

# Pediatric transplantation

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**Analysis of the OPTN/SRTR database demonstrates that, in 2002, pediatric recipients accounted for 7% of all recipients, while pediatric individuals accounted for 14% of deceased organ donors. For children fortunate enough to receive a transplant, there has been continued improvement in outcomes following all forms of transplantation. Current 1-year graft survival is generally excellent, with survival rates following transplantation in many cases equaling or exceeding those of all other recipients. In renal transplantation, despite excellent early graft survival, there is evidence that long-term graft survival for adolescent recipients is well below that of other recipients. A causative role for noncompliance is possible. While the significant improvements in graft and patient survival are laudable, waiting list mortality remains excessive. Pediatric candidates awaiting liver, intestine, and thoracic transplantation face mortality rates generally greater than those of their adult counterparts. This finding is particularly pronounced in patients aged 5 years and younger. While mortality awaiting transplantation is an important consideration in refining organ allocation**

**Notes on Sources:** The articles in this report are based on the reference tables in the 2003 OPTN/SRTR Annual Report, which are not included in this publication. Many relevant data appear in figures and tables included here; other tables from the Annual Report that serve as the basis for this article include the following: Tables 1.4, 1.11, 2.1–2.7, 2.9, 5.1–5.10b, 9.1–9.5, 9.7, 9.9a–9.11a, 10.1–10.5, 10.7, 10.9–10.12, 11.1–11.5, 11.7, 11.10, 11.11, 12.1–12.5, 12.8–12.11, 13.1–13.4, and 13.11. All of these tables are also available online at <http://www.ustransplant.org>.

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**strategies, it is important to realize that other issues, in addition to mortality, are critical for children. Consideration of the impact of end-stage organ disease on growth and development is often equally important, both while awaiting and after transplantation.**

**Key words:** Deceased donors, graft survival, immunosuppression, living donors, organ donation, patient survival, pediatric transplantation, SRTR, waiting list

## Introduction

The data and analysis presented here are meant to provide a comprehensive overview of issues related specifically to pediatric transplantation. The data are collected across all transplant procedures for patients aged 17 years and under from the OPTN/SRTR database. Unless otherwise noted, the statistics in this article come from reference tables in the 2003 OPTN/SRTR Annual Report. Two companion articles in this report, 'Transplant data: sources, collection, and caveats' and 'Analytical approaches for transplant research', explain the methods of data collection, organization, and analysis that serve as the basis for this article (1,2). Additional detail on the methods of analysis may be found in the reference tables themselves or in the Technical Notes of the OPTN/SRTR Annual Report, both available online at <http://www.ustransplant.org>.

In considering transplantation as a therapy for pediatric patients, it is vital to recognize the many and substantial differences between adults and children. These differences transcend age and size, extending to diverse factors that include etiology of end-stage organ disease, physiology, technical considerations, donor factors, availability of suitably sized grafts, immunology, pharmacokinetics, and post-transplant complications. In addition to these factors, the unique effects of end-stage organ disease and transplantation on development and growth must be carefully considered.

Over the years, significant progress has been made in pediatric transplantation. Much of this success can be attributed to lessons learned from analyses of registry data. Along with specific pediatric registries such as the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) and Studies of Pediatric Liver Transplantation (SPLIT), analyses of data submitted to the OPTN have shaped practices and policies. One way the SRTR has contributed to this effort is by providing the first cohesive

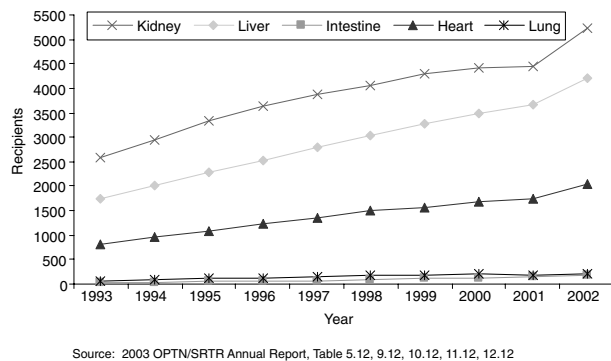
review of pediatric registry data from the OPTN across all forms of organ transplantation in children (3). Perhaps more importantly, the SRTR provides ongoing data analyses and modeling for OPTN committees. Since 2001, the SRTR has performed 15 analyses for the OPTN pediatric committee. Examples of such analyses are included in the sections that follow.

**Waiting list overview**

At the end of 2002 there were 2307 transplant candidates younger than 18 years on the waiting lists for various organs, accounting for 3% of all candidates awaiting transplantation. This represents a modest decline from 2382 candidates the previous year and is the first decline in the last 10 years. This decrease was observed in all pediatric age groups except those 6–10 years old, where the number of candidates awaiting transplantation increased minimally. As reviewed in subsequent sections, the decrease in the total number of pediatric waiting list candidates reflects a decline in the size of the liver and lung waiting lists. Overall, pediatric candidates, expressed as the percentage of all candidates on the waiting list, have remained stable at around 3% for the last 4 years, although the continued disproportionate growth of adult candidates has led to, and will continue to lead to, a gradual decline in the percentage of the waiting list represented by pediatric candidates.

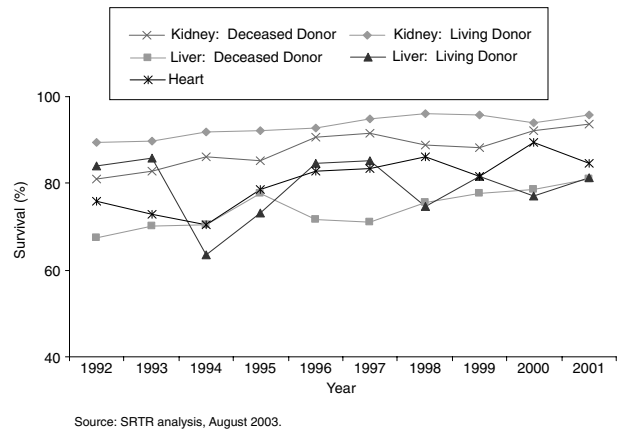
**Transplant recipients**

In 2002, there were 1757 pediatric transplant recipients, representing 7% of all recipients. This percentage has been relatively stable over the last 3 years. The more than twofold higher representation of children among recipients vs. among candidates may, in part, reflect the preferential allocation policies in effect that favor pediatric transplantation. The success of pediatric transplantation is evident by the prevalence of pediatric recipients who are alive with functioning grafts (Figure 1).



Source: 2003 OPTN/SRTR Annual Report, Table 5.12, 9.12, 10.12, 11.12, 12.12

**Figure 1:** Prevalence of pediatric transplant recipients living with a functioning transplant at year-end.



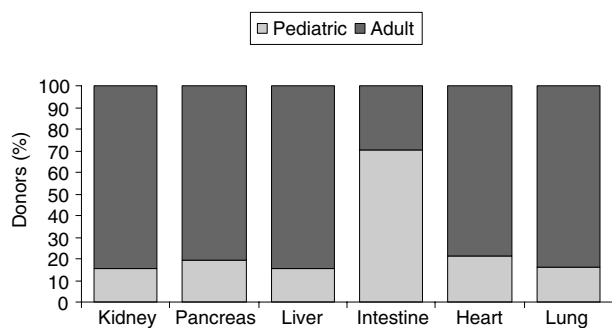
Source: SRTR analysis, August 2003.

**Figure 2:** Adjusted 1-year graft survival for pediatric kidney, liver, and heart recipients, 1992–2001.

The significant progress made in pediatric transplantation is apparent when one examines 1-year graft survival for the three most frequent organ transplants performed each year over the last decade (Figure 2). When analyzing changes in outcomes over time, it is particularly important to correct for any differences in the population under study that may affect the outcomes. The current report marks the first attempt to provide adjusted graft and patient survival for all transplant recipients accounting for a variety of factors, including age, sex, race, and primary diagnosis. Attempts to carry out all adjustments in the pediatric patient population are limited because of the smaller numbers of patients; consequently, the adjusted pediatric survival figures primarily reflect the impact of race and sex. Despite this limitation, examination of outcomes over the decade is still instructive. For pediatric recipients, deceased donor kidney graft survival has increased from 81% in 1992 to 94% for 2001 transplants (Figure 2). Graft survival following living donor kidney transplantation has also increased (from 90% to 96%). Similarly, deceased donor liver graft survival has also progressively improved over the decade, with 1-year graft survival of 81% for transplants performed in 2001 compared with 68% a decade previously. Deceased donor liver graft survival now equals graft survival following living donor liver transplantation. Graft survival for heart transplantation has also increased from 76% to 85% over the same time period. Further discussion regarding current graft and patient survival follows in the organ-specific sections.

**Pediatric donor overview**

In 2002, there were 931 pediatric deceased donors, representing 15% of all deceased donors. Over 56% of these pediatric donors were aged 11 years and older. The total number of pediatric deceased donors has declined modestly from a high of 1214 in 1995, although this trend appears to have stabilized during the last 4 years. The modest decline in total pediatric donors, combined with



Source: 2003 OPTN/SRTR Annual Report Tables 2.2–2.7.

