transplantation and who were likely to die before receiving an organ. Indeed, excessive wait list mortality was documented among certain patient populations, such as those with idiopathic pulmonary

fibrosis and cystic fibrosis, as compared with patients who have COPD [67]. In response to the perceived inequities of the time-based system, and under mandate of the federal government, a new system was implemented in May of 2005 that allocates lungs on the basis of both medical urgency (ie, risk of death without a transplant) and net transplantation benefit (the difference between predicted survival after transplantation and survival with continued waiting) [8]. By incorporating this latter concept, the system attempts to avoid the pitfall of preferentially allocating the scarce donor organ pool to desperately ill patients who have an unacceptably high posttransplantation mortality rate.

The new model, derived from a multivariate analysis of data from the comprehensive UNOS national database, identifies 10 factors independently predictive of death on the waiting list and seven predictive of death after transplantation. For each patient, these factors are used to calculate predicted 1-year survival with and without transplantation. Patients who demonstrate a large net difference in survival (predicted posttransplantation – pretransplantation survival) in conjunction with a high degree of medical urgency (low predicted pretransplantation survival) receive the highest priority scores. Several concerns have been raised about the new system that will have to be addressed in an ongoing evaluation of its merits:

1. The predictive model employed has not been prospectively validated.
2. The calculation of net transplant benefit is based on predicted 1-year posttransplantation survival, which is heavily influenced by differences in disease-specific perioperative mortality rates and does not truly reflect long-term outcomes.
3. Net transplant benefit is defined exclusively in terms of survival and does not acknowledge dramatically improved functional status and quality of life as a net benefit.

Surgical procedures

Heart-lung transplantation was the first procedure to be performed successfully, but it has largely been supplanted by techniques to replace the lungs alone. Heart-lung transplantation now is principally restricted to Eisenmenger's syndrome with surgically irreparable cardiac lesions and advanced lung disease with concurrent left ventricular dysfunction or severe coronary artery disease. Previously, the presence of severe right ventricular dysfunction was deemed an

indication for heart-lung transplantation. Subsequent experience with isolated lung transplantation, however, has demonstrated the remarkable ability of the right ventricle to recover once pulmonary artery pressures are normalized.

Single-lung transplantation is the procedure of choice for pulmonary fibrosis and for older patients who have chronic obstructive pulmonary disease but is contraindicated in patients who have suppurative lung disorders such as cystic fibrosis. Most centers also consider severe pulmonary hypertension to be a contraindication to single-lung transplantation. In this setting, single-lung transplantation would result in diversion of nearly the entire cardiac output through the allograft, because of the high vascular resistance in the remaining native lung, and this diversion can contribute to exaggerated reperfusion pulmonary edema in the allograft. Major advantages of single-lung transplantation are its technical ease and its efficient use of the limited donor pool, permitting two recipients to benefit from a single donor.

Bilateral sequential lung transplantation involves the performance of two single-lung transplantation procedures in succession during a single operative session. In the absence of severe pulmonary hypertension, cardiopulmonary bypass often can be avoided by sustaining the patient on the contralateral lung during implantation of each allograft. The primary indications for this procedure are cystic fibrosis, other forms of bronchiectasis, and pulmonary vascular disorders. Additionally, some programs have advocated its use in younger patients who have emphysema, arguing that it offers functional and survival advantages over single-lung transplantation [68].

Living-donor bilateral lobar transplantation is the newest procedure to be introduced and is still uncommonly performed. It involves the implantation of right and left lower lobes harvested from two living, blood group-compatible donors. The procedure generally has been reserved for candidates whose deteriorating status does not permit them to wait for a cadaveric donor. Given the inherently undersized nature of the grafts, it is preferable that the donors be considerably taller than the recipient. Patients who have cystic fibrosis are particularly well suited as a target population because even as adults they tend to be of small stature. Concerns about excessive risk to the donor have thus far proven to be unfounded. In the largest experience reported to date, there were no deaths among 253 donors, and there were only eight complications of sufficient magnitude to warrant surgical re-exploration [69]. Donation of a lobe results in an average decrement in vital capacity of 17%.

