6 Pediatric transplantation

William Harmon
Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts, USA

Although organ failure is far less common in children than in adults, pediatric organ transplantation has held an important position in the transplant community since its earliest days. Children make up a small fraction of all organ recipients. They represent about 2.3% of all active candidates and about 6.8% of all recipients. Children make up the majority of those receiving intestinal transplants. In contrast, virtually no children received pancreas transplants. Although the indications for transplantation, techniques, procedures, and immunosuppression for children are similar to those in adults, there are important differences in the approaches to treatment, e.g., the causes of end-stage organ failure in children are substantially different from those seen in adults. The lack of appreciation for the consequences of those etiologies could compromise graft and patient survival. Furthermore, the long-term goals of transplantation in children may be substantially different than those in adults, once again providing important guidance for the proper treatment and care of these patients, e.g., growth and development are clearly recognized as unique end-points for children, and immunosuppression plans and monitoring protocols are often modified based on this concern.

Furthermore, as current immunosuppression requires constant and unrelenting adherence to fixed schedules, it should not be surprising that older children and adolescents are at high risk for failure to follow the protocols and that they suffer the inevitable consequences. Thus, appropriate research efforts designed to minimize the number and frequency of administration of immunosuppressive medications, and to eliminate the medications with the worst side effects (particularly cosmetic side effects) become high-priority projects. Recent studies have shown outstanding outcomes in young children, suggesting that their immune responses are not a substantive barrier, and that they may become ideal candidates for long-term tolerance protocols. This is particularly relevant because children, who have the longest projected lifespan after organ transplantation, have the most to gain from long-term graft function and freedom from serious complications of chronic immunosuppression.

Considering the developmental phases of children, especially as they progress through adolescence, it is universally understood that they should have individually defined follow-up programs, designed to assure appropriate care of their grafts while providing them full rehabilitation status so that they can undertake all of the activities common to their peers. Recognizing the importance of pediatric organ transplant procedures as well as the substantial differences in their care, the National Institutes of Health, through the National Institute of Allergy and Infectious Diseases, has sponsored specific pediatric organ transplant research initiatives for over a decade. The first of these was the Collaborative Clinical Trials in Pediatric Transplantation (CCTPT), which supported several immunosuppression minimization studies in pediatric kidney transplantation.

Primer on Transplantation, 3rd edition.
Edited by Donald Hricik.

The CCTPT has been replaced by the more comprehensive Clinical Trials in Organ Transplantation in Children (CTOTC) which has recently established multicenter clinical trial consortia in pediatric kidney, heart, and lung transplantation. Importantly, these groups will be undertaking innovative trials designed to enhance immunosuppression for children while defining their unique immunologic responses, not only to the graft but also to infectious diseases. Each of these trials involves important mechanistic studies.

Pediatric organ transplantation is not a large clinical program in any single transplant center. Thus, pediatric transplant professionals, including physicians, surgeons, nurses, and investigators, have formed multicenter data registries designed to collect and analyze information concerning indications, outcomes, and complications of their procedures. Examples of these include the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), Studies in Pediatric Liver Transplantation (SPLIT), the Registry of the International Society of Heart and Lung Transplant's (ISHLT) pediatric section, and the Pediatric Heart Transplant Study Group (PHTSG). Each of these registries has provided invaluable information about all aspects of organ transplantation in children and they have made these data available through periodic reports and websites. Importantly, their results have spawned subsequent prospective research trials. Nevertheless, the small numbers of pediatric transplant procedures results in an inevitable lack of precision of epidemiologic and outcome data in children compared with adults. Furthermore, clinical trials in children obviously require longer enrollment periods because of the inevitable paucity of appropriate candidates. Despite these handicaps, the determined efforts by the pediatric transplant community to cooperate in both data collection and multicenter clinical trials has resulted in a vibrant collaborative effort to describe and improve organ transplantation in children.

The fundamental indications for organ transplantation, the basic surgical procedures, the immune response to a solid organ transplant, and the complications of the immunosuppressive agents are similar or identical in children and adults. Insofar as these issues have been addressed by other chapters in this text, they are not repeated in this chapter. However, those issues that are clearly unique for pediatric recipients of organ transplants or which require substantial modification of typical protocols will be described in detail. Thus, this chapter is an important adjunct to the other resources provided in this primer, but it does not replace them. The data to support the information in this chapter come from multiple sources. However, the data about transplant rates, death on the waiting list, and outcomes come from the Scientific Registry of Transplant Recipients (SRTR) and represent transplantation in the USA.

Causes, demographics, and conservative treatment of children with end-stage organ disease

The etiologies of end-stage organ failure in children are generally substantially different than those in adults. Many children are born with congenital malformations that affect vital organs or have hereditary diseases that are expressed early in life. There are several consequences of these disorders. First, unlike adults whose acquired diseases are frequently degenerative and progressive, children with congenital organ malformations have fixed or unchanging disorders. Thus, the number of complicating conditions may be substantially reduced. On the other hand, abnormal organ function dating from the earliest period of life can seriously impair growth and development, resulting in additional handicaps. Furthermore, as many of these lesions, such as congenital heart disease or serious urologic malformations, require surgical reconstruction, many young patients with end-stage organ failure have had substantial surgical histories before requiring organ transplantation. And, although these specific malformations will not recur in a transplanted organ, any associated anatomic or physiologic abnormalities will require ongoing vigilance and repair. Furthermore, hereditary disorders, such as cystic fibrosis, autosomal recessive polycystic kidney disease, or cystinosis, may not be cured by an organ transplant. The ongoing physiologic abnormalities associated with these disorders may affect the new organ as well as other organ systems. Thus, those treating children with these types of disorders should have broad experience in dealing with their consequences.

End-stage renal disease

In general, adults develop end-stage renal disease (ESRD) from the complications of diabetes mellitus, hypertension, or simply growing older. As life expectancy lengthens, the potential for ESRD resulting from these disorders increases, probably explaining the marked increase in the number of patients receiving chronic dialysis in the USA. These types of disorders are rarely seen in children. Although children can suffer from hypertension, renal disease is typically the cause rather than the consequence of the hypertension. Although children certainly can develop diabetes mellitus at an early age, and despite the fact that the incidence of type 2 diabetes is expanding rapidly (particularly in the obese adolescent population), it is quite unusual for end-stage diabetic nephropathy to occur before the third decade of life. Congenital kidney and urologic abnormalities are major causes of the ESRD in children, but are rarely seen in adults. Furthermore, most hereditary disorders have an onset early in life and thus are generally expressed in the youngest patients.

One important exception to that general rule is autosomal dominant polycystic kidney disease. This disease, the most common lethal inherited disorder in white people, typically is not fully expressed until adulthood and is rarely appreciated in children, except as the earliest manifestations found in family members of affected patients. Comparisons of the causes of ESRD are shown in Table 6.1. For children, hereditary and congenital abnormalities, such as reflux nephropathy and renal dysplasia, account for slightly more than 50% of the cases of ESRD in children presenting for kidney transplantation. Focal sclerosis and various forms of glomerulonephritis account for about a quarter of the cases. Diabetes mellitus as a cause of ESRD in children is barely noticeable, and hypertension is not reported as a cause. In contrast, diabetes and hypertension account for slightly more than 70% of adults with ESRD. Urinary tract disorders and cystic kidney disease account for less than 5% and glomerulonephritis is the etiology in approximately the same percentage of adults as children with ESRD. Clearly, these differences in the causes of ESRD in children and adults require substantially different approaches to treatment and follow-up.

Overall, there are slightly more boys than girls who develop ESRD, probably related to obstructive uropathy and other urinary tract disorders found early in life. In general, 60% of children receiving kidney transplants are boys. There is a slightly higher incidence of ESRD in African–American children compared with their prevalence in the overall population, approximately 17%. This fraction is substantially smaller than what is reported in adults. White children represent 61% and Hispanic children about 16% of pediatric kidney transplant recipients. Although children might have ESRD from birth, transplantation is frequently performed later in life as chronic kidney disease progresses into ESRD. Adolescents make up about 50% of pediatric kidney transplant recipients, with 6–10 year olds and 1–5 year olds representing 25% each. It is unusual for children aged <1 year to be treated with kidney transplantation. They are typically treated with conservative measures and dialysis until they are big enough to receive a kidney from an adult donor (see below). The incidence of ESRD in children, in contrast to what is reported in adults, has been relatively constant over the past 30 years. In general, there are about 500 pediatric kidney transplant candidates who are active on the deceased

Table 6.1 Etiology of end-stage renal disease in children and adults

Etiology	Pediatric (%)	Adult (%)
Dysplasia/Hypoplasia	16.0	
Urinary tract disorders	24.0	2.0
Polycystic kidneys	5.7	2.4
Hereditary	5.0	
FSGS	11.7	
Glomerulonephritis	10.9	7.6
Pyelonephritis	1.8	
SLE and immune	1.9	
Tumor	0.5	
Infarct/Trauma	1.3	
Diabetes	0.1	43.8
Hypertension		27.1
Other	9.5	11.6
Unknown	6.1	5.0

Pediatric data abstracted from NAPRTCS. *Pediatr Transpl* 2007;**11**:366.
Adult data abstracted from USRDS Annual Report 2007.
FSGS, focal glomerulosclerosis; SLE, systemic lupus erythematosus.

donor waiting list at any time and the number of living and deceased donor kidney transplants performed each year is in the range of 700–900.

Treatment with chronic dialysis is generally safe and effective in children with ESRD. Annual mortality rate of children treated with chronic dialysis is much lower than that reported in adults, probably 1% in contrast to the 15–20% reported for adults. Thus, the life-saving potential for kidney transplantation in children is not quite as acute as it is for adults. The one exception to this is in small infants for whom mortality rates of both dialysis and transplantation are much higher than in older children. Mortality risk, therefore, may make kidney transplantation more immediately necessary in infants who are not stable on dialysis. Nevertheless, virtually all programs agree that kidney transplantation is a much more appropriate and successful treatment than dialysis for ESRD in children.

There are indications that the outcome of preemptive kidney transplantation in children is superior to that in children who have undergone chronic dialysis. As children often receive living donor kidney transplants and as they have preference on the deceased donor list, there is no reason as such for them to have long periods of chronic dialysis before transplantation. Nevertheless, given the relative safety of dialysis and the substantial benefits of optimal preparation before transplantation, children with ESRD can be best prepared for kidney transplantation by undergoing necessary corrective surgery, such as urologic reconstruction, and necessary preparation such as completion of immunization schedules, and maximization of nutritional status, before the transplant procedure. In general, there are almost no emergency indications for pediatric kidney transplantation and a pediatric transplant program will collaborate with the dialysis team to provide optimal comprehensive care for children with ESRD. There are virtually no contraindications to kidney transplantation for children with ESRD, except perhaps for a very limited life expectancy, such as in children with metastatic Wilms' tumor or other organ failures.

Case: recurrent disease in kidney transplantation

A 12-year-old boy underwent living related donor kidney transplantation for focal segmental glomerulosclerosis (FSGS). The onset of FSGS occurred 3 years before that, with nephrotic syndrome that was not responsive to typical corticosteroid treatment. He was also treated with plasmapheresis, cyclophosphamide, and mycophenolate mofetil (MMF) at various times, all without any response. His renal function deteriorated over a 2-year span and he began chronic peritoneal dialysis 6 months before transplantation. As a result of sustained hypertension and proteinuria, measured at 5 g/day, he underwent bilateral native nephrectomies 3 months before transplantation. Both parents were ABO compatible and his mother volunteered to be the donor. He received three treatments of plasmapheresis and he was started on cyclosporine 5 days before transplantation. The transplant was technically successful and he started to make urine immediately. Within the first 24 hours, he made 6.5 L of urine and his serum creatinine fell from 7.5 mg/dL to 1.2 mg/dL in that time span. On the second postoperative day, his urine protein:creatinine ratio was 4.4, suggesting recurrence of FSGS.