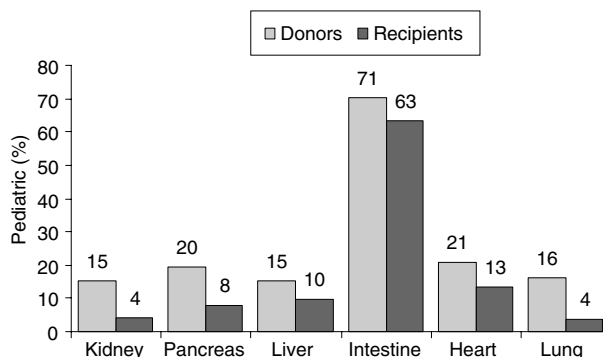
**Figure 3:** Deceased donor organs, pediatric vs. adult, 2002.

the significant increase in the total number of adult deceased donors, has caused the relative contribution of pediatric donors to decline over the decade from a high of 23% in 1993. The relative contributions of pediatric donors to specific deceased organ donation are summarized in Figure 3.

As highlighted in the analysis a year ago, pediatric deceased donors continue to be more likely to donate each specific organ compared with adult deceased donors (3). This observation remains true. In 2002, pediatric deceased donors were more likely than adult deceased donors to be pancreas donors (40% vs. 29%), intestine donors (9% vs. 0.6%), and heart donors (50% vs. 33%). The percentage of pediatric deceased donors compared with adult deceased donors who donated kidneys, livers, and lungs was similar (92% vs. 91%, 87% vs. 85%, and 16% vs. 15%, respectively).

Over the last 10 years, the relative percentage of pediatric deceased donors who were kidney, liver, and lung donors has remained relatively stable. During the same time, there has been a slight decrease in the percentage of pediatric donors who were heart donors (from 59% to 50%), while there has been a significant increase in the percentage of donors who donated pancreata (23% to 40%) and intestines (2% to 8%). This trend suggests that there has been an under-utilization of pancreata and intestines from deceased pediatric donors in the past. Recent reports demonstrating good long-term results following en bloc transplantation of kidneys from small pediatric donors into selected recipients may further increase use of kidneys from pediatric donors (4).

In addition to being more likely to donate a particular organ compared with adult deceased donors, pediatric patients contributed to the total deceased donor organ pool at a rate higher than the rate pediatric recipients received such organs (Figure 4). While this observation may reflect an inability to find a suitable pediatric recipient for a given cadaveric organ, it demonstrates that the pediatric popula-



Source: 2003 OPTN/SRTR Annual Report, Tables 2.1–2.7, 5.4, 6.4, 7.4, 9.4, 10.4, 11.4, 12.4.

**Figure 4:** Pediatric deceased donors vs. pediatric recipients of deceased donor organs, 2002.

tion is not receiving a disproportionate share of deceased donor organs.

There has been a gradually increasing interest in donation after cardiac death (DCD) over the past several years. A recent SRTR analysis showed that, in 2002, there were 191 DCD donors, of which 32 were younger than 18 years of age (16.8% of total DCD donors). While pediatric donors constitute a significant percentage of DCD donors, pediatric recipients do not appear to be receiving organs from this expanding donor population. In 2002, there were 291 kidney transplants using DCD donor organs, only three of which were received by pediatric recipients. During the same time, there were 78 liver transplants performed with DCD donor livers, only one of which involved a pediatric recipient. The limited use of DCD donor organs in pediatric recipients may reflect concern regarding long-term graft function of such organs. Widespread use of DCD donor grafts in pediatric recipients is unlikely until further data regarding this issue are available.

## Kidney Transplantation

The transplant community has long recognized that indications, endpoints, procedures, complications, pharmacokinetics, and outcomes of kidney transplantation are different for children than they are for adults. In response to those differences, dedicated pediatric registries, such as the NAPRTCS and multicenter studies such as Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) have been developed to address the special requirements of children (5,6). At the same time, more comprehensive databases, such as the SRTR, are essential for defining the comparative outcomes of children and adults and for defining opportunities for improving the outcomes of both groups (3).

In the past, young kidney recipients have been considered high risk, with diminished graft survival compared with older children and adults (6,7). In many reports, the worst survivals were seen in the youngest patients. However, many improvements by pediatric kidney transplant teams, including changes in surgical technique, donor selection, immunosuppression practices, and development of dedicated pediatric kidney transplant research programs have led to marked improvements in patient and kidney graft survival for infants and young children (5,8–10). As a result, recent analyses, including last year's SRTR report, have identified that infants and young children currently have the best long-term survivals of all age groups (3). In fact, one report has identified the subgroup of young recipients of adult-sized kidneys who have immediate graft function as having the longest projected graft half-lives of all recipient groups, exceeding even those of adult recipients of 2-haplotype matched living donor transplants (11). Unfortunately, adolescent kidney transplant recipients have worse outcomes than infants and younger children, and research efforts should be redirected to that age group to identify the causes of inferior results and to correct any deficiencies, as has been done for younger children over the past decade.

### **Waiting list**

The incidence of end-stage renal disease in children has increased only slightly during the past decade, and this has been reflected in the waiting list for diseased donor kidney transplants. In 1993, there were 591 children aged under 18 years listed for kidney transplants; by 2002 there were 708, an increase of only 20%. In contrast, the number of listed adults more than doubled, from 22 905 to 50 147. It is of note that the increases were not seen uniformly throughout the adult age groups. While the number of young adults aged 18–34 years increased by just 27% during that time frame, those aged 50–64 years increased by more than threefold, and those over 65 years by over fivefold. The waiting list is indeed ageing. As a result, the percentage of children on the kidney waiting list decreased from 2.5% to just 1.4% during the past decade. The relative distribution by pediatric age groups has remained stable over the last 10 years. Of the pediatric patients on the waiting list at the end of 2002, 70% were in the 11–17 years age range. Children under 1 year are rarely listed for cadaveric renal transplant, and only one such patient was on the waiting list at the end of 2002.

Another perspective of relative incidence can be gained from analyzing the number of new kidney waiting list registrations in different time periods. In 1993, 420 children under 18 years were added to the kidney waiting list, whereas in 2002, 546 were added, a 30% increase. In the same time period, the numbers of adults were 14 598 and 21 373, respectively. Thus, children represented about 3% of new registrants throughout the decade. Within the pediatric population, the greatest increase in new registrants

over the last 10 years has been in the 11–17 years age range.

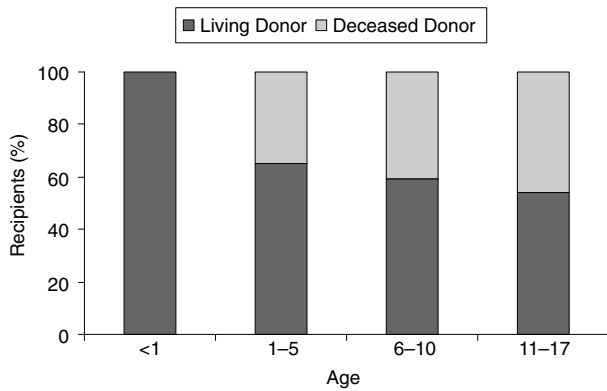
Annual death rates for pediatric registrants awaiting renal transplantation are low and have remained relatively constant over the last 10 years. Last year 23 children died while awaiting kidney transplantation. The death rate for children aged 1–5 years was the highest of all pediatric patients awaiting renal transplantation (61 per 1000 patient years at risk), while the lowest rate was observed in the 6–10 years age range (17 per 1000 patient years at risk). The latter age group had the lowest annual death rate of any age patient awaiting transplantation, while the death rate observed in younger children approached that seen in adults aged 50–64 years. Children aged 11–17 years had an annual death rate equal to adults in the 18–34 years age group.

The OPTN has always provided preference for children awaiting deceased donor renal transplants. Initially, children were preferentially allocated kidneys from young deceased donors under 10 years. Unfortunately, these donors turned out to be high risk, probably because of technical complications; young recipients seemed particularly susceptible to graft failure, often related to graft thrombosis (12,13). Subsequently, the allocation system was changed, first by additional points and next to the present system of placing the pediatric patients at the top of the waiting list after waiting times between 6 and 18 months. This newer system has contributed to improvement in graft outcome for children while maintaining relatively short waiting times. The median waiting times for those aged 6–10 years at listing, for example, was 310 days in 1993 and 379 days in 2002; for those 11–17 years old it decreased from 450 days in 1993 to 415 days in 2001. The waiting times for other pediatric age groups remained comparably low while the median waiting times of adults have increased to over 1000 days.

Pediatric patients are rarely listed for pancreas transplant or, even less frequently, for kidney-pancreas transplant. As a consequence of the small number of pediatric patients who are candidates for these transplants, meaningful analysis of wait time or mortality awaiting transplant is not feasible.

### **Transplantation and survival**

There were 769 pediatric kidney transplant recipients in 2002 compared with 661 in 1993. Last year, deceased donor renal transplants accounted for 327 (43%), while 442 were living donors (57%). Overall, a greater percentage of pediatric patients received a living donor kidney compared with adults, because only 41% of adult recipients received a living donor kidney transplant. The proportion of living donor renal transplants was inversely related to recipient age (Figure 5). With respect to deceased donor kidneys, there is essentially no use of extended criteria donor (ECD) kidneys in pediatric recipients. In 1998, 17 children

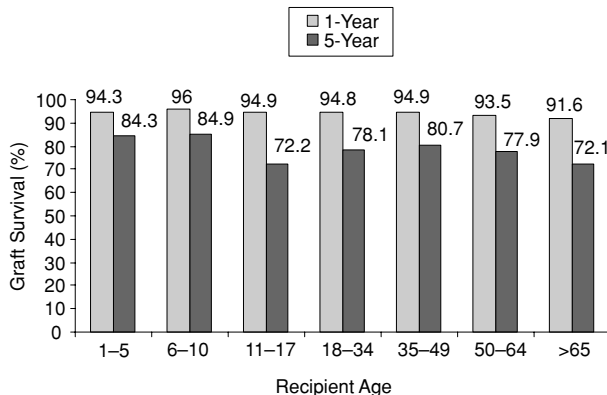


Source: 2003 OPTN/SRTR Annual Report, Table 5.4

Figure 5: Pediatric kidney transplants, by recipient age, 2002.