Outcomes

Current 1-, 3-, and 5-year survival rates are 80%, 61%, and 46%, respectively [16]. Primary graft failure and infection are the most common causes of early deaths; bronchiolitis obliterans is the leading cause of late deaths. There has been a modest improvement in 1-year survival during the past decade [16]. Unfortunately, 5-year survival rate has not changed and remains considerably below the 70% 5-year survival achieved after liver and heart transplantation.

For patients who have COPD, survival for recipients younger than 60 years of age is superior after bilateral than after single-lung transplantation [70], but the converse has been demonstrated for those who have pulmonary fibrosis. Survival after living-donor transplantation is comparable with that achieved after cadaveric transplantation [71].

Pancreas transplantation

Background and history

Pancreas transplantation has evolved during the past 40 years for the treatment of type I diabetes. The first pancreas transplants were performed in 1966 and were associated with dismal results because of technical limitations and ineffective immunosuppression [72]. Increasing experience, coupled with procedural refinement and the emergence of superior immunosuppression, resulted in improving outcomes and, ultimately, the wider acceptance of pancreas transplantation as an effective treatment option. Since the late 1980s, the field has enjoyed unabated growth [73]. In total, 18,843 pancreas transplantations had been performed worldwide as of October 2002. The annual number of pancreas transplantations has increased from approximately 200 in 1988 to more than 1400 in 2002 [73].

Transplantation options for patients who have diabetes

Pancreas transplantation almost always is reserved for patients who have type I diabetes, although it has occasionally been performed in type II diabetics as well. Pancreatic allografts usually are procured from deceased donors because the reduction in residual islet mass in living donors may increase the subsequent risk of glucose intolerance

in such individuals. Pancreas transplantation takes place in one of three settings:

1. Simultaneous pancreas-kidney transplantation (SPK), in which the pancreas and a kidney from the same donor are transplanted into a recipient with advanced kidney disease during one operation
2. Pancreas after kidney transplantation (PAK), in which a pancreas is transplanted into a patient who has previously received a kidney from a different living or deceased donor
3. Pancreas transplantation alone (PTA), usually reserved for patients who have hyperlabile glycemic control and well-preserved renal function

Currently more than 2400 patients are waitlisted for SPK, and about 1700 patients are listed for isolated pancreas transplantation, either as PAK or PTA [1].

Goals and rationale of pancreas transplantation

Studies have demonstrated that intensive insulin therapy in type I diabetics is associated with fewer long-term complications and, thereby, enhanced life expectancy [74]. Pancreas transplantation represents an alternative to chronic insulin therapy, with goals of effecting chronic euglycemia while simultaneously eliminating the need for exogenous insulin administration. In this way, successfully transplanted pancreas recipients experience an improvement in quality of life and eliminate both the need for chronic glucose monitoring and the life-threatening risks of hypoglycemic unawareness. Additional benefits of pancreas transplantation include the prevention and reversal of diabetic nephropathy as well as some amelioration of sensory, motor, and autonomic neuropathy [75].

Indications for pancreas transplantation

As a rule, all pancreas transplant candidates should be C-peptide deficient. Patients who have advanced diabetic kidney disease are potentially eligible for SPK transplantation. Indications for isolated pancreas transplantation are less well established, although the widely endorsed American Diabetes Association's position is that this procedure should be reserved for patients who have life-threatening hypoglycemic unawareness, frequent acute metabolic complications associated with hy-

perlabile glycemic control, or failure of conventional insulin therapies to prevent acute complications [76]. Historically, older candidate age (above 45 years) and the presence of cardiovascular disease were relative contraindications to pancreas transplantation, based on their association with worse outcomes [77]. Ongoing experience during the past decade and improving results have seen an increase in age, as well as comorbidity, of potential pancreas recipients [73].