Liver failure in children

The number of children awaiting liver transplantation has been relatively stable for the past several years. The number of pediatric liver candidates on the waiting list grew from 492 in 1997 to a peak of 703 in 2001, and has subsequently declined to 361 in 2006. This change in absolute numbers of candidates has been similar for both adults and children. A large number of children on the waiting list had been in an inactive status, likely representing early listing in order to be eligible for accumulation of waiting time credit. The change of allocation system in the USA in the early twenty-first century made urgency, rather than waiting time, the primary indication for liver transplantation. Subsequently, the number of children and adults awaiting liver transplantation has decreased, probably reflecting a more realistic estimate of the need for transplantation. Most commonly, diseases that inevitably progress to liver failure, rather than acute irreversible liver failure, account for the diagnoses of over 90% of the children listed for liver transplantation. Among these, cholestatic liver disease, principally biliary atresia, represents over 50% of the total population. Eighty percent of the children with biliary atresia are aged <5 years at the time of transplantation. Thus pediatric liver transplantation tends to be a procedure performed largely in infants and young children.

Attempts to prevent progression of biliary atresia with various surgical techniques, such as Kasai's pro-

cedure, are still recommended but are eventually unsuccessful in the majority of cases. If successful, however, the procedure does produce outcomes that are generally as good as liver transplantation. Metabolic liver diseases represent the next most common indication for liver transplantation, representing about 12% of recipients. In some cases, the children do not have overall liver failure but may lack specific functions, such as defects in the urea cycle. In these cases, morbidity results from acute and unexpected episodes of hyperammonemia which can sometimes be treated and prevented by appropriate diet and medications. In patients with Crigler–Najjar syndrome, hyperbilirubinemia can be treated with phototherapy and enteric administration of binding agents. As above, however, intermittent episodes of kernicterus can result and become irreversible despite supportive treatment. In other circumstances, an isolated liver dysfunction may result in other organ damage, such as occurs in primary oxalosis. In this setting, most programs will recommend simultaneous liver and kidney transplantation in order to prevent recurrent oxalate damage to kidneys and other organs. Wilson's disease can often be managed medically for long periods of time but will sometimes progress to chronic liver disease or acute fulminant liver failure. The indications and timing of liver transplantation in these unusual situations generally require judgment that is best developed through experience in specialized pediatric liver transplant programs. In some cases, liver function is not affected, but portal hypertension and its consequences can be the indication for transplantation, such as in autosomal recessive polycystic kidney disease or cystic fibrosis.

The next most common indication for liver transplantation in children is fulminant liver failure which most commonly occurs in either infancy or early adolescence. Unfortunately, the cause of the liver failure is often unknown, probably in more than half the cases. Another 15% are related to acetaminophen toxicity. The decision to proceed with liver transplantation in this setting of liver failure in children is very difficult, because some of these patients will recover spontaneously. Once again, the need for experience-based decision-making is paramount. Cirrhosis represents about 10% of the children receiving liver transplantation, most commonly resulting from autoimmune hepatitis. As with other forms of liver failure, a large fraction of these children have an undefined etiology. Liver tumors are very uncommon in children and represent less than 5% of children undergoing liver transplantation. Hepatoblastoma represents about 1% of all pediatric cancers but most of these patients are unsuitable for surgical resection because of the extensiveness of the tumor. Most of these patients undergo pretransplant chemotherapy and radiation to reduce the chance of recurrence. Often, this leads to primary treatment of the tumor and avoidance of transplantation. Those who require transplantation frequently have excellent outcomes. On the other hand, hepatocellular carcinoma often recurs after liver transplantation, obviously limiting its success. Clearly, active collaboration among oncologists, pediatric hepatologists, and the liver transplant team is essential to assure the best outcome for these patients. The typical diagnoses of adult liver transplant candidates, such as hepatitis C, alcoholic liver disease, and cirrhosis, are uncommon in children.

Case: a jaundiced patient

The parents of a 9-month-old infant just moved from Saint Lucia to the USA and bring their jaundiced infant son to the pediatric hospital. The child had been noted to be jaundiced soon after birth and was not responsive to phototherapy. He was taken to the UK, where the diagnosis of biliary atresia was made and he was treated with Kasai's procedure. His jaundice stabilized but did not resolve. He did not thrive well and was always noted to have ascites and to be jaundiced. Despite special diets, he now weighs only 5.2 kg, and some of that is clearly related to the ascites. He is deeply jaundiced, although his liver function tests are all normal. His serum bilirubin is 32 mg/dL, with 28 mg/dL noted to be direct. He has had no immunizations because he has been "too sick."

Evaluation of children for liver transplantation requires an experienced multidisciplinary approach that assesses both the indications for transplantation and the likelihood that a successful transplantation will improve the candidate's medical status. Contraindications to pediatric liver transplantation include extrahepatic malignancy, uncontrolled systemic or locally invasive infection, multisystem organ failure, irreversible neurologic injury, and other uncorrectable systemic disorders. The benefits of

liver transplantation have to be weighed against the potential complications and early mortality, especially for disorders that have other modes of treatment, such as metabolic diseases. The management of children awaiting liver transplantation is essential for good outcomes and particular attention must be paid to the nutritional status of the recipients, particularly infants. There has been recent focus on mortality among children awaiting liver transplantation and there has been a proposal that no child should die awaiting organ transplantation. The mortality among pediatric liver transplant candidates is highly dependent on age: children older than 6 years of age have a mortality rate similar to that found in adults, but younger children have the highest death rates among all candidates. This rate is approximately 600–800 per 1000 patient-years at risk, and is three to four times greater than that observed in all other age groups. At total of 103 pediatric liver transplant candidates died in 2006 before transplantation. Recent attempts to preferentially allocate donors to high-risk pediatric recipients have been undertaken in an attempt to lower this rate. As with kidney transplantation, the number of liver transplantations performed in children each year has been quite stable, averaging 500–600 per year over the past decade.

Heart failure in children

About 25% of children considered or listed for heart transplantation are aged <1 year, with the remainder evenly split between cohorts aged 1–10 and those aged 11–17 years. There appears to be a slight predominance of boys, and the ethnicity generally reflects the overall population. The two major etiologies of heart failure in children are cardiomyopathy and congenital structural heart disease. The ratio of these two diagnoses is highly dependent on candidate age at listing: for infants aged <1 year, most have congenital structural heart disease – as high as 75% in previous years. However, as the surgical techniques for repairing congenital lesions have improved, the number of children listed for transplantation has decreased and the proportion listed because of cardiomyopathy has increased from 25% to 35%. Cardiomyopathy accounts for 50% of heart failure cases for children aged 1–10 years and for 75% for adolescents listed for heart transplantation. A small fraction, <5% in all age groups, is listed for other reasons, such as retransplantation. Hypoplastic left heart syndrome has been the predominant diagnosis in infants undergoing heart transplantation. In infants, if heart transplantation is performed, it is generally done as a primary treatment, whereas, in older children and adolescents, it is performed after corrective surgery has been unsuccessful. More recently, the use of heart transplantation as primary therapy for infants has been decreasing, probably reflecting increased use of corrective, staged repairs. Cardiomyopathy subtypes are not evenly distributed: dilated cardiomyopathy represents about 75% of those listed for heart transplantation, with smaller fractions of restrictive cardiomyopathy (12%), myocarditis (8%), and hypertrophic cardiomyopathy (5%).

The number of children listed for heart transplantation has remained relatively stable over the last decade, during which here have been 400–500 children listed for heart transplantation at any time in the USA. More recently, the number of patients who have received transplants has increased slightly to 314 in 2006. The number of children who died while awaiting heart transplantation decreased to 59 in 2006, likely reflecting improvements in the treatment of chronic heart failure and adjustments in the allocation system that have provided better opportunities for children to receive heart transplants in a timely manner.

Support for pediatric heart transplant candidates by the use of extracorporeal devices is still uncommon but is increasing in frequency. Ventricular-assist devices (VADs) appropriate for young children and infants have been developed only recently. On the other hand, extracorporeal membrane oxygenation (ECMO) has been used more successfully in young children than in adults. In addition, the increased use of VADs and human homograft material for those who require surgery has resulted in higher rates of sensitization among pediatric heart transplant candidates. Unfortunately, the presence of anti-donor antibodies results in longer times on the waiting list, less likelihood of being appropriately matched for transplant, and poorer graft survival than that observed in unsensitized recipients. Techniques for reducing, preventing, and treating pre-sensitization are currently under investigation.

As with other transplant evaluations, pediatric heart transplant candidates must be assessed for clear indications for heart transplantation and to determine whether or not transplantation represents a viable option. Thorough evaluation of the candidate's pulmonary vascular resistance is an essential component of the overall evaluation process. As is the case with other pediatric organ transplant candidates, there are very few absolute contraindications to heart transplantation, and these include active and severe infection, active malignancy, immunodeficiency states that would be worsened by chronic immunosuppression, and severe and uncorrectable organ failure or dysfunction, particularly neurologic dysfunction.

Chronic lung disease in children

The number of pediatric lung transplants reached a peak in the late 1990s at slightly fewer than 100 transplants per year. The number has been stable since 2000 at about 60–70 per year. For infants aged <1 year, congenital heart disease and pulmonary vascular disease are the primary indications for lung transplantation. Certain congenital abnormalities such as surfactant protein B deficiency can also be treated with lung transplantation. In older children, aged 1–10 years, cystic fibrosis is the most common diagnosis, representing about a third of cases. Idiopathic pulmonary arterial hypertension is another important indication. About 75% of lung transplant candidates are adolescents and cystic fibrosis is the primary diagnosis for about two-thirds of them. There are over 30 000 patients with cystic fibrosis in the USA. Despite the identification of the gene responsible for cystic fibrosis, treatment currently remains symptomatic and supportive rather than curative. Nevertheless, these treatments have been very successful and mean survival time has improved over the past 30 years from the mid-teens to age >30 years. Most of the deaths are related to respiratory failure. As a result of the prolonged survival time, at least 80% of transplant candidates for lung transplantation who have cystic fibrosis are aged >18 years at the time of listing. The indications for listing and transplantation are somewhat subjective but typically include a decline in pulmonary function as measured by the forced expiratory volume in 1 second (FEV_1) of 30% or more.

Key points 6.1 Cystic fibrosis and pediatric lung transplantation

Over 30 000 patients in the USA have cystic fibrosis (CF)

CF accounts for approximately a third of lung transplantations performed in children between ages 1 and 10

CF accounts for approximately two-thirds of lung transplantations performed in adolescents

Intestinal failure in children

Children make up the predominance of candidates awaiting intestinal transplantation, comprising about three-quarters of the list. The number of pediatric candidates on the intestine waiting list has increased almost threefold, to 140 in 2006. The primary diagnoses leading to intestinal failure and indication for transplantation include three major categories. The first is the anatomic loss of the intestine due to short bowel syndrome, most commonly related to jejunal–ileal atresia, midgut volvulus, and abdominal wall defects such as omphalocele. Also, neonates may suffer necrotizing enterocolitis, midgut volvulus, and vascular thrombosis. In general, infants with <35 cm of small bowel and an ileocecal valve are likely to remain dependent on total parenteral nutrition (TPN), eventually becoming transplant candidates. Infants requiring more than 50% of their caloric intake via intravenous routes are also likely to require intestinal and possibly liver transplantation. The second category of disorders includes neuropathic diseases such as Hirschsprung's disease or myopathic diseases such as chronic interstitial pseudo-obstruction syndrome. The third category consists of congenital diseases of the intestinal epithelium such as microvillous inclusion disease and epithelial dysplasia.