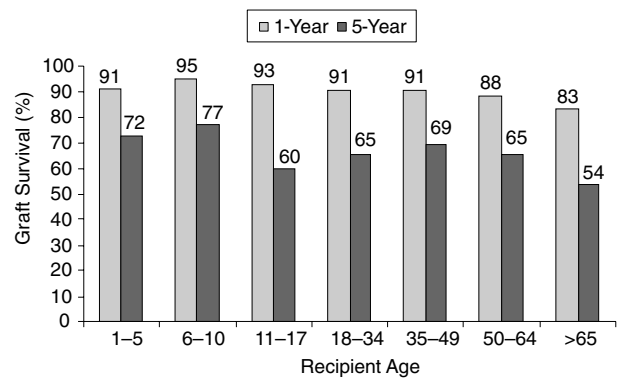
received ECD deceased donor kidneys, but the number fell to just one in 2002.

Graft survival rates of pediatric kidney recipients have improved substantially during the past decade and now rank among the best of all transplants (10). This outcome may seem surprising in view of the previous perception of children having poor outcomes of kidney transplantation. Pediatric recipients younger than 10 years who received living donor kidney transplants have 5-year adjusted graft survival rates that were better than all age groups of adults (88% for those under age 1 year, 84% for those 1–5 years, and 85% for those 6–10 years) (Figure 6). The results of deceased donor kidney transplants are similar, with the 1–5 year old recipients having a 72% 5-year adjusted graft survival rate and those 6–10 years having the best adjusted graft survival rate of all age groups at 77% (Figure 7). In contrast, the best outcome seen in adults is 69% 5-year graft survival in 35–49 year olds. These outcomes are in



Source: 2003 OPTN/SRTR Annual Report, Table 5.8b.

Figure 6: Adjusted 1- and 5-year graft survival of living donor kidney transplants by recipient age, 2002.

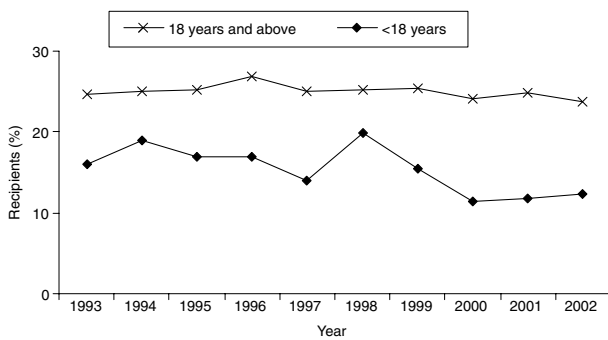


Source: 2003 OPTN/SRTR Annual Report, Table 5.8a.

Figure 7: Adjusted 1- and 5-year graft survival of deceased donor kidney transplants by recipient age, 2002.

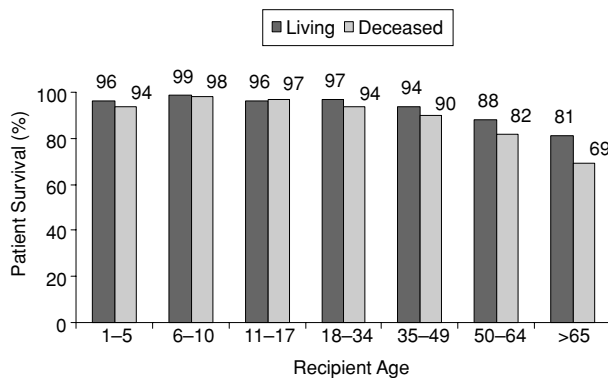
concert with recent reports showing that the longest half-lives of all recipients are in the youngest recipients, especially the pediatric recipients of adult-sized grafts who have immediate graft function (8,11). Unfortunately, these excellent results in young children are not seen in adolescent recipients. For 11–17 year old recipients, the 5-year adjusted graft survival rate of living donor kidneys is only 72%; for deceased donor kidneys it is 60%. These results are worse than all other age groups except those older than 65 years. These recipients generally have excellent short-term (3-month and 1-year) graft survival rates, but graft losses between 3 and 5 years are striking. The reasons for this poor outcome are not known, but there is speculation about the role of compliance with immunosuppressive medications (14). Thus far, no studies have been done to determine all the factors leading to the lower graft survival in this adolescent cohort. Of course, other causes are also possible (15), including an unexplained high frequency of graft thrombosis (16) and the high incidence of recurrence of focal segmental glomerulosclerosis (FSGS), which is the most common acquired cause of ESRD in this age group (17). Until the causes of this diminished graft survival are known, special attention should be paid to this new high-risk age group.

Recent studies suggest that in the pediatric age group, the difference between short-term graft survival for deceased donor kidneys vs. living donor kidneys appears to be decreasing (18). The current data support that finding; 1-year unadjusted graft survival in children older than 1 year of age ranged from 93% to 95% for deceased donor kidney transplants and 94% to 96% for living donor kidney transplants. This probably reflects advances in overall management, as well as improved selection of deceased kidney donors. The impact of better donor selection is suggested by the percentage of pediatric deceased donor recipients who receive dialysis in the first week after transplantation (Figure 8). The percentage of pediatric recipients requiring



Source: SRTR analysis, August 2003.

**Figure 8:** Deceased donor kidney transplant recipients receiving dialysis in first week following transplant.



Source: 2003 OPTN/SRTR Annual Report, Table 5.10a, 5.10b.

**Figure 9:** Adjusted five-year patient survival of living and deceased donor kidney transplants by recipient age, 2002.

dialysis is lower than adult recipients and has declined over the decade.

As expected, the death rates of pediatric kidney transplant recipients were generally lower than those of adults and 5-year patient survival rates were better (Figure 9). The adjusted 5-year patient survival rate of adolescent living donor kidney transplants was only 96%, and the reasons for this apparent recent decrease in survival deserve further study. There is some concern that infection rates following renal transplantation may be increasing and may pose a risk for patient survival (19,20). Also, the youngest recipients appear to have a slightly higher death rate than other children and young adults in some years. There are so few patients and deaths in this age group, however, that the significance of the finding is not clear, and, even if true, it may be difficult to define a cause of excess mortality.

The use of children as kidney donors has not been well studied. The number of pediatric deceased donors has declined slightly over the decade. In 1993, there were 1026 deceased kidney donors aged under 18 years; in 2002 there

were 853. Those numbers represented 22% and 15% of the total number of deceased donors in those years, respectively. As highlighted in the donor overview (Figure 4), the percentage of pediatric deceased donors currently is substantially greater than the percentage of pediatric candidates on the waiting list (1.5%) or deceased donor kidney recipients (4.5%). Kidneys from donors aged 11–17 years generally had the best graft survival rates, with a 5-year graft survival of 73%. Grafts from younger donors, however, were less successful. The 5-year graft survival rates from deceased donors aged 1–5 years was 66%, which is better than in previous years and equivalent to those from donors aged 35–49 years (65%) and superior to those of donors aged over 65 years (44%). Thus, kidneys from those very young donors are surviving much better than in the past, and the use of those donors for selected recipients should be encouraged (4,21). The use of children for living kidney donation remains highly controversial, and in general, most transplant programs will not use a donor younger than 18 years of age as a living kidney donor except in very limited circumstances, such as identical twins or an emancipated minor for his or her own child (22). There were 36 living adolescent kidney donors between 1993 and 2002. A recent analysis of OPTN data suggested that many of these donors were used for adult recipients (23).

In summary, the past decade has seen substantial improvement in graft survival for pediatric renal transplant recipients. Children under 10 years of age now have the best long-term graft and patient survival rates of all transplant recipients. This success, however, is not shared by adolescent recipients, and further study of the factors responsible for this finding is needed if improvement is to occur. Continued attention to recipient risk factors associated with graft loss (24), improvements in donor selection, operative techniques, immunosuppressive protocols, and long-term follow up are all possible approaches for improving the outcomes in pediatric recipients. Children are generally transplanted early in the course of ESRD care, because the majority of these patients receive grafts from living donors. Those on the list for deceased donor organs wait shorter periods of time than adults, because the allocation protocols provide them with preference.

### Liver Transplantation

As mentioned in the introduction, it is critical to recognize that pediatric liver transplant recipients are a distinct population, not only with respect to age, but also with respect to primary diagnosis, type of graft, donor population, and post-transplant complications. Consequently, the effect of changes in organ allocation and care processes cannot be generalized from adults to children. As part of its ongoing data analyses, the SRTR regularly performs in-depth examination related to pediatric patients, examples of which are included in this section. Additionally, the SRTR is committed to ongoing collaboration with other efforts specifically

focusing on the study of liver disease and liver transplantation in pediatric patients, including SPLIT and the recent NIH initiative, BARC (Biliary Atresia Research Consortium).

### **Waiting list**

At the end of 2002, 955 candidates under 18 years of age were awaiting liver transplantation, compared with 427 pediatric candidates in 1993. While the number of children on the waiting list has increased more than twofold since 1993, the total number of adults has increased sixfold, and the number of those older than 50 years has increased eightfold. As a result, pediatric candidates now account for 6% of the waiting list compared with 15% in 1993. Nevertheless, since 1998, the proportion of children on the waiting list has been stable, ranging between 5.6% and 6.8% of registrants.