Surgical considerations in pancreas transplantation

Several surgical issues require consideration in pancreas transplantation. The transplant pancreas, together with a small segment of the adjacent duodenum (containing the sphincter of Oddi), is procured en bloc from the donor. Although transplantation of the whole pancreas serves as the source of abundant functioning islets, the graft's exocrine drainage through the pancreatic duct must be accommodated. The first widely adopted technique involved pancreatic duct drainage into the urinary bladder through a pancreaticoduodenocystostomy, but this procedure was associated with frequent complications [78]. Enteric drainage was developed as an alternative option to the bladder route [79]. With enteric drainage, the segment of transplant duodenum is attached to the small bowel either with a Roux-en-Y anastomosis or directly end-to-side [79,80].

Another surgical issue is the method of venous drainage for the transplant pancreas. Initially, most procedures were performed with venous drainage through the iliac vessels. With this technique, insulin released from the pancreas enters the systemic circulation directly, avoiding the physiologic first-pass effect in the liver. This technique results in systemic hyperinsulinemia, although there is no evidence that this form of chronic hyperinsulinemia has any adverse consequence [81]. During the past decade, the technique of draining the venous outflow directly into the portal vein has become increasingly common [82]. Although this approach approximates the normal trafficking of insulin through the liver, registry data do not demonstrate any outcome differences between the two routes of venous drainage [73].

The immediate posttransplantation course typically is characterized by rapid improvements in blood glucose levels. Failure of such improvement should prompt a high index of suspicion for an early complication, such as graft thrombosis, rejection, pancreatitis, duct leaks, or infection. International Registry data continue to indicate a technical failure

rate of 7% to 14%, depending on the technique involved and type of pancreas transplantation performed [73].

Monitoring for pancreas rejection remains imprecise. Hyperglycemia is a late marker, developing only after most of the islet mass has been damaged. Elevations in amylase and lipase levels raise the suspicion of graft dysfunction and warrant imaging studies and consideration for biopsy.

Outcomes after pancreas transplantation

Historically, pancreas outcomes after SPK transplantation were superior to those after either PAK or PTA. This difference was attributed to increased immunologic problems observed in isolated-pancreas transplantation and to the ability of the creatinine to serve as a reliable surrogate of graft function in patients receiving SPK [83]. With superior immunosuppression and greater expertise, 1-year pancreas graft survival rates are now similar for all three types of transplantation, although by 5 years SPK recipients continue to exhibit the best pancreas outcomes at 69% [50]. Registry analyses further indicate that, compared with remaining on the waiting list, SPK transplantation is associated with lower mortality rates, although this advantage has not been established unequivocally for PAK or PTA recipients [84,85]. SPK transplantation is also associated with better patient and kidney graft survival than transplantation of a deceased-donor kidney alone but offers no advantage over a kidney from a living donor [86,87]. Based on these data, the following clinical approach to type I diabetics with advanced chronic kidney disease is recommended. Pre-emptive transplantation should be pursued if at all possible to minimize or avoid the need for dialysis, a poor outcome determinant. For patients who have acceptable comorbidity, a living-donor kidney should be used if available, followed by subsequent PAK; patients without living donors should be waitlisted and transplanted with a deceased-donor SPK. Patients in whom pancreas transplantation is contraindicated should receive a kidney alone, from either a living (preferable) or deceased donor.

Long-term pancreas graft failure is characterized by hyperglycemia and the need to restart conventional glucose-lowering therapies. In this setting, hyperglycemia may be a manifestation of either (1) islet failure (low C-peptide and insulin levels) secondary to alloimmune (acute or chronic rejection) or recurrent autoimmune-mediated injury, or (2) insulin resistance (high C-peptide and insulin levels), asso-

ciated with posttransplantation weight gain and some immunosuppressive therapies.

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