Most of these children can be treated and can thrive through the use of chronic TPN. Indeed, TPN may allow intestinal adaptation to occur if provided for a long enough period of time, and it is certainly possible for children to have normal growth and development while receiving TPN. Current survival rates for home TPN at 1 and 5 years are 90% and 75% respectively. The complications of chronic TPN include sepsis,

liver failure, and loss of central venous access sites. Thus, the decision to progress to listing for intestinal transplantation may be similar to that for kidney transplantation, i.e., the alternative treatment is quite safe and effective, although it seriously impairs quality of life. The decision about intestinal transplantation is, however, complicated by the relatively poor outcome of the procedure, in contrast to that of kidney transplantation.

Pancreatic failure in children

The incidence of diabetes mellitus in children is increasing, similar to what is seen in adults. Other causes of pancreatic failure in children include hemolytic–uremic syndrome, cystic fibrosis, and chronic pancreatitis. The major complications of these latter forms of pancreatic failure are gastrointestinal dysfunction and diabetes mellitus. Both of these disorders can, however, be treated with exogenous medications such as oral pancreatic enzymes and insulin. As a result of the low morbidity and high efficacy of these treatments, replacement of pancreatic function by pancreas or islet transplantation is of questionable utility. Indeed, only a handful of children have received pancreas transplants, so few in fact that virtually no registries include those numbers. The balance of clinical improvement related to pancreas transplantation, the burden of chronic immunosuppression, and overall long-term success rates has generally resulted in decisions not to transplant children.

Donors for pediatric organ transplantation

Living donors

Children traditionally have been more likely to receive organ transplants from living donors than have adults. There are several reasons for this practice. Outcomes of living donor kidneys have had superior outcomes compared with deceased donor kidneys, with half-lives that may be up to twice as long as even ideal deceased donors. Parents generally are very willing to be donors for their own children. Transplant surgery has progressed to the point that an adult kidney may be transplanted into an infant as small as 6 kg, the size typically achieved by such children at the first birthday (Figure 6.1 and see below). Indeed the longest projected half-lives are achieved when a living adult donor kidney is transplanted into an infant.

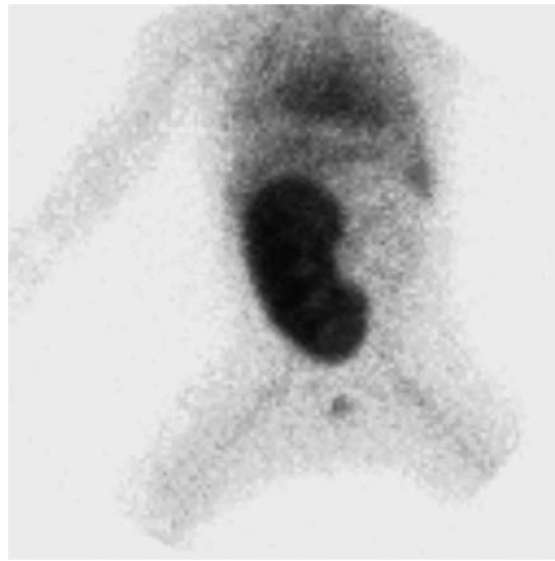

Figure 6.1 Mag-3 nuclear scan of an adult living-donor kidney into a 6.5 kg infant. The graft is well perfused but not concentrating tracer yet. Note the relative size of the graft compared to the recipient's liver and heart.

Evaluation and preparation of living donors for pediatric kidney transplantation should follow the same guidelines as for any other recipient. It is important to understand, however, that minors aged <18 years cannot be used as living donors. There is virtually universal agreement on this issue, as stipulated in the outcome of the Amsterdam Conference on the Care of Living Donors and on World Health Organization Guiding Principles on Human Cell, Tissue and Organ Transplantation that have been reiterated in the recent Istanbul Declaration. The principle underlying this prohibition against using minors as living donors is based on the ethical concept of volunteerism. Typically, minors are not considered capable of providing independent and truly voluntary permission.

The use of living donors for pediatric liver and lung transplantation has probably been more widely practiced than for adult recipients. Small lobes of donor

liver or lung can be utilized as satisfactory organs for young children. The morbidity and mortality for such living donors is probably less than when living donors are used for adult recipients, although such statistics are very difficult to come by. Evaluation of potential donors for pediatric liver or lung transplantation should follow the usual protocols and standards. The outcome of these types of living liver or lung transplant procedures may not, however, be uniformly superior to deceased donor transplants as is the case with kidney transplantation. Therefore, the proper use of living donors for pediatric liver and lung transplant candidates remains controversial.

Deceased donors

Pediatric candidates remain a small fraction of all potential organ transplant recipients. In some cases, size matching of organs between donor and recipient is quite important, particularly in heart and lung transplantations. However, as noted above, adult kidneys can be used for even small infants if proper techniques are used (see Figure 6.1). Also, adult livers can be "split" with the smaller component or lobe going to be pediatric recipient and the remainder of the liver going to another recipient, typically an adult. Similar techniques can be utilized for deceased donor lungs. However, here are technical complications related to these reduction or splitting techniques, and recipients of such organs typically have more complications, and lower graft survival rates and half-lives. In addition, adult recipients of split livers may also have complications relating to the procedures performed on the donor graft.

The Organ Procurement and Transplant Network (OPTN), which is responsible for allocation of organs for transplantation in USA, has generally provided preference for pediatric recipients in all of its allocation rules. This was first evident in the initial allocation policy for deceased donor kidneys. Pediatric candidates aged <15 years were provided preference for organs that were recovered from donors aged <10 years. Unfortunately, this allocation policy, although probably shortening the time that pediatric candidates were required to spend waiting for a transplant, preferentially provided some young recipients with high-risk donor kidneys. Specifically, graft thrombosis became an important cause of early graft failure, affecting up to 5% of pediatric deceased donor transplants. A retrospective analysis of risk factors for graft thrombosis identified young donors and young recipients independently to be at high risk. Thus, a policy that specifically assigned high-risk donors to high-risk recipients could have been predicted to result in suboptimal outcomes. Indeed, infants receiving deceased donor transplants during that era had the worst outcomes of any age group.

A change in allocation policy that provided additional "points" to pediatric candidates was substituted. This policy provided these points only after a certain waiting time, varying between 6 and 18 months depending on the candidate's age. This prescribed waiting time was provided in order to allow pediatric candidates sufficient time to receive offers from well-matched donors. Unfortunately, the number of points necessary to reach the top of the waiting list varied among regions and eras. In addition, the waiting time provided to candidates to permit sufficient opportunity for well-matched donors almost invariably did not result in transplants as planned. More recently, therefore, the OPTN once again changed its allocation policy to provide preference for pediatric recipients. The most recent change permits pediatric candidates to be placed at the top of the waiting list for donors aged <35 years as soon as they are listed. This new policy has resulted in a marked decrease in waiting time for pediatric kidney candidates; many of them now receive grafts within 6 months of listing. Unfortunately, another unintended consequence has occurred. It appears as if this strong preference has shifted the ratio of living donor and deceased donor grafts for children. before this allocation policy, up to 60% of donors for pediatric kidney transplants were living donors. For the first 1–2 years after this allocation change, that ratio has reversed. The pediatric community is currently reviewing these results but early analysis suggests that the ease of obtaining deceased donors and the rapidity with which these grafts can be transplanted have to be balanced against the expected shorter half-life of deceased donor transplants compared with living donor grafts.

The OPTN has also provided preference for pediatric candidates awaiting liver, heart, and lung transplantation with varying policies, e.g., children have a separate urgency score, known as pediatric end-stage liver disease (PELD), rather than the model used for adult liver allocation, known as model for end-stage

liver disease (MELD). In general, PELD provides better assessment of mortality risk for children awaiting liver transplant than MELD. However, recent analysis demonstrated that the MELD score is numerically higher for adolescents than the PELD one, and thus it has been substituted. In addition, OPTN has provided specific status 1 criteria for pediatric liver recipients which provides some preference for the sickest candidates. As candidates for combined liver–intestinal transplantation may have higher mortality while awaiting transplant, there are efforts to further refine liver allocation to provide additional benefit for them. The number of both candidates and size-specific donors is small, and wider sharing of these donors beyond typical OPO borders might alleviate some prolonged waiting episodes, and perhaps mortality, for infants and young children awaiting liver transplantation.

Similarly, despite the potential complications in adult recipients of split livers, policies that may require consideration of splitting donor livers more frequently could reduce pediatric candidate mortality. These latter two policies are currently under consideration by the OPTN. As a result of the stringent need for matching size of donor and recipient for heart transplants, small pediatric recipients may have a severe handicap because of the lack of size-matched donors in their local area. Also, adolescents will be in competition with adults of about the same size. Thus the OPTN has been focused on broader sharing of pediatric donor hearts because an appropriately sized donor for a small recipient may be a greater distance than is typically true for adult transplantation. Sharing even at a national level is being considered. Furthermore, children are now being given preference for organs recovered from pediatric donors in an effort to shorten waiting time. The allocation of lungs for transplant is based on a new system that assesses both the urgency of the recipient and the probability of good outcome. As children aged <12 years have a different mix of the etiologies for chronic lung failure, they are allocated donor lungs in a manner different from older children and adults. There are considerations of providing preference for pediatric lung candidates to receive young donor lungs, comparable to the kidney, liver, and heart allocation systems.

Death on the waiting list

Unfortunately, some candidates die while awaiting organ transplantation. The mortality on the waiting list may be higher for young pediatric candidates than for older children and adults. The number of children awaiting all types of deceased donor organ transplants over the past decade is shown in Figure 6.2. This figure shows the number of active transplants on the last day of each calendar year and is a relatively accurate indicator of the balance of additional new candidates and candidates who have either received grafts or died. As noted, the number of listed pediatric candidates has actually decreased over the last 5 years, probably because of more appropriate listing criteria for liver and lung transplantation. As a result of the success of chronic dialysis, death on the waiting list for kidney transplantation tends to be lower than for other organs. In contrast, waiting list deaths for liver transplant candidates are more common. The development of the PELD and MELD systems was designed to allocate organs to

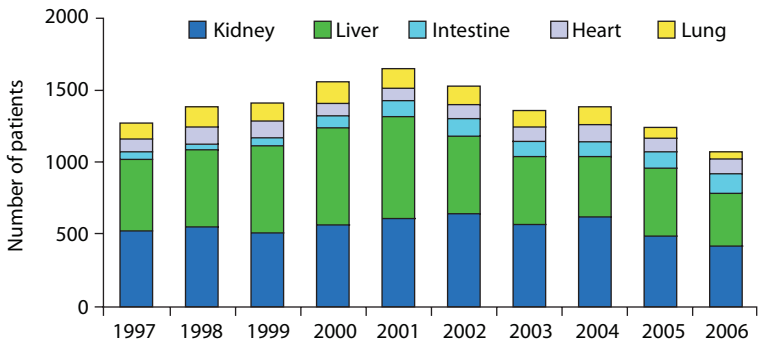

Figure 6.2 Number of pediatric transplant candidates on the deceased donor waiting list on the last calendar day of each year, by type of graft. (Reprinted from Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997–2006. *Am J Transplant* 2008;8:935–45.)

those most urgently in need of them. However, because of their declining health condition, the mortality risk rises substantially. Currently, children older than 6 years have a mortality risk the same or slightly lower than that of older children and adults, approximately 50 deaths per 1000 patient-years at risk. However, the risk for infants aged <1 year is 10- to 20-fold higher, between 500 and 1000 deaths per 1000 patient-years at risk. In 2006, 103 pediatric candidates for liver transplantation died before they could receive a graft.