In 2002, the first decline in a decade was seen in the number of new registrants placed on the liver transplant waiting list. There were 804 new pediatric registrations in 2002 compared with 984 in 2001. A similar decline was noted for adult registrants; 8141 adults were listed in 2002 compared with 9361 in 2001. Within the pediatric age groups, this decline in new registrations was noted across all age groups but was greatest in the 11–17 year old age range, where there was a 29% decrease in new registrations compared with 2001. The significance of this decline is undetermined, but it may represent changes in practice after the introduction of allocation based on the Model for End-stage Liver Disease (MELD) and its counterpart for children, the Pediatric End-stage Liver Disease (PELD) model. Now that waiting time no longer plays a meaningful role in the allocation of deceased donor livers, patients do not need to become listed simply to accrue waiting time. It is unlikely that this decline reflects a decrease in the incidence of end-stage liver disease or the introduction of other treatment alternatives.

Despite the increased waiting list and a limited pool of organs, the median time from listing to transplantation for pediatric candidates has not increased from 1993 to 2002. In contrast, the median time to transplantation for candidates older than 18 years has increased fivefold over the same time period. The observations indicate that the increased demand for adult liver transplantation has not adversely affected the availability of deceased organ donors for pediatric candidates. Within the pediatric population, the median time to transplant for pediatric registrants listed in 2002 is higher in children younger than 1 year and those aged 1–5 years (209 and 203 days, respectively), compared with children aged 6–10 and 11–17 years (170 and 147 days, respectively).

On February 27, 2002, the MELD and PELD scoring systems were implemented for allocation of deceased donor livers. The median time to transplant was 243 days for registrants listed with a PELD score of 11 or less, 138 days for registrants with a PELD score of 11–20, 125 days for

registrants with a PELD score of 21–30, and 15 days for registrants with a PELD score greater than 30. The longer waiting times for adult recipients mean that the median time to transplant as a function of MELD score is available only for candidates with scores greater than 20. For these two groups (MELD scores of 21–30 and greater than 30), the median time to transplant was 128 days and 29 days, respectively, similar to the time to transplant for children with comparable PELD scores.

At present, a robust analysis of the impact of the PELD system on pediatric liver transplantation is not possible, given the small numbers of pediatric candidates. With this caveat, analysis performed by the SRTR has suggested some trends worthy of future study, including the observation that patients with an increasing PELD score over time were found to have a higher mortality than children with a stable PELD score. In an accompanying article in this report, 'Improving liver allocation: MELD and PELD', by Freeman et al., an increasing PELD score over the previous 30 days ( $\Delta$ PELD) was found to significantly increase the relative risk of death on the waiting list (RR = 1.10,  $p < 0.0001$ ) (25).

Pretransplant mortality is a critical endpoint in examining the outcome of the waiting list process. The total number of deaths for all candidates on the liver waiting list has increased from 579 in 1993 to 1818 in 2002. During the same period, the number of pediatric candidates who died awaiting liver transplantation remained stable, but the proportion of deaths accounted for by pediatric candidates on the waiting list decreased. Candidates under 18 years of age accounted for only 5% of deaths on the waiting list in 2002 compared with 15% in 1993. This decline parallels the decreasing proportion of pediatric patients awaiting transplantation compared with adult recipients, although there has been a decline in the annual death rate for both children and adults over the decade. While the total number of deaths has increased, the annual death rate per 1000 patient years decreased from 225 in 1993 to 106 in 2002 for all age groups. The trend has been gradual and consistent for all candidates older than 1 year. For children younger than 1 year, however, the death rate in 2002 was 766 per 1000 patient years, which is sixfold higher than the overall death rate for all candidates and exceeds the rate observed among patients listed as OPTN/UNOS Status I. Furthermore, in marked contrast to the decline observed in all other age groups, the death rate for infants, on average, has not changed since 1993. The reason for the high death rate in these infants is probably multifactorial. Reasons may include an allocation system that does not fully reflect the relative risk of mortality for these small children, limitations in the medical management of listed patients, difficulty finding suitable grafts, and other factors related to the ability to offer transplantation as a therapeutic option to this particularly complex and technically challenging subset of children. Additionally, patients awaiting a liver-intestine transplant are also considered in the analysis of liver

waiting list mortality. While the number of liver-intestine candidates is small, they are disproportionately represented among children younger than 5 years of age.

**Deceased donor liver transplantation**

In 2002, 482 children aged under 18 years received deceased donor liver transplants, a figure that has remained relatively stable over the last decade. However, when we examine the proportion of deceased donor liver transplants allocated to children, the results differ. Specifically, this proportion has progressively declined in increments over the course of the decade. In 1993 and 1994, approximately 14% of deceased donor organs were allocated to pediatric recipients; from 1995 through 1998, this figure was 12%; and in 1999, it declined to 10%. The proportion has remained stable since that time.

**Living donor liver transplantation**

In an effort to address the shortage of deceased donor livers, living donor liver transplantation was introduced in 1989. Until 1999, the majority of living donor liver transplant recipients were pediatric patients. With the introduction of adult-to-adult living donor transplants, the percentage of total living donors in children has decreased. The total number of adults and children who received living donor liver transplants has generally increased over the decade, although there was a modest decline in total living donor liver transplants performed in 2002.

In 2002, 72 children received living donor liver transplants, accounting for 20% of all living donor liver transplant recipients. The proportion of pediatric recipients in each age group who received living donor liver transplants compared with deceased donor liver transplants was inversely proportional to age (Figure 10). Children aged 5 years and younger accounted for 86% of pediatric living donor liver recipients. There was a modest decrease in the number of living donor transplants performed in children in this younger age range in 2002 compared with the previous year (62 in 2002; 79 in 2001). The introduction of right lobe living donor liver

transplant has not significantly affected the overall number of living donor liver transplants performed in children in the 11–17 year age range. It is likely that these recipients are too small for an adult right lobe graft, thus limiting the applicability of this technique to a small number of older pediatric patients.

**Patient and graft survival**

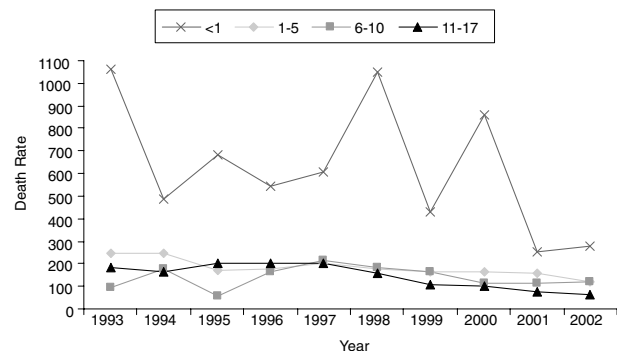
Patient survival in the first year after transplant, expressed as annual death rates per 1000 patient years, was similar for all age groups except children younger than 1 year (Figure 11). Prior to 2001, the death rate for this group was at least twofold higher than that of any other age group. For such infant recipients transplanted in 2001 and 2002, there was a marked decline in the death rate, although the rate currently remains higher than that for all age groups. For children aged 1–5 years and those aged 11–17 years, the time trend indicates a decreasing death rate.

Deceased donor graft survival was similar for all ages, with the exception of those transplant recipients younger than 1 year or older than 65 years, both of whom had lower survival rates at 3 months, 1 year, 3 years, and 5 years after liver transplantation than other intermediate age groups, although many of the differences are not statistically significant. Across all age groups, current 1-year patient survival after deceased donor liver transplant is highest among recipients 6–10 and 11–17 years of age (94% and 93%, respectively), whereas 1-year adult patient survival ranges from 86% to 88% for recipients under 65 years of age (Figure 12). When examined as a function of donor type, graft and patient survival for children younger than 1 year was greater if they received an allograft from a living donor compared with a deceased donor, a trend not detected for any other age group (Figure 13). This trend reached statistical significance for the cohort at the 5-year time point. This finding is consistent with preliminary data presented by two groups at the American Transplant Congress; the risk of mortality and graft loss was less for children younger



Source: 2003 OPTN/SRTR Annual Report, Table 9.4

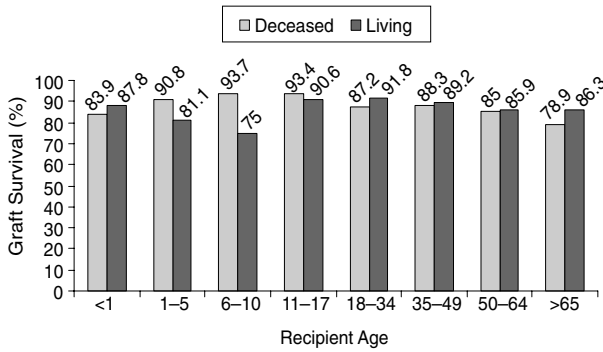
**Figure 10:** Pediatric living donor liver transplants, by recipient age, 2002.



Source: 2003 OPTN/SRTR Annual Report, Table 9.7

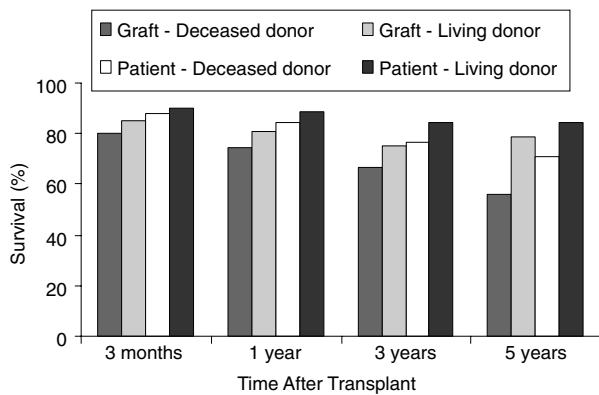
**Figure 11:** Death rate in the first year following liver transplant, 1993–2002.





Source: 2003 OPTN/SRTR Annual Report, Table 9.11a and 9.11b

**Figure 12:** One-year unadjusted patient survival of deceased and living donor liver transplants by recipient age, 2002.

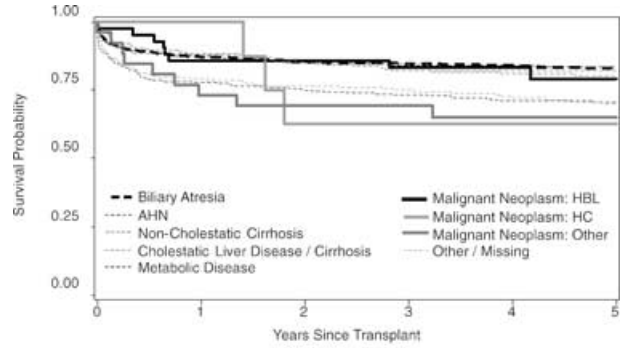


Source: 2003 OPTN/SRTR Annual Report, Tables 9.9a, 9.9b, 9.11a, 9.11b

**Figure 13:** Unadjusted liver graft and patient survival for children less than 1 year of age.

than 2 years if they received an allograft from a living donor compared with a deceased donor (26,27).

The effect of primary diagnosis on long-term outcome following liver transplantation was recently examined as part of a data request by the OPTN Pediatric Transplant Committee. Pediatric recipients who received a primary liver transplant between 1995 and 1999 were followed until death or 5-year follow-up was reached. A total of 2134 recipients were identified. The most common primary diagnoses were biliary atresia (46%), acute hepatic necrosis (14%), metabolic diseases (12%), noncholestatic cirrhosis (10%), and cholestatic liver disease (4%). Recipients with other diagnoses or missing diagnosis accounted for 10%. As demonstrated in Figure 14, patient survival for biliary atresia, metabolic diseases, noncholestatic cirrhosis, and cholestatic liver disease was similar, with 1-year survival of 87–88% and 5-year survival of 80–84%. As expected, recipients with acute hepatic necrosis had lower survival; 78% at 1 year and 71% at 5 years. Children transplanted



Source: SRTR analysis, August 2003. Includes patients <18 years receiving a liver transplant between 1995 and 1999, followed for up to 5 years.

**Figure 14:** Kaplan-Meier survival curves by primary diagnosis, pediatric recipients of livers.

with hepatocellular carcinoma (n = 8), and other malignant neoplasms (n = 26) had 5-year survival of 63% and 65%, respectively. Although the numbers of such patients are small, the results after transplantation in this patient population are discouraging. Children transplanted for hepatoblastoma (n = 42) appear to fare better than those transplanted for other malignancies, with 86% survival at 1 year and 79% survival at 5 years, but the confidence intervals are wide because of the small sample sizes.

In summary, despite increased demand for liver transplantation and increased waiting time to transplantation, pretransplant mortality has decreased and patient and deceased donor allograft survival have improved. When compared with other age groups, however, children aged under 1 year continue to have increased pretransplant mortality and lower patient and allograft survival. Patients in this group tend to show improved survival when receiving an allograft from a living donor compared with those who receive an allograft from a deceased donor. While this advantage is at times small, it suggests that these patients should at least be considered for living donor transplant if the severity of their liver disease warrants this intervention.

## Intestinal Transplantation

Intestinal transplantation has become a clinical reality over the past decade, as witnessed by reports from the University of Pittsburgh (28), University of Nebraska (29), University of Miami (30), Mt. Sinai Medical Center (31), and the University of California, Los Angeles (32). Infection and rejection continue to be barriers to more widespread application of the procedure. Finding organs of suitable size and quality for this unique group of transplant recipients is another major challenge facing the field. This fact was highlighted by a recent report demonstrating the higher waiting list mortality among candidates for intestinal grafts (33). Overall, there has been a marked

improvement since 1997 in outcomes following intestinal transplantation.

### **Waiting list**

There have been no major changes in the listing status of patients awaiting intestinal transplantation, because all are listed as urgent, nonurgent, or inactive. For patients awaiting intestines in combination with the liver, there have been major changes in the allocation of liver grafts after the introduction of MELD/PELD. The MELD/PELD allocation system was tested in a cohort of end-stage liver disease patients that excluded liver-intestine candidates, therefore it does not adequately predict death rates for patients with total parenteral nutrition (TPN)-associated/intestinal failure type of liver disease (33). A recent SRTR analysis of waiting list mortality for pediatric liver candidates and liver intestine candidates revealed that while PELD was predictive of mortality in both patient populations, the mortality risk for the same PELD score is higher for liver-intestine candidates compared with candidates awaiting liver transplant alone. This finding has led to changes in OPTN/UNOS organ allocation policy, wherein patients awaiting liver-intestine transplant automatically receive an increase in their MELD/PELD score equivalent to a 10% risk of 3-month mortality. Additionally, livers may be offered to multi-organ recipients after Status 1 liver candidates but before other isolated liver transplant candidates (OPTN/UNOS Policies 3.6.4.7, 3.9.3, and 3.11.4) (34).

Over the past decade, the demand for intestine transplants has increased significantly. There were a total of 187 candidates on the waiting list at the end of 2002, of whom 137 were younger than 18 years of age. While this represents a substantial increase from 1993, there was little change from the previous year. Nearly 50% of all candidates awaiting intestinal transplantation were younger than 5 years, and the majority were non-Hispanic/non-Latino whites. These ratios have remained relatively constant.

The number of new registrants in each age range has remained stable over the past 3 years. Of the total 129 new pediatric registrants in 2002, 80 were younger than 1 year and 31 were in the 1–5 year age range. The median time to transplant reflects the difficulty facing these candidates awaiting intestinal transplantation. The overall median time to transplant for all candidates in 2002 was 310 days, a figure that has not changed substantially since 1998. Median time to transplant is lowest for candidates in the 50–64 year age range and between 200 and 300 days for all other age groups. A median time to transplant cannot be calculated yet for infant candidates (<1 year old), reflecting the long waiting time to transplant in this age group.

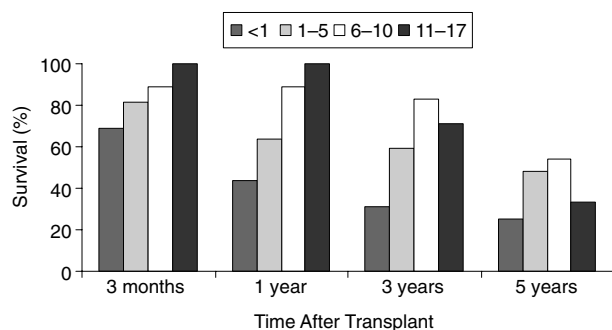
The substantial waiting times for intestinal transplantation translate into significant waiting list mortality. In 2002, the annual death rate per 1000 patient years was 298 for the total candidate group. These rates were even more stag-

gering in the groups aged under 1 year and 1–5 years (631 and 371, respectively). This waiting list mortality is particularly troublesome when one considers the number of deceased donors in 2002. In that year, there were 6182 deceased donors, while there were only 187 candidates awaiting intestinal transplantation. Taking potential technical considerations related to size into account, even for small children (age 5 years and under), there were 270 deceased donors in this age range and 96 potential recipients in the same age range. This discrepancy between the number of deceased donors, candidate waiting times, and candidate waiting list mortality point to the imperative of addressing long waiting times and the difficulty of matching donor intestines to potential recipients. Other current literature also support the data showing that the waiting list death rates in this group of patients are substantially higher than those reported for any other group of solid organ transplant candidates. Pretransplant mortality rates as high as 50% have been reported in the literature from individual transplant centers (35,36). The advanced medical condition of these patients at the time of evaluation and the limited availability of organs of suitable size and quality no doubt contribute to the high mortality rates among these patients.

### **Transplantation and survival**

In 2002, there were 67 intestinal transplants in pediatric recipients, accounting for 63% of all intestinal transplants performed. Within the pediatric population, 66% of these recipients were aged 5 years or younger. The characteristics of these intestinal transplant recipients are similar to those of the intestinal transplant candidates described above. The incidence of intestinal transplants per one million population is very low, and this figure has not changed much over the past several years. As compared with kidney transplants (incidence 51.22 per one million population) and liver transplants (incidence 18.47 per one million population), the incidence of intestinal transplants in 2002 was 0.37 per one million population. The age groups with the highest incidence of intestinal transplants are infants (under 1 year of age) and 1–5 year olds (incidence 5.27 per one million population). This low incidence reflects the smaller number of patients currently considered candidates for intestinal transplantation. It is not possible to know if the low incidence also reflects limited access for patients to the few centers that actually perform these transplants on a regular basis.