The number of heart transplant candidates who died before they could receive a graft has declined slightly over the past decade, to 59 deaths in 2006, equivalent to 89 deaths per 1000 patient-years. In that same year, 54 pediatric candidates received lung transplants but 16 died while waiting. There has been great variation in the mortality rate while awaiting intestinal transplant, likely due to small numbers of candidates awaiting combined liver–intestinal transplantation. For candidates listed initially for intestinal-alone transplantation across all age ranges, the death rate was 379 per 1000 patient-years in 2006. As a result of all of these death rates, the OPTN set a strategic goal of eliminating death on the waiting list for pediatric organ transplant candidates. Obviously, accomplishment of that goal would require improvement in artificial life support for children with organ failure, substantial preference for children compared with adults on the waiting list, wider sharing of appropriate organs from size-matched young donors, and perhaps innovative surgical techniques. Although elusive and ambitious hopefully this goal is achievable.

Key points 6.2 Death on organ transplant waiting lists among children

In 2006:

- 103 liver transplant candidates
- 59 heart transplant candidates
- 16 lung transplant candidates

Strategic goal of the Organ Procurement Transplant Network: eliminate all deaths among children on organ transplant waiting lists!

Pediatric organ donors

Although the accidental death rate among children is lower than in adults, it does rise during adolescence. Furthermore, as children frequently have few complicating medical disorders, they are more likely to be appropriate organ donor candidates if they have terminal disorders. The number and percentage of pediatric organ donors have decreased somewhat over the past 10 years. The distribution of generations has, however remained constant, with about 60% of donors ranging between the ages of 11 and 17 years. And, while the number of adult donors is substantially greater than that of pediatric donors, the percentage of organs transplanted versus the organs recovered from deceased donors is dramatically greater. Within the pediatric age range the vast majority of organs recovered from pediatric donors are transplanted. What may be even more striking is the balance between pediatric organ donors and pediatric transplant recipients. As shown in Figure 6.3, less than 10% of kidneys recovered from pediatric donors were transplanted into pediatric recipients early in this decade. This ratio may be changing with the new pediatric kidney allocation system. Nevertheless, the number of pediatric donor kidneys that were transplanted into adults was more than five times the number of adult donor kidneys that were transplanted into children. The same patterns are similar for pediatric heart, lung, and liver donors. Only in pediatric intestinal transplants are the majority of organs recovered from pediatric donors transplanted into pediatric recipients.

Given the present shortage of deceased organ donors and in view of the decreased number of pediatric organ donors, there has been a broad range of efforts to increase organ donations including donation after cardiac death (DCD). DCD has been increasing among all donor age groups from just a handful in the late 1990s to 647 in 2006. Children comprise about 12% of DCD donors and about 8% of pediatric donors were from DCD. As organ donation is generally unusual in a pediatric hospital, the introduction of DCD protocols may require more time and effort to be developed and enforced. Pediatric intensive care units have well-developed end-of-life and withdrawal-of-support practices in place, and these were developed before the DCD

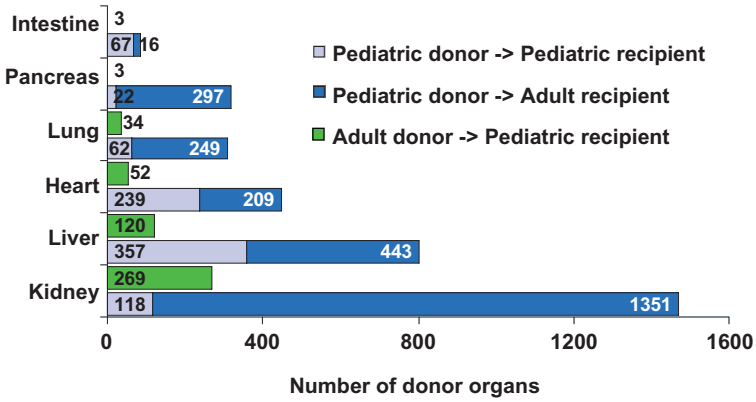

Figure 6.3 Number of deceased donor grafts recovered from pediatric and adult donors and transplanted into pediatric and adult recipients by organ type, 2003. More pediatric donor organs are transplanted into adults than adult organs into children. (Adapted from Magee JC, Bucuvalas JC, Farmer DG, et al. Pediatric transplantation. *Am J Transplant* 2004;**4**(suppl 9):54.)

protocols became practical. Based on recent policies advanced by the Joint Commission (JCAHO) and the OPTN, there is new emphasis on developing DCD protocols.

Key points 6.3 Pediatric organ donors

Higher conversion rates than adult donors, usually because of absent comorbidities

Currently comprise 12% of DCD donors

Organs from very young donors associated with more thrombosis and other technical problems

The large majority of kidneys, hearts, lungs, and livers procured from children are transplanted into adult recipients

Wait list management

As pediatric organ transplant programs are generally small and perform fewer than 50–100 transplantations per year, the complexity and difficulties of managing a large list of transplant candidates is generally not as common as in adult programs. Nevertheless, the need to assure that the candidate listing data are correct and up to date is equally important for pediatric candidates. Of similar importance is the need to assure that the candidate's transplant status is stable and unaffected by intercurrent illness or severity of disease.

Peritransplant procedures

Successful organ transplantation requires careful preparation of the candidate before transplantation, a team effort in the immediate postoperative setting, and careful maintenance of the graft after the patient is discharged from the hospital. Each of the organ systems has unique components of this effort.

Pediatric kidney transplantation

Histocompatibility matching used to play a large role in allocation of deceased donor kidneys and in choosing a living donor. Although better donor matching does result in longer graft half-lives, this influence has been lessened because of overall improvement in immunosuppression. However, kidney transplants still require blood-type matching and negative cross-matches between donors and recipients. Both of these requirements have been modified lately based on more sensitive cross-match techniques, and desensitization procedures in a few circumstances. As chronic hemodialysis or peritoneal dialysis provides a lifesaving option, pediatric kidney transplantation does not have to be undertaken as an emergency procedure under any circumstances. Indeed, the presence of chronic dialysis permits preparation of the candidate so that the transplantation can be undertaken under the best possible circumstances rather than under the most risky or difficult circumstances. As noted above, approximately 25% of children receive kidney transplants pre-emptively, i.e., without prior dialysis treatment. Other children may undergo periods of chronic

dialysis in order to stabilize their nutrition, to perform necessary corrective surgery before transplantation, or because suitable donors have not been identified. In addition, particularly for children with acquired diseases such as FSGS or lupus nephritis, a period of chronic dialysis permits the underlying disease to "burn out" and for the child to have previously used medications such as steroids or cytotoxic agents tapered and discontinued. Sometimes, renal function deteriorates suddenly and dialysis is necessary before transplantation can be undertaken.

There are several indications for native nephrectomies, either before transplantation or during the transplantation procedure. Children who have urologic malformations and obstructive uropathy may develop a urinary-concentrating defect and have large amounts of urine output. If this continues after transplantation, appropriate hydration, particularly if the recipient is an infant, may be compromised. If children have ongoing proteinuria, particularly those infants who have congenital nephrotic syndrome with extraordinary protein losses, these conditions will also compromise postoperative care. Pyelonephritis in kidneys of children with serious urogenital malformations may also complicate post-transplant care. Sometimes, chronic kidney disease in children can cause serious hypertension. When hypertension either is difficult to control or requires substantial antihypertensive medications, consideration of pretransplant nephrectomy may be appropriate. Thus, polyuria, proteinuria, ongoing hypertension, and infection may be indications for elective pretransplant native nephrectomy. In some programs, this is performed before the transplantation procedure and, in others, during it. In the particular circumstance of children with severe proteinuria, however, the native nephrectomies are preferentially performed before the transplantation in order to allow sufficient time for the candidate's nutritional status to be improved. One other special circumstance for which pre-transplant nephrectomy should be considered is the transplantation of an adult kidney into an infant recipient. In that situation, there is ongoing concern about sufficiency of blood flow to the transplanted kidney (see Figure 6.1). Perfusion of native kidneys may add a complicating factor to this concern for adequate blood flow and may suggest that they be removed before implantation of the new graft.

Generally, children >30 kg can receive the same surgical implantation techniques as adults. Smaller children and infants will require an individualized approach, for which the key issue is the appropriate matching of blood vessel size and anticipation of circulatory volume requirements. For young children and infants, <10 kg, the transplant incision is generally a midline laparotomy with anastomosis of the donor kidney onto the aorta and inferior vena cava. For slightly older children, there is reasonable variability based on the relative size of the donor organ and the recipient, and any pretransplant surgery performed on the recipient. Thus, the anastomosis may be to the great vessels or to the femoral or iliac vessels, depending on the relative size of the donor and recipient vessels. In addition, some children have vascular abnormalities that require special techniques. In some situations, en bloc implantation of organs recovered from infant donors may be used, as shown in Figure 6.4. The implantation of the transplant ureter into the recipient's bladder is typically performed in a manner designed to prevent vesicoureteral reflux. Perioperative management of the pediatric recipient also requires attention to specific or unique details. Intraoperatively, there is substantial emphasis on prevention of complications from underlying systemic disease and maintenance of optimal perfusion of the transplanted kidney. In general, particularly when there is a substantial size mismatch between the donor graft and the recipient, there is a need to

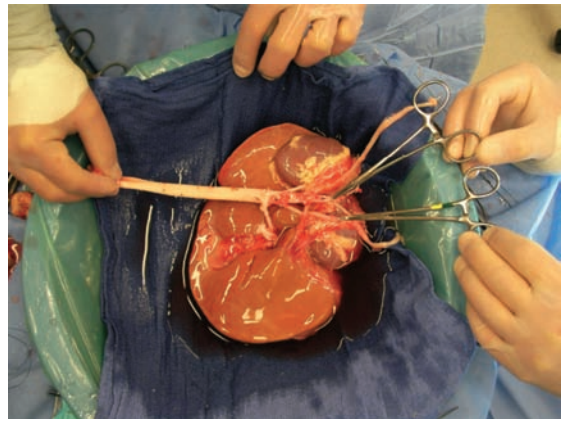

Figure 6.4 En bloc infant donor kidneys recovered for transplantation into infant requiring combined liver–kidney transplantation. Note long segment of vena cava recovered to replace a thrombosed segment in recipient.

expand the circulatory volume to allow for adequate perfusion of the adult donor allograft. In extreme circumstances, the recipient's cardiac output doubles after perfusion of the graft is achieved, and up to 50% of the cardiac output is directed toward perfusion of the transplanted kidney. In general, central venous pressure is kept high, in the range of 8–12 cmH_2O with a mean arterial pressure >70 mmHg. Sometimes, an infusion of dopamine is required. Postoperatively, the child is often cared for in an intensive care unit or at least requires intensive care nurse monitoring. Typically, the urine output for the first 48 h is replaced on an equal basis and may reach extraordinary levels. In this setting, careful management of fluid and electrolyte status by experienced staff is essential. Hyperglycemia, hyponatremia, hypocalcemia, acidosis, and hypokalemia are all possible without appropriate management. After 48 h, fluid intakes are gradually tapered to more usual levels. In the circumstance of adult kidneys being transplanted into young children or infants, the recipients must continue to receive greater than usual amounts of fluid for many months or years, to avoid underperfusion of the graft.

Children who have delayed graft function may need to undergo hemodialysis or peritoneal dialysis until the renal dysfunction resolves. Of course, this complicates postoperative care substantially. If transplant biopsy is required to assess for acute rejection or to determine the status of the graft, it can be performed in the usual percutaneous manner, generally under ultrasound guidance, even if the graft is intraperitoneal. In this latter circumstance, however, bleeding is more common because of lack of appropriate tamponade, so appropriate vigilance is necessary.

Case: infant kidney transplant

A 6-month-old infant is referred to the pediatric hospital for treatment of congenital nephrotic syndrome. An older brother with the same disorder had died at 3 months of age from sepsis and peritonitis. He has an 11-year-old sister who appears healthy. His mother's pregnancy was complicated by polyhydramnios and an amniocentesis had demonstrated elevated levels of α-fetoprotein. Soon after birth, severe proteinuria was noted. He was treated with periodic infusions of salt-poor albumin, but had many complications. He became dehydrated at 3 months of age and infarcted the tips of two toes on his left foot. He developed an episode of *E. coli* peritonitis just before referral and was treated with intravenous antibiotics, albumin infusions, and intravenous immune globulin. On presentation, he was markedly malnourished with depleted muscle mass, with marked anasarca. He weighs 5.9 kg. His hematocrit is 24%, blood urea nitrogen (BUN) 12 mg/dL, serum creatinine 0.1 mg/dL, and serum albumin 0.9 g/dL. Both parents wish to be worked up as possible kidney donors as well as his sister and two uncles.

Pediatric liver transplantation

Blood type compatibility is generally observed for liver transplantation, with possible exceptions for the youngest recipients. Histocompatibility matching is typically not performed and cross-matching is performed only after the procedure. As noted above, allocation of deceased donor livers for transplantation is based on a medical urgency, indicating that grafts are allocated to recipients most likely to die without a transplant. Thus, it is highly likely that these candidates will be quite unstable at the time of transplantation. To the credit of the transplant teams, postoperative mortality does not seem to be related to the severely compromised condition of these candidates at the time of transplantation. For pediatric recipients, particularly infants, careful attention must be paid to assuring adequate nutritional support before transplantation. Recovery of deceased donor livers follows typical protocols, but particular care must be provided to the graft vessels and supplemental splenic or carotid arteries should be recovered. Living donor liver recovery also has been previously described and the approach depends upon the lobe to be removed. Laparoscopic left lateral lobe recovery has been reported, but open procedures are more common. The actual procedure is dependent on the source of the graft, with some variations related to whole versus reduced-sized grafts. Up to 50% of children receive technical variant grafts, including living donor liver grafts and reduced-sized grafts. These partial liver transplants tend to have complicated vascular and biliary anastomoses, creating postoperative problems with graft perfusion and biliary outflow. In addition, those with a cut edge tend to have biliary leaks and postoperative infections. Improvements in surgical techniques and preoperative management have reduced the need for lengthy hospitalization following liver transplantation. Typically patients

requiring intense monitoring and abdominal ultrasonography is performed to assess perfusion of the graft on a periodic basis. As with kidney transplantation, fluid management is undertaken to assure adequacy of graft perfusion. Frequently anticoagulants in the form of aspirin, heparin dextrans, or prostacyclin are provided to prevent graft thrombosis. Careful assessment for postoperative complications, including bleeding and bile leaks as well as for infection and electrolyte abnormalities, is essential.

Pediatric heart transplantation

Blood-type-compatible donors are typically used for heart transplantation. However, very young candidates, aged <2 years, may receive blood-type-incompatible grafts if their anti-A and anti-B antibody levels are low. Typically, allocation of hearts for transplantation is not based on histocompatibility matching, although knowledge of donor antigens may be valuable to predict positive cross-matches. Although these cross-matches cannot typically be performed before transplantation, they certainly complicate the postoperative management and success, so knowledge about potentially positive cross-matches, based on specificity of pre-formed antibodies, may be valuable. As noted above, many infants and young children have high levels of anti-HLA antibodies, likely related to extracorporeal perfusion or the use of homografts before transplantation. As this level of sensitization limits transplant options for these patients, new protocols designed to "de-sensitize" them are being explored.

As with liver transplantation, allocation of hearts for transplantation is based on urgency criteria, but, in addition, there are stronger restrictions with respect to size mismatches. Therefore, children, particularly young children, may wait and suffer many complications related to chronic heart failure before the transplantation. Importantly, until very recently, there were no appropriate VADs available for small children. Heart transplant surgical techniques have been described previously. These techniques may be complicated by prior surgery for correction of congenital heart disease, leading to more complex surgery requirements for the transplant. In addition, abnormal placement of the great arteries and other structures might require innovative approaches to ensure that the donor heart functions properly. In general, postoperative management is similar to that provided to other children undergoing cardiopulmonary bypass. Systolic function often recovers rapidly but diastolic dysfunction may persist for weeks. Particular attention must be paid to pulmonary vascular resistance which can cause right heart failure. In addition, cardiac arrhythmias are more common in this setting. Maintenance of an appropriate heart rate is important for maintaining cardiac output and can be regulated by atrial pacing or chronotropic agents. Surveillance for acute rejection is typically performed by routine intracardiac biopsy. Many programs perform biopsies on a weekly basis in the early postoperative period.

Pediatric lung transplantation

Matching on the basis of blood type and histocompatibility typing for lung transplant is similar to what is done for heart transplant. In general, there is no time for performing pretransplant cross-matches but attention to recipient antibodies to donor HLA antigens might provide predictive value. Typically, bilateral sequential lung transplants rather than single lung transplant is the procedure of choice in children because of the concern for growth of the implanted lungs. Postoperatively, attention is paid to graft dysfunction related to reperfusion injury. All patients undergo bronchoscopy and perfusion lung scan soon after transplantation. Infection is the most common longer-term complication. The lung is the only transplanted solid organ exposed constantly to outside contamination. Maintenance of appropriate fluid and electrolyte balance is necessary in order to avoid pulmonary edema. If living donors are used, typically there are two donors, each of whom supply a single lobe. The results of the living donor transplants seem to be about as good as those for deceased donor transplants.

Pediatric intestinal transplantation

In general, identical blood group matching is preferred for intestinal transplantation, although the clinical condition of the recipient would dictate the possible use of ABO-incompatible blood types. Critically ill liver–intestine or multivisceral recipients may possibly receive ABO-incompatible grafts, but this practice is generally avoided in isolated intestine

transplants. The non-identical blood type transplants may be associated with hemolytic reactions because of the large lymphoid load included with the allograft. In general, cytotoxic cross-matches should be negative before implementation because of a detrimental effect of positive cross-matches on outcome. This is particularly true for isolated intestinal transplants. In the setting of a combined liver–intestine transplant, however, cross-matching may not be necessary. Size matching is important for successful intestinal transplantation and, indeed, donors smaller than the recipient may be necessary because of a smaller abdominal cavity. Unfortunately, organs from intestinal donors seem more susceptible to necrotizing enterocolitis. As the intestine is so sensitive to perfusion injury, meticulous care of the donor before transplantation to avoid cardiac arrest or circulatory collapse is important. The recipient operation may be complicated by vascular abnormalities occurring before transplantation. In all these cases, concern for maintenance of adequate graft perfusion is uppermost. As surveillance for rejection requires appropriate biopsy material, and as allograft mucosal biopsy remains the only method to confirm clinically suspected acute rejection, appropriate access to a site for biopsy is necessary.

Post-transplant monitoring

Pediatric recipients of organ transplants are typically followed very closely by members of the transplant team in the immediate post-transplant period. Many programs have established protocols for the frequency of surveillance and its components. The American Society of Transplantation developed a clinical practice guideline for follow-up of the kidney transplantation and this contained proposed guidelines for the follow-up of pediatric kidney transplant recipients. In general, the pediatric community felt that more frequent and more intense follow-up was necessary for children, based on their unique complications, the possibility of more frequent early acute rejection episodes, the potential for infection related to a more naïve immune response to pathogens before transplantation, and the potential for non-adherence to prescribed immunosuppression protocols. Typically, these transplant recipients are assessed for graft function and complications of both the transplant and the immunosuppressive medications being used. Pediatric programs usually taper the initial immunosuppression slowly to lower maintenance levels during the first post-transplant year.

Some programs, typically heart and intestinal transplant programs, perform surveillance graft biopsies in order to be vigilant for acute rejection. Kidney transplant programs, based on excellent outcomes from multicenter clinical trials, have started to perform surveillance kidney biopsies also, but more frequently to assess for nephrotoxicity than for acute rejection. In general, although patients are frequently referred back to their primary care physicians or subspecialists closer to home, pediatric transplant recipients continue to be monitored at their transplant centers on a periodic basis. Appropriate adjustment of immunosuppressive medication as the patient grows becomes increasingly important with lengthening time after transplantation. Of equal importance is the assessment of adherence to the transplant follow-up protocols. Unfortunately, there have been multiple reports of children, particularly adolescents, who have lost their grafts from presumed non-adherence to immunosuppression regimens. Without good methods of assessing adherence, however, it is very difficult to determine whether these reports are accurate. In the same vein, proposals for behavior modification that may lessen the incidence of non-adherence are compromised by lack of accuracy of assessment of their efficacy. Nevertheless, increasing attention is being paid to this problem by pediatric care teams because of its detrimental effects on long-term outcomes. Perhaps the combination of behavioral techniques to improved adherence as well as the development of immunosuppressive agents or protocols that require less vigilance on the individual patient's part may prove to be successful in the future.

Immunosuppression for pediatric transplantation

In general, children receive the same immunosuppressive medications after organ transplantation as adults. However, most of these medications have not been tested in controlled clinical trials and few of them have specific pediatric indications. This situation is changing, however, because the Food and Drug Administration (FDA) provides some benefit to phar-

maceutical companies that seek and achieve pediatric indications. Furthermore, the establishment of multicenter clinical trial groups permits specific testing of some of these medications in children. Dosing of medications for children is usually indexed against some measure of body mass, either weight or body surface area. Furthermore, infants and young children cannot swallow pills and they frequently metabolize medications at substantially different rates from adults. Thus, they frequently require special formulations and schedules.

Virtually all organ transplant recipients receive multidrug regimens, typically double or triple therapy. In addition, many receive induction therapy with lymphocytotoxic or modifying antibodies. Many of the protocols are center specific and based on experience rather than controlled trials. Recently, some trials sponsored by the CCTPT have evaluated certain combinations. In most cases, the immunosuppression is maximized soon after the transplantation, and then is very slowly tapered to lower maintenance levels over several months to years. In general, kidney transplant recipients receive substantial immunosuppression in order to prevent acute rejections because every acute rejection leaves the transplanted kidney damaged and shortens the ultimate graft survival. Most commonly, these patients receive triple immunosuppression, including corticosteroids, and at least half receive treatment with an induction antibody. Heart transplant recipients also receive substantial immunosuppression but much more frequently receive steroid-free protocols because of their long-term detrimental cardiovascular complications. They often receive high doses of calcineurin inhibitors (CNIs) early after transplantation and that may account for the high incidence of nephrotoxicity in these patients.

Liver transplant recipients infrequently receive induction antibody treatment and often have steroid-free immunosuppression protocols. The overwhelming majority of liver transplant recipients have a CNI-based immunosuppression protocol, most often tacrolimus. Typically, tapering of immunosuppression is more aggressive in these recipients; they do have higher frequencies of acute rejection but the regenerative capabilities of the liver probably account for the fact that the rejection episodes have less deleterious effects on long-term outcome. Some liver transplant recipients are reduced to monotherapy for maintenance. There is less information about intestinal and lung transplant recipients because of the low number of procedures performed each year. However, intestinal transplant recipients frequently receive very high levels of immunosuppression, particularly early on because of the frequency and severity of acute rejection. Similarly, lung transplant recipients may also have high rates of rejection. Unfortunately both of these types of transplants have substantial morbidity related to post-transplant infections, thereby complicating the decision about immunosuppressive techniques even more.