Outcomes after intestinal transplantation have generally improved over the last 10 years. In 2002, the overall recipient death rate in the first year after intestinal transplant per 1000 patient years at risk was 318. For comparison, the corresponding figure for recipients of liver transplants was 145. In the intestinal transplant data, the death rate has shown an overall decrease since 1993, but it remains highest in the 1–5 year and 6–10 year age groups (384 and 513, respectively). The death rate is also affected,



Source: 2003 OPTN/SRTR Annual Report, Table 10.11

**Figure 15:** Unadjusted intestine patient survival for children by recipient age.

notably by donor age, such that recipients of intestines from donors aged 6–10 years had a substantially higher death rate. Graft survival rates after intestinal transplant for all age groups at 3 months, 1 year, 3 years, and 5 years were 86%, 71%, 43%, and 33%, respectively. It should be noted that graft survival rates were much higher for recipients of liver transplants than for intestinal transplant recipients.

Overall patient survival rates in 2002 following intestinal transplantation at 3 months, 1 year, 3 years, and 5 years were 81%, 70%, 57%, and 44%, respectively. As illustrated in Figure 15, 1-year patient survival rates in the 6–10 and 11–17 year ranges (89% and 100%, respectively) appear higher than those observed in younger children (44% for patients aged less than 1 year and 64% for recipients aged 1–5 years). The corresponding survival rates for recipients of liver transplants were much higher than those for intestinal transplant recipients.

To put these outcome data into perspective, one needs to examine the existing literature on intestinal transplantation. The International Intestinal Transplant Registry (37) is the only data source with comparable patient numbers. The most recent publication reports 273 transplants in 260 patients. A combined liver-intestinal graft was used in 48% of recipients, while an isolated intestinal graft was used in 41%. The most common pediatric indications for transplant were volvulus, gastroschisis, and necrotizing enterocolitis; the most common indications in adults were ischemia, Crohn's disease, trauma, and desmoid tumors. There was a better outcome in patients transplanted since 1995 and in patients transplanted in centers that had performed 10 or more total transplants. Although the survival is only calculated to 2 years post-transplant, the figures are comparable to those cited in this report. These published findings mirror the registry's most recent in-depth analysis of 437 intestine transplants performed in 405 pediatric recipients as of May 2001 (38). Overall patient and graft survival appear to be improving. Pediatric recipients now account for 63%

of the total transplants in the registry. The major cause of death after transplant remains sepsis. Other published series overwhelmingly indicate that the major cause of graft loss after intestinal transplantation is immunological due to acute or chronic rejection (28–32).

Publications from large, single-center studies also indicate overall improving outcomes (28–32). Five-year patient and graft survival rates from 55% to 90% and from 50% to 60%, respectively, have been reported recently. The reasons for these improvements are multifactorial. Earlier referral for transplantation facilitates obtaining suitable donor organs prior to the deterioration of the recipient's clinical condition. The experience of the transplant center may also play a role, as outlined above. Improvements in immunotherapy with the introduction of interleukin-2 receptor antagonists (39,40), rapamycin (31), thymoglobulin (41), and alemtuzumab (42) have led to the reduction in the incidence and severity of graft loss and patient morbidity. Furthermore, improvements in antimicrobial prophylaxis and treatment of organisms such as cytomegalovirus and Epstein-Barr virus have reduced the effect of these viruses after intestinal transplantation (43).

In summary, the data demonstrate a small but growing population of candidates and recipients waiting for and undergoing intestinal transplantation. The vast majority of these patients are currently managed in four or five transplant centers in the USA. The data demonstrate that mortality on the intestinal transplant candidate waiting list is unacceptably high. These findings have led to recent changes in the allocation system. It remains to be seen if these changes will affect waiting list outcomes. The data also show a very small number of individuals being listed for intestinal transplantation. Whether this indicates a small incidence of the diseases that lead to intestinal failure or a low rate of patients with these diseases being referred and listed for intestinal transplantation remains speculative. Outcomes after intestinal transplantation, particularly in the short term, are steadily improving.

## Heart Transplantation

### Waiting list

While the number of pediatric patients awaiting heart transplantation has been relatively steady over the last 5 years, the 262 patients listed at the end of 2002 represent a 10% increase compared with the end of 2001. Pediatric patients continue to account for 5–7% of all of those awaiting heart transplants. Of all pediatric patients on the waiting list at the end of 2002, 40% were in the 1–5 year age range. Following the trend of the last 3 years, the number of new pediatric heart transplant registrants aged less than 1 year continued to increase and to predominate over the other pediatric age groups in 2002. An increase in the number of new pediatric heart registrants in the 1–5 year age range seen in 2001 was sustained in 2002, and the number in

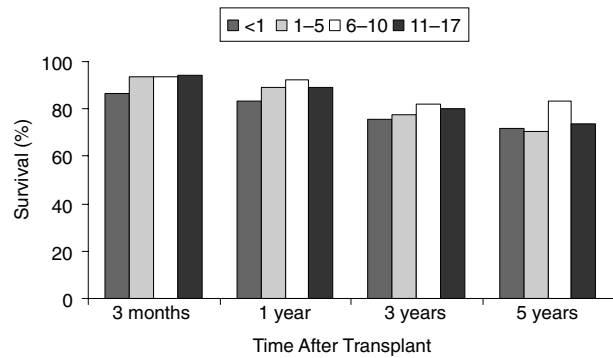
the 6–10 year group rose to levels approximating those of the last half decade after an unexplained decline last year. High-risk congenital cardiac anomalies unsuitable for surgical intervention or those for which surgical repair has not provided adequate palliation are the most frequent indications resulting in transplant in candidates under 1 year of age. The diagnosis of cardiomyopathy ultimately accounts for the majority of transplants performed in children (1–10 years of age), as well as adolescents (11–17 years of age), although congenital heart disease does account for 25% of transplants in the latter group (44).

Pediatric groups older than 1 year of age have a median waiting time to transplant of less than 3 months; those less than 1 year have insufficient data to make this determination because of longer waiting times and extremely high waiting list mortality in the infant population. The time to transplant for children older than 1 year remains substantially shorter than for adult registrants. Also of note is median time to transplant for candidates in the 1–5 year age range, which was 50% shorter in 2002 compared with 2000. Despite this shorter waiting time, the rate of death on the waiting list in pediatric registrants remains a major problem. The death rate for all pediatric heart waiting list patients is well above the rate for all adult age groups. Infants (aged less than 1 year) have a death rate more than six times that seen in other pediatric age groups and more than 10 times the overall cardiac waiting list mortality rate. This reflects both the severity and the unstable nature of the pathophysiology associated with these complex congenital heart lesions. These data emphasize the critical issue of a shortage of donor organs as well as the inadequacy of extracorporeal support systems for children.

**Transplantation and survival**

Over the last 10 years, children have accounted for approximately 13% of all heart transplant recipients. Similarly, over this same period, the percentage of all heart recipients who carried the primary diagnosis of congenital heart disease has remained stable at just over 8%. The number of transplants performed has remained relatively stable in each pediatric age group over the last 5 years, with 60–80 transplants annually in infants, 55–82 transplants in recipients aged 1–5 years, 28–46 transplants in the 5–10 year age range, and 88–99 transplants in adolescents. After patients in the 50–64 year age range, infants consistently have the second highest incidence of heart transplant, with a range of 16–28 per one million population over the last 10 years. Excluding individuals in the 50–64 year age group, this incidence is approximately three to eight times that seen in all other age groups.

Over the last 10 years, donor or recipient age under 1 year has generally been associated with a higher annual death rate per 1000 patient years for recipients in the first year after heart transplantation. There are several postulated reasons for higher mortality in this age group. First, the complex congenital heart lesions that are not amenable to surgical palliation are frequently associated with pul-



Source: 2003 OPTN/SRTR Annual Report, Table 11.11

**Figure 16:** Unadjusted heart patient survival for children by recipient age.

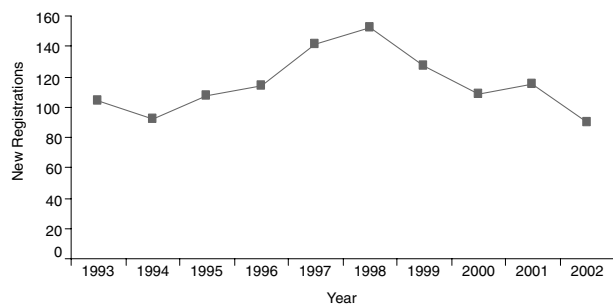
monary over-circulation and can result in both decreased end organ perfusion as well as elevated pulmonary vascular resistance as the patient awaits a suitable donor organ. Furthermore, from the aspect of the donor organ, there may be a poorly understood susceptibility of the immature myocardium to preservation or reperfusion injury. Despite this higher mortality in the first year following transplant in infant recipients, at 5 years following transplantation, the survival is similar to that seen in all other age groups (Figure 16). This equilibration in survival that occurs by 5 years following the transplant may be related to emerging evidence that rejection is reduced in thoracic organ recipients when transplanted in the first year of life (45). Transplantation performed in infancy may confer some type of immunologic tolerance that, as of yet, is not well understood. Notably, 5-year patient survival for recipients in the 6–10 year age range is higher than that seen in any other age group, including the adult population. The reasons for this are unclear from available data and warrant further investigation.

In summary, the issue of inadequate donor organ supply remains an obvious obstacle in pediatric heart transplantation. The number of candidates on the waiting list, the number of transplants performed, and outcomes following transplantation have all remained relatively stable. Innovative technology for supporting ill candidates to the time of transplant, aggressive approaches for expanding the donor pool—including the continued development of novel strategies such as nonheartbeating donors and ABO incompatible donors and the development of novel forms of immunosuppression—are essential for future improvement in the field.