Induction antibodies

Retrospective data from the NAPRTCS registry have consistently shown a beneficial effect of prophylactic induction antibody use in pediatric kidney transplant recipients. Several studies have demonstrated an 8–10% improvement in 5-year graft survival for both living and deceased donor kidney transplant recipients who received induction antibody compared with those who did not. However, a large randomized controlled trial of the monoclonal antibody OKT3 showed no beneficial effect other than a delay of the first acute rejection episode. Similarly, retrospective analyses of interleukin-2 (IL-2) receptor-blocking antibodies have shown that they are well tolerated and may delay or prevent acute rejections. Nevertheless, well-controlled trials of their efficacy on long-term graft survival are lacking, so the use of these antibodies for pediatric organ transplant recipients is based mostly on center bias and experience. Currently, there are two polyclonal antibodies available, ATGAM and Thymoglobulin. The latter is much more commonly used. Typically it is provided, particularly in the setting of delayed graft function, for 10–14 days after transplantation. A recent report suggests daily monitoring of CD3+ lymphocyte subsets as a guide to therapy: the daily dose is given only when the CD3+ lymphocyte count exceeds a certain level, such as 20 cells/mm^3.

There is an increasing trend for the use of Thymoglobulin after pediatric kidney and heart transplantation, and it is proving to be both safe and probably effective in preventing acute rejection in the early post-transplantation period. Orthoclone OKT3 is a mouse monoclonal antibody directed against the T3 antigen on most circulating lymphocytes. Although

it apparently depletes lymphocytes from the peripheral circulation, it is not truly a "lytic" antibody because mouse antibodies do not bind human complement. As noted above, a controlled trial of Orthoclone OKT3 in pediatric kidney transplant recipients demonstrated delay of the first acute rejection episode but no effect on long-term graft survival or the incidence of acute rejections. Currently, Orthoclone OKT3 is not used for induction treatment in virtually any pediatric organ transplant recipients but it is sometimes used for treatment of acute rejection episodes, particularly in intestinal transplant recipients.

A newer monoclonal antibody, alemtuzumab (Campath-1H) causes profound lymphocyte depletion for at least 3–6 months. Recent innovative protocols utilizing alemtuzumab induction for pediatric kidney and liver transplants have demonstrated that it is generally safe and quite effective in preventing early acute rejection episodes and allowing minimization protocols for these recipients. Larger studies will be necessary before alemtuzumab is more widely utilized. There are two non-depleting antibodies that block the IL-2 receptor on mature lymphocytes, daclizumab and basiliximab. Both of these antibodies have been utilized for induction treatment in children and there is broad experience with their safety. In general, they are used only during the immediate post-transplant period. However, some innovative protocols suggest that longer-term use may be safe and possibly allow pediatric recipients to avoid other toxic immunosuppressants, specifically corticosteroids. Experimentation with chronic use of these antibodies has started, but unfortunately daclizumab production has now ceased, making further study unlikely.

Maintenance immunosuppressive drugs

There are currently six classes of immunosuppressive medications that are used for chronic prophylactic treatment for pediatric transplant recipients. Each class is discussed below.

Corticosteroids

Corticosteroids have been used for many decades and were felt to be necessary for graft survival for kidney transplantation until recently. Typically, corticosteroids are given in high doses immediately after the transplantation and then tapered to low daily or alternate-day schedules. Lower doses and less frequent dosing have been associated with fewer chronic side effects. These side effects are particularly difficult for pediatric recipients, and include hypertension, hyperglycemia, cosmetic changes, specifically cushingoid appearance and weight gain, psychological changes, osteoporosis, growth retardation, hypercholesterolemia, etc. The growth retardation effects are particularly noticeable after kidney transplantation. As noted, alternate-day dosing can ameliorate many of these effects but steroid withdrawal or avoidance is the most preferable. Until very recently all attempts to withdraw steroids from pediatric kidney transplant recipients were unsuccessful. However, in at least four recent trials, two of which were randomized and controlled, steroids have been completely eliminated after pediatric kidney transplantation, so it is likely that the appropriate use of other medications will permit steroid-free transplantation for a large number of pediatric kidney transplant recipients. As noted above, liver and heart transplant recipients frequently avoid or withdraw steroids altogether.

Azathioprine and mycophenolate mofetil

Azathioprine and MMF are anti-proliferative agents that have been used frequently in pediatric transplant recipients. More recently, enteric-coated mycophenolic acid (Myfortic), has been introduced as an alternative, but there is less pediatric experience with its use. Myfortic dosing studies in children have demonstrated slightly higher area values for under the curve (AUC) than in adults with comparable doses, but the clinical significance of this is not known. Azathioprine was the first approved medication shown to prevent rejection and it has had wide applicability. However, for the past decade, it has been principally replaced by MMF. In general, both of these medications can cause granulocytopenia and MMF has been associated with gastrointestinal complications, particularly in younger children. Although several studies have assessed the pharmacokinetics and safety of MMF, there are no clear guidelines to concentration-controlled dosing. MMF has been used in combination with all other immunosuppressants except azathioprine and there are no contraindications to these combinations. MMF dosing has been evaluated in children and the dosing is typically prescribed based on the body surface area, with recommended

doses ranging between 600 and 1200 mg/m^2 per day in two to three divided doses. When diarrhea occurs, the more frequent dosing with lower dose amounts has been tried, but often azathioprine is substituted instead, in doses of 1–2 mg/kg per day. More precise dosing of MMF or azathioprine can be achieved by compounding liquid preparations from the pill forms that are supplied.

Calcineurin inhibitors

CNIs have been the mainstay of organ transplantation for the past 20–30 years. Cyclosporine was the first of this class of medications that was introduced and its use led to marked improvements in virtually all types of organ transplant outcomes. Early use of cyclosporine in children was, however, somewhat complicated by a lack of clinical trials and understanding of its pharmacokinetics. Young children, in particular, were found to metabolize cyclosporine more quickly than adults, and this led to underdosing. The proper dosing was corrected only after institution of protocols using two to three times a day dosing and indexing based on body surface area. Typical starting doses for children aged <6 years are 500 mg/m^2 per day, administered three times a day, whereas older children receive 15 mg/kg per day, administered twice daily. Doses are adjusted to attain protocol-specific target blood levels.

The complications of cyclosporine in children are similar to those in adults and include nephrotoxicity, hypertension, and hyperlipidemia. However, hypertrichosis, gingival hyperplasia, and facial dysmorphism are particularly disturbing to children, especially adolescents, so long-term use has been compromised. Tacrolimus was first approved for liver transplantation but subsequently has been used extensively for kidney, intestine, heart, and lung transplantation. It is particularly attractive for pediatric use because it lacks the cosmetic side effects of cyclosporine, although it shares most of the other complications. Early use of tacrolimus in children was marred by a very high incidence of post-transplant lymphoproliferative disease (PTLD) and other serious side effects such as hyperglycemia. However, these complications may have been related to doses that were excessive. Subsequent protocols, utilizing lower doses, have had fewer side effects. In general, oral dosing of tacrolimus begins at 0.1 mg/kg twice daily, but are adjusted to achieve target trough blood levels. Typical levels are 5–20 ng/L, with more recent maintenance levels closer to the lower level, in order to avoid nephrotoxicity. Both cyclosporine and tacrolimus come in liquid preparations, which makes pediatric dosing more convenient. Unfortunately, the taste of both is unpleasant.

TOR inhibitors

Target of rapamycin (TOR) inhibitors include sirolimus and everolimus, although the latter is not available in the USA at this time. These new drugs have unique mechanisms of action, which means that they can be combined with virtually all other immunosuppressants, although caution should be observed in the combination of a CNI and a TOR inhibitor for children. These medications have long durations of action, resulting in a once-a-day dosing for adults. Children appear to have quicker metabolism, however, and they often need to be administered twice a day. Sirolimus is available as pills or liquid and its dose can therefore be tailored easily for children. Typical target levels are between 7 and 15 ng/mL, but these seem to be center specific. Major complications of the TOR inhibitors include hyperlipidemia, thrombocytopenia, impaired wound healing, and proteinuria.

Co-stimulation blockade

Co-stimulation blockade is the general term used to describe a novel immunosuppression strategy. Most immunosuppressants have been designed to eliminate or block the action of lymphocytes which typically mediate organ transplant rejection. This new approach, on the other hand, is designed to enhance natural regulatory mechanism or block activation stimuli. Antigen recognition alone is not sufficient for full T-cell activation. T cells require two distinct signals for full activation. The first signal is provided by the engagement of the T-cell receptor (TCR) with the MHC plus peptide complex on antigen-presenting cells (APCs) and the second "co-stimulatory" signal is provided by engagement of one or more T-cell surface receptors with their specific ligand on APCs. Signaling through the TCR alone without a co-stimulatory signal can lead to a prolonged state of T-cell anergy.

The best characterized and perhaps most important co-stimulatory signal is that provided by interaction of CD28 on T cells with either B7-1 or B7-2 on APCs.

The CD28/CTLA-4–B7-1/B7-2 T-cell co-stimulatory pathway is a unique and complex pathway that regulates T-cell activation. After activation, T cells express another CD28 family member, CTLA-4, that has a higher affinity for B7-1 and B7-2, and functions to provide a "negative" signal resulting in physiologic termination of T-cell responses. Ligation of CD28 by B7-1 or B7-2 is blocked by CTLA4Ig, a recombinant fusion protein that contains the extracellular domain of CTLA-4 fused to an IgG heavy chain tail. There have been several candidate molecules tested in preclinical and pilot human trials. There is only one molecule, belatacept, in final clinical testing and likely to become widely available in the near future. Belatacept is slightly modified variant of CTL-4–Ig and its initial trials in human renal transplant recipients has been encouraging. As belatacept is administered parenterally once a month, there is promise that its chronic use may lead to improved adherence among recipients, which might be particularly appropriate for adolescents.

Immunosuppression combinations and minimization protocols

As noted above, most protocols for pediatric organ transplant recipients consist of two or three drugs. The most common regimen for kidney transplantation is prednisone–MMF–tacrolimus. Liver and heart transplant programs are more likely to use steroid-sparing regimens and typically two-drug protocols. The combination of prednisone–CNI–rapamycin is particularly potent in preventing acute rejection, but is also associated with an unacceptably high incidence of PTLD in susceptible pediatric recipients, specifically those who are seronegative for Epstein–Barr virus (EBV) at the time of transplantation and receive an organ from an EBV-seropositive donor. Recently, minimization protocols involving tacrolimus alone or the combination MMF–sirolimus have been proposed in small pilot trials and offer some promise.

Outcomes of pediatric organ transplantation

Pediatric kidney transplantation

Young children used to have the worst outcomes after kidney transplantation, but recent reports show that children aged <10 years now have the best long-term outcomes of all age groups of children and adults (Figure 6.5), with 5-year living donor graft survival rates at 85–89%. Unfortunately, these excellent outcomes are not shared by adolescent recipients whose graft survival rates are worse than any other

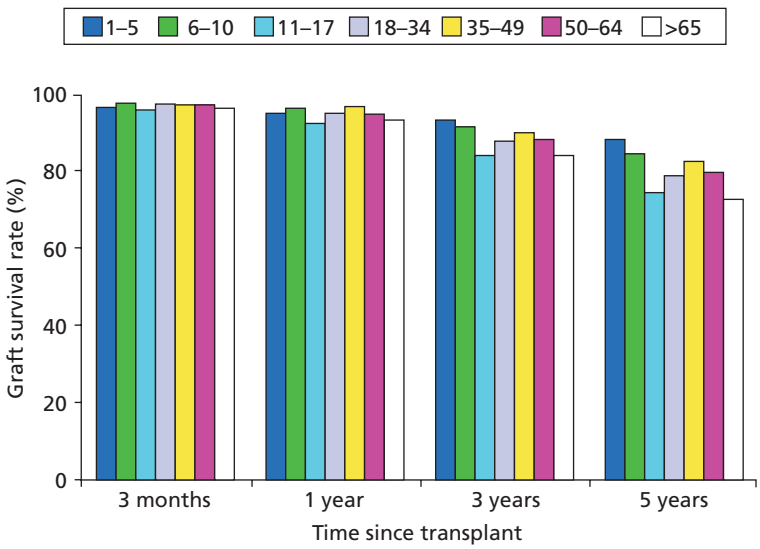

Figure 6.5 Living donor kidney transplant graft survival rates in various age group cohorts. Recipients aged <10 years have the best 5-year graft survival rates of all age groups whereas adolescents are worse than all except elderly recipients. (Reprinted from Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997–2006. *Am J Transplant* 2008;8:935–45.)

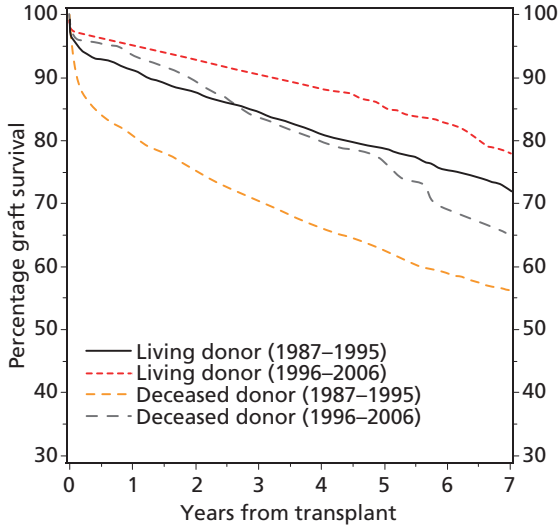

Figure 6.6 Living and deceased donor graft survival rates from two eras. Note the overall improvement in graft survival. Living donor grafts have better long-term survival than deceased donor grafts in both eras. (Adapted from Smith JM, Stablein DM, Munoz R, Hebert D, McDonald RA. Contributions of the Transplant Registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). *Pediatr Transplant* 2007;**11**:366–73.)

age groups except very elderly people, with 5-year graft survival rates for living donor transplants of about 74%. Although graft survival after deceased donor kidney transplantation has improved significantly over the past decade, the results of living donor kidney transplants remain significantly better than deceased donor (Figure 6.6), between 10% and 15% better at 5 years, depending on recipient age. The major causes of graft failure are, in order, chronic allograft nephropathy, vascular thrombosis, recurrent disease, and acute rejection. Acute rejection rates have fallen substantially in kidney transplantation and only about 15–20% of pediatric kidney transplant recipients have an acute rejection episode in the first year. Mortality rates after kidney transplantation are very low, probably because of excellent early graft survival and alternative treatments if the graft does fail. Current 5-year patient survival rate is about 95%, with slightly higher survival after living donor compared with deceased donor transplants and also higher for older children and adolescents compared with infants. The major causes of death are, in order, infection, cardiovascular causes, and malignancy.

Pediatric liver transplantations

Mortality rates after liver transplantation in children have improved substantially over the past decade, especially for infants, whose 1-year patient survival rates are now about equal to all other age groups (Figure 6.7). Overall 3-year patient survival rate is about 84% in children. The best 5-year patient survival rates are seen in the 6–10 year olds, at 89%. Graft survival for living donor recipients are better than for deceased donor recipients for all age groups: 3-year graft survival rates for living versus deceased donor recipients were 83% versus 80% for <1 year olds and 79% versus 76% for 1–5 year olds. Overall long-term graft survival rates from the SPLIT registry are shown in Figure 6.8. Risk factors for poor outcome include size and malnutrition at the time of transplant, re-transplantation, malignancy, and fulminant hepatic failure. Very young children have lower acute rejection rates, as with other organ transplants, but have somewhat lower graft and patient survival, probably related to technical and donor issues. In general, technical variant grafts (split livers, reduced-size donors) do not have outcomes as good as whole-liver grafts.

One study showed that living donor grafts for infants did better than split deceased donor grafts. The major cause of death after liver transplantation is infection. Bacterial infections are the most common cause for many of the early years, but fungal and viral sources, principally EBV and cytomegalovirus (CMV), are also important. Graft failure is another important cause of mortality. Although up to 50% of pediatric liver recipients have acute rejection episodes in the first 6 months, virtually all are reversed and few cause graft failure or death. Chronic rejection occurs in up to 25% by 10 years, but late graft loss is much less common in liver transplant recipients than in other organ transplants. About 10% of liver transplant recipients develop PTLD. Ten years after transplantation, about three-quarters of pediatric liver transplant recipients have mild-to-severe chronic kidney disease.

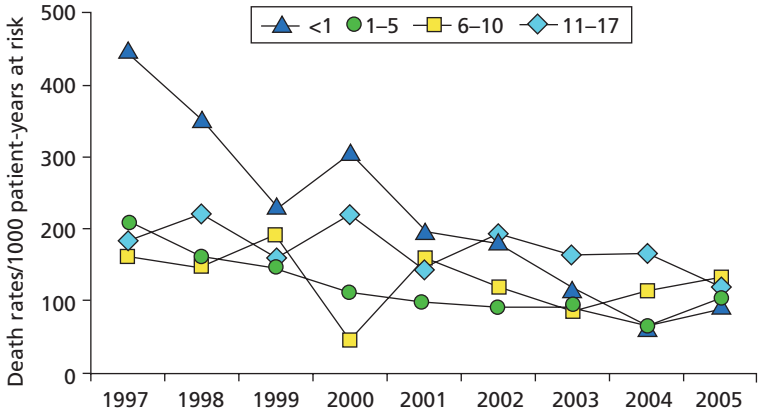

Figure 6.7 Death rates for various pediatric age groups during the first year after deceased donor liver transplantation. Very young candidates now have the same risk as older children. (Reprinted from Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997–2006. *Am J Transplant* 2008;8:935–45.)

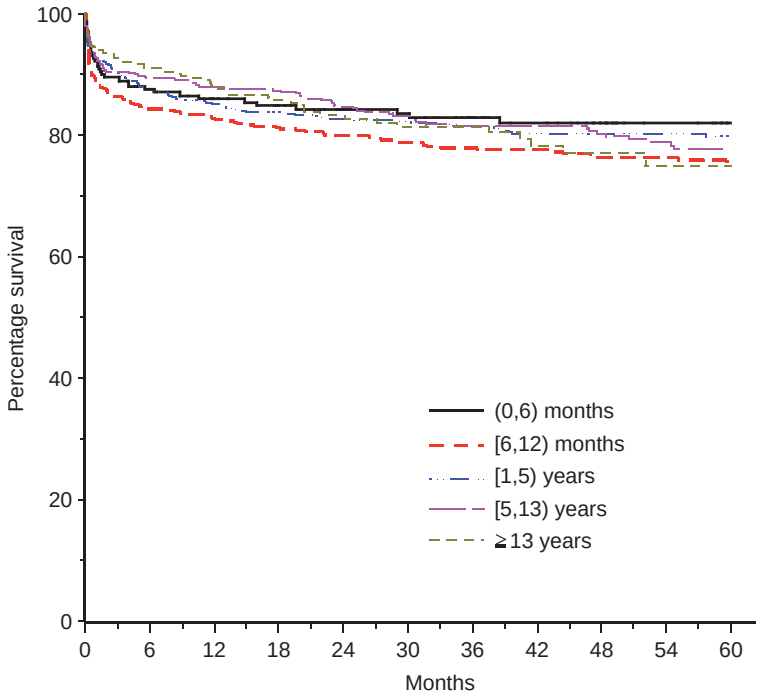

Figure 6.8 Graft survival rates for various pediatric age groups after liver transplantation by age. (From SPLIT Annual Report, with permission [unpublished].)

Pediatric heart transplantation

Overall patient survival rates after heart transplantation in children, according to the Pediatric Heart Transplant Study Group, are 85%, 75% and 64%, respectively, at 1, 5 and 10 years post-transplantation. As with organ transplants in children, outcomes of pediatric heart transplants have improved over the past decade and now are similar or better than those in adults. Graft and patient survival rates are related to recipient age. Infants have a 1-year patient survival rate of 81% compared with 91% for adolescents

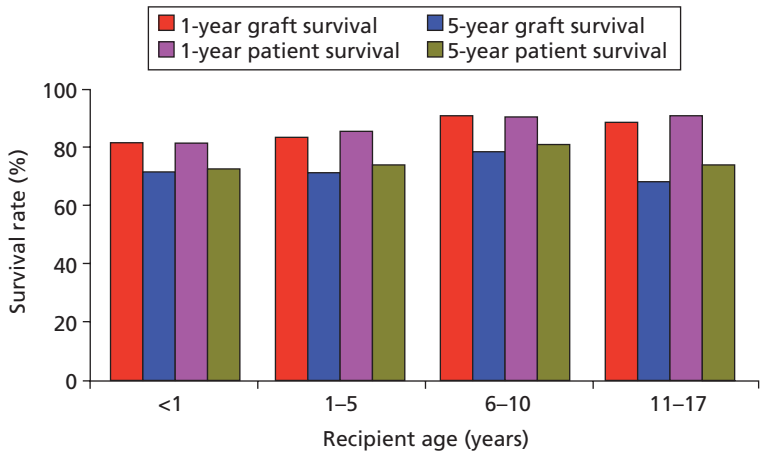

Figure 6.9 One- and five-year patient and graft survival after heart transplantation by age group cohort. Note poor long-term outcomes in adolescents. (Reprinted from Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997–2006. *Am J Transplant* 2008;8:935–45.)

(Figure 6.9). However, 6–10 year olds have the best 5-year survival rate – 81%. Adolescents have disappointingly low long-term graft survival rates, similar to kidney transplants. Infants tend to have lower survival rates overall, as do those who required cardiac assist devices or respirators pretransplantation. Congenital heart disease as an indication for heart transplantation was thought to be a risk factor for poor outcome, but recent data show that these children do as well as children without congenital heart disease. Nevertheless, children with previous Fontan procedures, especially those with protein-losing enteropathies, are probably at risk for post-transplant complications and worse outcomes. With increasing graft survival rates, attention has turned to long-term morbidity. Recent studies have shown progressive decline in renal function late after heart transplantation in children. There is a 10-year actuarial risk of 12% for chronic kidney disease and 4% for ESRD. Importantly, those who develop renal disease have a ninefold risk of death compared with those who do not.

Case: a second heart transplant

A 17-year-old girl received a heart transplant in 1996 because of presumed viral myocarditis. Her transplant worked well initially, but she had three acute rejection episodes in the first postoperative year. All three episodes were treated with methylprednisolone pulse therapy, and the last one was also treated with intravenous anti-lymphocyte globulin when the response to steroids was thought to be incomplete. After that, her surveillance biopsies did not show acute rejection, but apparently did show some "chronic changes." She was treated with cyclosporine, azathioprine, and low-dose steroids for several years. In the past 2 years, however, her cardiac echoes have shown a "stiff" heart and she was hospitalized three times for treatment of pulmonary edema. During the most recent hospitalization, her serum creatinine was noted to be 3.5 mg/dL, and a review of her chart revealed that her renal function had been deteriorating slowly over the past 5 years. A 24-hour urine collection contained 2.5 g protein. She is now developing ascites and is hospitalized for fluid control.