**Lung Transplantation**

**Waiting list**

Similar to the heart transplant population, pediatric patients represented only 5–6% of all patients on the lung



Source: 2003 OPTN/SRTR Annual Report, Table 12.2

**Figure 17:** New pediatric registrations on the lung transplantation waiting list, 1993–2002.

transplant waiting list over the last 10 years. While the total number of pediatric patients is small, some trends can be identified. With respect to the waiting list, at the end of 2002, the 19 registrants aged 1–5 years represent continued growth, while the 37 recipients in the 6–10 year age range was down to levels seen in 1998 after hitting a peak of 49 in 2001. The reason for this decline is directly related to the number of new registrants in this age group, which has dropped drastically from a peak of 28 seen in 1999 to only six in the last year. This decline in new registrants was paralleled in children 11–17 years of age, where the number had fallen to 61, the second lowest for this age group in the last 10 years. In fact, the number of new registrants in the entire pediatric age range has continued to notably decline, such that the 90 new registrants in 2002 represent the lowest number in the last 10 years (Figure 17). While this may reflect better medical care for patients with cystic fibrosis (CF), it is not clear whether this is the entire explanation. It is also unlikely that this decline is in any way related to the advent of living donor lobar lung transplantation, because the majority of the recipients of this type of transplant are also listed for a cadaveric organ. Finally, this decline does not reflect a decrease in listing patients with previous lung or heart-lung transplants, because these patients have never comprised more than 2–3% of patients on the waiting list, reflecting a continued general unwillingness for practitioners to proceed with retransplantation for bronchiolitis obliterans.

Analyses of median waiting times to lung transplantation in the pediatric age groups cannot be performed because of the high death rates and long waiting times characteristic of this age group. Examining instead the time until 25% of listed patients are transplanted, new registrants younger than 1 year have a substantially shorter waiting time than other pediatric and adult age groups. This may be related to the very small number of new registrants and thus a low level of competition for organs in this age group. There is growing interest in directing pediatric deceased lung donors to pediatric recipients, a policy already established by the OPTN for heart transplant donors.

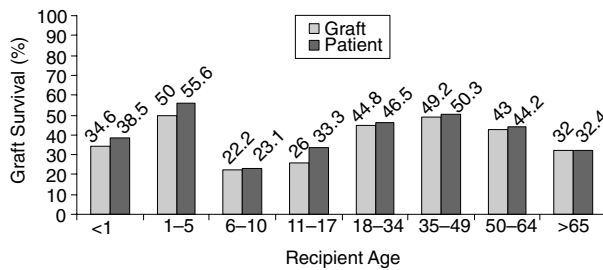
Waiting list mortality for the overall lung transplant candidate group has gradually declined over the last 10 years. The rate of 131 per 1000 patient years at risk in 2002 is close to one-half of the 1993 rate. This may reflect more appropriate timing of listing of registrants for transplant and better medical care. It does not reflect shorter waiting times, because the time to transplant has generally increased.

Within the pediatric population, registrants under 18 years of age had a notably higher death rate while on the waiting list than did their adult counterparts. In comparison with the aforementioned rate of 131 per 1000 patient years at risk for the overall lung transplant registrant population, the rate in patients 1–5 years of age was 238 per 1000 patient years at risk, the rate in patients 6–10 years of age was 210 per 1000 patient years at risk, and that in the teenage group (10–17 years of age) was 148 per 1000 patient years at risk. These data reflect the severity of illness for which these candidates are being listed for lung transplantation, as well as the scarcity of suitable donor organs. Examples of some of the entities for which these younger patients are being listed include forms of pulmonary alveolar proteinosis (such as surfactant protein B deficiency), pulmonary veno-occlusive disease, infantile interstitial pneumonitis, and idiopathic or secondary pulmonary hypertension. These entities can be very difficult to palliate, and use of an extra-corporeal membrane oxygenator as a bridge to transplant is rare, given the technical limitations associated with extracorporeal support in small pediatric patients.

### **Transplantation and survival**

In 2002, a total of 44 pediatric lung transplants (39 deceased and five living donors) were performed. Over the last 10 years, pediatric lung transplants have accounted for 3–6% of all recipients. Other than the group labeled congenital disease (CF not included), the relative distribution of the primary disease entities leading to transplantation has also remained stable over the 10-year period. The congenital disease group accounted for 6% of lung transplants in 1993 and in 2002 accounted for less than 1%. The numbers of transplants performed have stayed relatively stable in each pediatric age group over the last 5 years. The majority (64%) of pediatric recipients were in the 11–17 year old age group, with CF being the most common disease in these adolescent lung transplant recipients. CF was also the primary diagnosis in the majority of living donor lung transplants.

The number of living donor lung transplants performed in the pediatric population peaked at 14 in 1998. The five transplants performed in 2002 represent the lowest activity since 1996. In contrast with deceased donor lung transplant recipients, in whom the primary diagnosis of retransplant/graft failure has perennially accounted for 2–3% of all transplants, in the living donor lung transplant population, retransplantation/graft failure has accounted for 8–16% of



Source: 2003 OPTN/SRTR Annual Report, Table 12.9a and 12.11a.

**Figure 18:** Unadjusted 5-year graft and patient survival of deceased donor lung transplants by recipient age, 2002.

transplants. This observation may suggest a practice to offer retransplantation only in cases where a living donor can be identified.

The incidence of lung transplantation in all pediatric age groups was less than one per million population, well below the incidence of heart transplantation in children. This figure is also substantially below the incidence of lung transplantation observed in adults.

A history of prior organ transplant of any kind and the need for life support at the time of transplant continue to be associated with approximately double the annual death rate per patient year at risk for recipients in the first year after lung transplant. Because of the relatively small numbers of pediatric lung transplants, analysis of patient and graft survival is difficult. As demonstrated in Figure 18, however, the available data suggest that 5-year graft and patient survival is generally similar between pediatric and adult recipients. Outcomes following living donor lung transplantation are similar to those observed with deceased donor transplantation. This lends further credibility to the importance of living donor lung transplantation as an acceptable mode of expanding the donor organ pool.

Overall, the number of pediatric lung transplant recipients and their survival has remained relatively stable, while the number of new registrants and candidates on the waiting list has declined. The survival benefit due to transplantation in infancy (aged under 1 year) suggested by the pediatric cardiac transplant data does not seem to be borne out in the infant lung transplant survival data. The development of novel forms of immunosuppression and other therapies that obviate the development of bronchiolitis obliterans are concepts that remain at the forefront for future improvement in outcomes. While living donor lung transplantation has been established as a viable mode of expanding the donor pool, other options must be explored. It remains to be seen whether ABO mismatched transplantation, which has been introduced in infant cardiac transplantation, will eventually be attempted with lung transplantation.

## Heart-Lung Transplantation

### Waiting list

Pediatric registrants have accounted for 16–18% of all heart-lung waiting list patients for the past 4 years. This percentage is slightly larger than that seen in either the pediatric heart or pediatric lung transplant populations. After hitting a peak of 51 in 1998, the absolute number of pediatric registrants awaiting heart-lung transplant has steadily declined to 31 seen at year-end in 2002. The number of new heart-lung transplant registrants reached its lowest level in 10 years; the number of new registrants in 2002 (88) is approaching almost half of what it was in 1993 (162). At 19, the number of new registrants in the pediatric age range is the lowest recorded in the last 10 years. This finding is probably multifactorial and includes the widespread acceptance of lung transplantation and not heart-lung transplantation as the procedure of choice for CF. Furthermore, in patients with pulmonary hypertension associated with a correctable congenital heart defect, transplant centers are tending to opt for combining lung transplantation with an intracardiac repair, unless there is a single ventricle cardiac defect or the left ventricular function is prohibitively diminished. The majority of pediatric registrants are in the 11–17 year age group.

There continue to be insufficient data for the entire heart-lung transplant waiting list population to determine median waiting time to transplant. The overall waiting list death rate among all heart-lung transplant candidates was 186 per 1000 patient years at risk. Children in the 1–5 year and 11–17 year age groups had rates notably higher at 333 and 326 per 1000 patient years at risk, respectively. These results may be related to a lack of circulatory support devices to assist as a bridge to transplantation in the pediatric population. Likewise, the competition for organs between the adult, adolescent, and pediatric populations may also factor into these results.

### Transplantation and survival

Over the last 10 years, pediatric candidates accounted for 8–23% of all heart-lung transplant recipients; of the 32 heart-lung transplants performed in 2002, 5 (16%) were pediatric. Congenital disease and primary pulmonary hypertension continue to be the most common diagnoses treated with heart-lung transplant. As has been the case throughout the last 10 years, the infrequency of heart-lung transplantation in the pediatric population precludes calculation of annual death rates following transplantation.

Five-year graft and patient survival are difficult to analyze in the pediatric patient heart-lung transplant population because the number of recipients is so low. For example, while 5-year patient survival in the 11–17 year age group is 50% and well above that of the overall heart-lung recipient population (37%), the standard error is so large as to make this relatively meaningless. It is generally accepted

that survival rates for heart-lung transplantation in the pediatric age range are similar to or slightly less than those obtained in pediatric lung transplant recipients. As long as heart-lung transplantation continues to be an unusual form of therapy, it will be difficult to meaningfully analyze its outcomes. As with all other forms of thoracic organ transplantation, availability of donor organs (heart-lung blocks) remains a limiting factor.