Pediatric lung transplantation

Survival after lung transplantation tends to be poorer than with other types of organ transplants. Figure 6.10 shows that 3-year graft survival rates for <1, 1–5, 6–10, and 11–17 year olds are 64%, 70%, 81%, and 57%, respectively. Unfortunately, graft survival continues to deteriorate subsequently and the 5-year graft survival rate for adolescents is 24%. The major cause of death immediately post-transplantation is infection, particularly pneumonia. By 1 year post-transplantation, bronchiolitis obliterans causes most graft failures. Risk factors for early graft loss include prolonged ischemia time, mechanical ventilation pre-transplantation, and early graft dysfunction. Risk factors for bronchiolitis obliterans include the incidence of acute rejection and prolonged ischemia time. Young children may be at decreased risk for

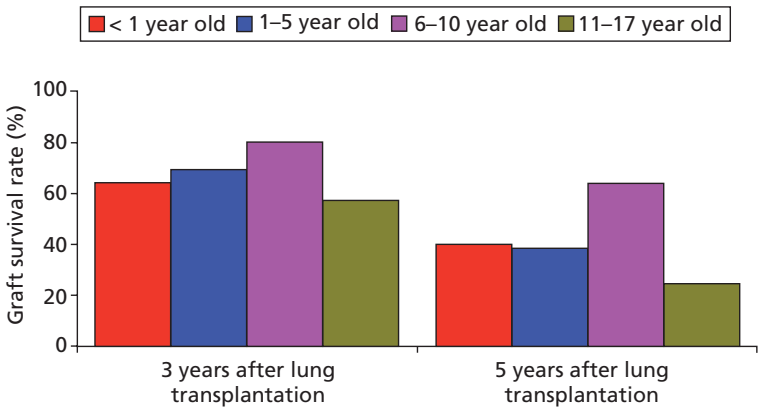

Figure 6.10 Three- and five-year lung transplant graft survival by recipient age group cohort. (Reprinted from Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997–2006. *Am J Transplant* 2008;**8**:935–45.)

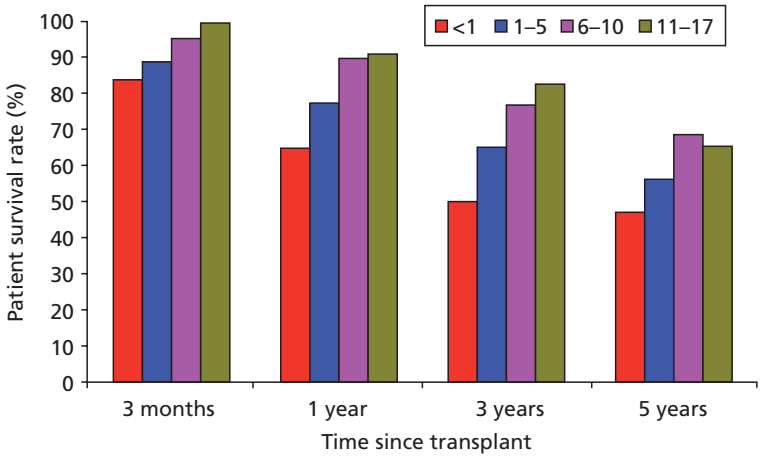

Figure 6.11 Short- and long-term patient survival after intestinal transplantation in pediatric age group cohorts. (Reprinted from Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997–2006. *Am J Transplant* 2008;**8**:935–45.)

bronchiolitis obliterans, possibly related to a lower incidence of acute rejections.

Case: cystic fibrosis

A 19-year-old girl has been followed at a pediatric hospital for her entire life because of cystic fibrosis. She has had multiple hospitalizations for pulmonary infections. During this time, her liver function has been normal, but she has developed low-level hyperglycemia, with fasting blood sugars in the 150–200 mg/dL range. Despite appropriate medications and dietary supplements, she appears to be malnourished and she currently weighs only 41 kg. Over the past year, her pulmonary function has been deteriorating more rapidly and her most recent FEV_1 is 40% less than it was last year. Although she finished her first year of college, she is now too weak to return for her sophomore year. She approaches the lung transplant program for information about lung transplantation.

Pediatric intestinal transplantation

Graft survival after intestinal transplantation tends to be poor. Five-year graft survival rates for <1, 1–5, 6–10, and 11–17 year olds are 39%, 54%, 45%, and 48%, respectively. As a result of alternative treatments, specifically TPN, patient survival is 5–25% higher at 5 years (Figure 6.11). Unlike other organ transplants, adolescents have better long-term survival. Acute rejection has been very common

after intestinal transplantation, with some reports as high as 70–90%. More recent data suggest lower levels, perhaps 40–50%. Acute rejection is reported as the major cause of graft loss and the cause of about 10% of the deaths. Infections are common, probably related to the intensity of immunosuppression; CMV and EBV infection are common and have recently been modulated by the introduction of specific monitoring, prophylaxis, and immunosuppression adjustments.

Key points 6.4 Post-transplant lymphoproliferative disease (PTLD) in pediatric transplantation

Higher incidence than in adults, in part because Epstein–Barr virus mismatches (seropositive donor to seronegative recipient) are more common

Incidence varies with the transplanted organs, in descending order:

Lung and intestinal transplants

Liver and heart transplants

Kidney transplants

Pediatric organ transplant complications

In general, children have the same complications and side effects of transplantation and chronic immunosuppression as adults, but two deserve special mention: PTLD and growth retardation.

PTLD is a serious complication of organ transplantation, and can be fatal, particularly if it progresses to lymphoma. PTLD is generally related to EBV infection and, although it can occur as a recurrent infection, it is much more common if the infection occurs anew during immunosuppression. For organ transplant recipients, the virus is often transmitted with the graft, especially when an organ from a seropositive donor is transplanted into a seronegative recipient. CMV infection has been associated with an increased risk of developing PTLD, as have several different types of immunosuppression. There is likely no single agent responsible for the severity of the infection, but the more intense the regimen, especially if lymphocytotoxic antibodies are used, the more likely the development of PTLD. The true incidence of disease is difficult to assess because there are substantial differences in reporting. In general, the incidence of PTLD after pediatric kidney transplantation is probably 5% or less, after liver or heart transplant 5–10% , and higher for lung and intestinal transplantation. There are indications that the incidence of PTLD might be decreasing, perhaps because of preventive measures. Some programs recommend prophylaxis with valganciclovir, perhaps to prevent concomitant CMV infection. Many programs now prospectively monitor blood by polymerase chain reaction (PCR) for EBV and adjust the immunosuppression when there is evidence of viremia.

Children with chronic organ dysfunction frequently exhibit growth retardation and developmental delays, likely related to metabolic disorders and malnutrition. This is particularly true for children with ESRD and the use of recombinant human growth hormone has been particularly useful in treating this disorder. If normal organ function can be established after transplantation and satisfactory nutrition established, satisfactory growth rates can be restored. The use of chronic corticosteroids will inhibit normal growth, however, so many programs are now avoiding or withdrawing chronic immunosuppression with steroids for this reason. If steroids must be given, alternate-day dosing has been shown to provide equivalent protection against rejection and much better growth potential. Growth hormone is not approved for use following organ transplantation and some reports have linked its use to increased rates of rejections.

Further reading

North American Pediatric Renal Trials and Collaborative Studies. *Annual Report*. Available at: www.naprtcs.org. accessed 22 September 2010.

Aurora P, Boucek MM, Christie J, et al. Registry of the International Society for Heart and Lung Transplantation: tenth official pediatric lung and heart/lung transplantation report – 2007. *J Heart Lung Transplant* 2007;**26**: 1223–8.

Bar-Dayan A, Bar-Nathan N, Shaharabani E, et al. Kidney transplantation from pediatric donors: size-match-based allocation. *Pediatr Transplant* 2008;**12**:469–73.

Bartosh SM, Ryckman FC, Shaddy R, Michaels MG, Platt JL, Sweet SC. A national conference to determine research priorities in pediatric solid organ transplantation. *Pediatr Transplant* 2008;**12**:153–66.

Benden C, Boehler A, Faro A. Pediatric lung transplantation: literature review 2006–2007. *Pediatr Transplant* 2008;**12**: 266–73.

Boucek MM, Aurora P, Edwards L, et al. Registry of the International Society for Heart and Lung Transplantation: Tenth Official Pediatric Heart Transplantation Report – 2007. *J Heart Lung Transplant* 2007;**26**:796.

Canter CE, Kirklin J, eds. *Pediatric Heart Transplant*, Vol **2**. ISHLT monograph series. Philadelphia: Elsevier, 2007.

Canter CE, Shaddy RE, Bernstein D, et al. Indications for heart transplantation in pediatric heart disease. *Circulation* 2007;**115**:658.

Chen JM, Davies RR, Mital SR, et al. Trends and outcomes in transplantation for complex congenital heart disease: 1984–2004. *Ann Thorac Surg* 2004;**78**:1352.

Ching YA, Gura K, Modi B, Jaksic T. Pediatric intestinal failure: nutrition, pharmacologic, and surgical approaches. *Nutr Clin Pract* 2007;**22**:653–63.

Dehghani SM, Derakhshan A, Taghavi SA, Gholami S, Jalaeian H, Malek-Hosseini SA. Prevalence and risk factors of renal dysfunction after liver transplant: a single-center experience. *Exp Clin Transplant* 2008;**6**:25–9.

Dharnidharka VR, Araya CE. Post-transplant lymphoproliferative disease. *Pediatr Nephrol* 2009;**24**:731–6.

Duffy JP, Farmer DG, Busuttil RW. A quarter century of liver transplantation at UCLA. *Clin Transpl* 2007:165–70.

Fine RN, Webber SA, Olthoff KM, Kelly DA, Harmon WE, eds. *Pediatric Solid Organ Transplantation*. Oxford: Blackwell, 2007.

Fine RN. Management of growth retardation in pediatric recipients of renal allografts. *Nature Clin Pract Nephrol* 2007;**3**:318–24.

Gupta J, Amaral S, Mahle WT. Renal transplantation after previous pediatric heart transplantation. *J Heart Lung Transplant* 2008;**27**:217–21.

Herlenius G, Fagerlind M, Krantz M, et al. Chronic kidney disease – a common and serious complication after intestinal transplantation. *Transplantation* 2008;**86**: 108–13.

KDIGO Clinical Practice Guideline for the Care of the Kidney Transplant Recipients. *Am J Transplant* 2009;**9** (supp 3).

Lacaille F, Vass N, Sauvat F, et al. Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation. *Gut* 2008;**57**:455–61.

Mazor R, Baden HP. Trends in pediatric organ donation after cardiac death. *Pediatrics* 2007;**120**:e960–6.

Merion RM, ed. SRTR Report on the State of Transplantation. *Am J Transplant* 2008;**8**:909–1026.

Mian SI, Dutta S, Le B, Esquivel CO, Davis K, Castillo RO. Factors affecting survival to intestinal transplantation in the very young pediatric patient. *Transplantation* 2008; **85**:1287–9.

Mohanka R, Basu A, Shapiro R, Kayler LK. Single versus en bloc kidney transplantation from pediatric donors less than or equal to 15 kg. *Transplantation* 2008;**86**:264–8.

Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. *Curr Opin Pediatr* 2008;**20**:272–8.

Pironi L, Forbes A, Joly F, et al. Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. *Gastroenterology* 2008;**135**:61–71.

Puliyanda DP, Toyoda M, Traum AZ, et al. Outcome of management strategies for BK virus replication in pediatric renal transplant recipients. *Pediatr Transplant* 2008;**12**: 180–6.

Smith JM, Stablein DM, Munoz R, Hebert D, McDonald RA. Contributions of the Transplant Registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). *Pediatric Transpl* 2007;**11**:366–73.

Souilamas R. Lung transplantation in cystic fibrosis pediatric population myth or reality. *J Cyst Fibros* 2008;**7**: 460.

Studies of Pediatric Liver Transplantation (SPLIT). A summary of the 2003 Annual Report. *Clin Transpl* 2003: 119–30.

Sweet SC, Aurora P, Benden C, et al. Lung transplantation and survival in children with cystic fibrosis: solid statistics – flawed interpretation. *Pediatr Transplant* 2008;**12**: 129–36.

Yashar S, Wu SS, Binder SW, Cotliar J. Acute graft-versus-host disease after pediatric solid organ transplant. *J Drugs Dermatol* 2008;**7**:467–9.