Reviewing all forms of thoracic transplantation in the pediatric population, we can say that while the number of new pediatric heart transplant registrants has reached its highest level in the last 5 years, the number of new pediatric lung and heart-lung registrants is declining. Waiting list mortality for pediatric heart, lung, and heart-lung registrants is higher than that seen among adult registrants. Increased severity of illness is one reason. The existence of few options for cardiac support in this population of candidates is another. Needless to say, an ongoing shortage of donor organs only serves to exacerbate this situation. While living donor lung transplantation, ABO mismatched infant cardiac transplant, and nonheartbeating donors have been established as viable methods of expanding the donor pool, other options must be explored.

## Immunosuppression

An accompanying article of this report, 'Immunosuppression practice and trends', provides an in-depth examination of practices across all types of organ transplants for recipients of all ages over the last 10 years (46). A similar detailed analysis, restricted to pediatric patients, is beyond the scope of this article. Nonetheless, an age-specific analysis of practices is worthy of study. There is growing evidence that the pharmacokinetics of many immunosuppressive agents are substantively different between adults and children (47–50). There are also different concerns re-

garding the specific side-effects and toxicities of individual agents that are age dependent, including cosmesis, growth, and development. Furthermore, as new immunosuppressive agents are introduced, there are frequently different rates of integration into organ specific immunosuppressive strategies. It is likely that such practice differences exist between pediatric and adult programs as well.

The current use of immunosuppression by organ in pediatric recipients is summarized in Table 1. The reported use of induction therapy has declined over the last few years, and the choice of agent has changed with the introduction of new agents. Induction use is still most common in kidney transplantation. Half of all renal recipients received an interleukin-2 receptor antagonist at time of transplant. With respect to calcineurin inhibitors, tacrolimus is used significantly more frequently than cyclosporin in kidney, liver, and intestine transplantation, whereas cyclosporin is used more frequently in heart and lung recipients. Rapamycin was used as maintenance therapy in nearly a fifth of all kidney transplants performed in 2002.

Comparison of the findings in Table 1 with data in the immunosuppression article in this report (46) reveals that indeed there are differences in practices between adults and children, and these differences are frequently organ specific. For example, in kidney transplantation, rapamycin was used in 18% of pediatric recipients at the time of transplant discharge compared with 15% of all renal recipients. It is not possible to determine the exact reason for this observation given the current data, but the greater use of rapamycin observed in children may reflect an attempt to introduce steroid-free protocols in the hope of avoiding steroid-associated effects on growth. The relationship between age and rapamycin use is reversed with respect to liver transplantation. Specifically, rapamycin was used in 3% of pediatric liver recipients at the time of

**Table 1:** Pediatric immunosuppression use (%) by organ

	Organ				
	Kidney	Liver	Intestine	Heart	Lung
<b>Induction drugs</b>					
ATGAM®	67.9	20.3	46.3	43.7	55.0
OKT3®	0.3	3.2	1.5	9.7	15.0
Thymoglobulin®	0.9	0.4	3.0	3.6	0.0
Zenapax®	18.8	3.6	20.9	18.6	10.0
Simulect®	23.2	8.3	9.0	7.5	30.0
	26.8	4.9	11.9	6.1	0.0
<b>Maintenance discharge/maintenance at end of first year</b>					
Calcineurin inhibitor use	93.4/90.8	97.9/97.0	98.2/100.0	98.8/93.9	94.7/91.7
Cyclosporine	22.5/30.8	11.3/9.4	0.0/0.0	60.9/48.9	57.9/16.7
Tacrolimus	71.4/60.6	88.3/88.6	98.2/100.0	43.0/45.5	42.1/75.0
Antimetabolite use	76.5/72.2	32.6/23.0	14.5/2.9	84.1/77.1	94.7/75.0
Azathioprine	5.0/9.5	3.8/2.1	0.0/0.0	35.7/22.9	63.2/33.3
Mycophenolate mofetil	72.6/63.1	28.8/20.8	14.5/2.9	58.9/54.1	36.8/41.7
Rapamycin use	18.2/13.9	3.4/4.9	18.2/8.6	1.9/3.5	5.3/0.0

Induction drugs and maintenance at discharge are for patients who received transplants in 2002; maintenance at 1 year following transplant is for patients who received transplants in 2001. Source: OPTN/SRTR data as of August 2003.

transplant discharge; overall use of rapamycin in liver recipients of all ages was 7%. In heart transplantation the difference was even more striking: only 2% of pediatric heart recipients were discharged on rapamycin, whereas the figure for heart transplant recipients of all ages is 10%. With respect to calcineurin inhibitors, tacrolimus use in renal recipients at discharge post-transplant is more common in pediatric recipients (71%) compared with kidney recipients of all ages (63%). Again, specific reasons for this difference cannot be determined, although it is possible there is greater concern for cyclosporine-associated cosmetic effects in the pediatric population. Tacrolimus use at the time of transplant discharge is more common in pediatric liver recipients (88%) compared with pediatric kidney recipients, and the use is similar to liver recipients of all ages (87%).

Another age-specific practice is apparent when examining the use of induction therapy in renal transplantation. With respect to polyclonal T-cell depleting agents, equine antithymocyte globulin ATGAM® (Pharmacia & Upjohn Co., Kalamazoo, MI) and rabbit antithymocyte globulin Thymoglobulin® (SangStat Medical Corp., Fremont, CA) were both used less in pediatric renal recipients compared with recipients of all ages (0.3% vs. 2% for ATG® and 19% vs. 26% for Thymoglobulin®). These practices may reflect concern over complications associated with aggressive induction therapy, for example post-transplant lymphoproliferative disorder, which is more common in the pediatric population. Compared with transplant-specific recipients of all ages, the use of interleukin-2 receptor antagonists appears more common in pediatric kidney recipients, less common in pediatric heart recipients, and approximately equivalent in pediatric liver recipients.

These limited observations highlight differences in practices that are age specific. Consideration of these differences is important when examining improvements in patient and graft survival across age groups, as well as immunosuppressive-associated morbidity.

## Conclusion

This analysis of the OPTN/SRTR database serves to document continued improvement with respect to graft and patient survival over the decade for those pediatric patients with end-stage organ disease who are fortunate enough to receive a transplant. While these advances have been observed for liver, intestine, and thoracic transplantation, these improvements have been best characterized in the renal transplant population. One-year graft survival for both living and deceased donor renal transplants is excellent across all pediatric age groups and now equals or exceeds the survival rates seen in adult recipients. Long-term graft survival is also excellent, except for adolescent recipients who have survival rates well below those of all but the very oldest adult recipients. The reasons for this striking

discrepancy within the pediatric population are not known. While there may be organ-specific factors responsible, many believe that issues related to compliance to the immunosuppressive regimen play a pivotal role in these adolescent recipients. Ongoing efforts to determine the potential role of noncompliance and to design interventions to improve outcomes should be encouraged. If compliance is indeed a causative factor, it is reasonable to postulate that this problem is age-specific rather than organ-specific, and progress made in this area could translate into improved outcomes for all adolescent transplant recipients.

While the significant improvements in graft and patient survival are laudable, waiting list mortality remains a significant issue. Pediatric candidates awaiting liver, intestine, and thoracic transplantation face mortality rates that are generally greater than their adult counterparts, and this effect is particularly pronounced in patients aged 5 years and younger. In certain subgroups, such as children aged under 1 year awaiting liver, intestine, and heart transplantation, this risk can be five- to sixfold higher than other patients awaiting transplantation. Strategies aimed at reducing waiting list mortality are vital. While improvements in care of children with end-stage organ disease can make an impact, improving access to transplantation is critical. To better address issues related to waiting list mortality, the transplantation community has attempted to develop fair allocation strategies that focus on medical urgency rather than waiting time. Some of these strategies, such as MELD/PELD, use predicted mortality as the measure of medical urgency. While mortality may be a reasonable starting point for adult patients, it is important to realize that other issues in addition to mortality are critical for children. Consideration of the effect of end-stage organ disease on growth and development is often equally important, both while awaiting transplant and after transplantation. Development of an evidence-based, quantitative approach to measuring the relative role of these other factors could prove crucial. It is to be hoped that continued refinements in allocation policy will continue to emphasize the importance of directing organs to those recipients most in need of transplantation and most likely to benefit from this therapy.

Within the pediatric population, several strategies may help to improve access to transplantation. In some cases, such as for patients awaiting liver and intestine transplantation, the initial allocation system underestimated the mortality risk faced by these patients. Based on ongoing data analysis, the allocation system has been adjusted accordingly. More donor organs are another obvious solution, although finding an appropriate donor can be challenging in small children. In kidney transplantation, graft size is not an issue, and the same is true to a lesser extent in liver transplantation. In the case of intestinal and thoracic organ transplantation, issues related to graft size directly affect the pool of potential donor organs. It is vital that no pediatric donor goes underutilized.



Pediatric patients accounted for 3% of all patients awaiting transplantation at the end of 2002 and 7% of all transplants performed. While, at first glance, these figures may seem unbalanced with respect to listing and transplantation, it is noteworthy that the representation of pediatric deceased organ donors is more than twofold higher compared with recipients of such organs. In 2002, individuals under 18 years of age accounted for 15% of all deceased donors. This observation should discredit any belief that pediatric patients are receiving a disproportionate share of this life-saving resource.

Significant progress has been made in the care of pediatric transplant patients. Changes in supportive therapy prior to transplant, donor selection, operative management, immunosuppressive therapy, and long-term follow up have all affected the care of these children. Some of these advances reflect lessons learned from across the pediatric population, whereas other advances reflect information gathered across all ages in organ-specific areas. It is vital to critically evaluate and integrate new information from all sources, while being mindful of the knowledge that these young patients represent a unique group, with issues distinct from their adult counterparts.

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