

# Pediatric Transplantation in the United States, 1995–2004

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**This article reviews trends in pediatric solid organ transplantation over the last decade, as reflected in OPTN/SRTR data. In 2004, children younger than 18 years made up nearly 3% of the 86 378 candidates for organ transplantation and nearly 7% of the 27 031 organ transplant recipients. Children accounted for nearly 14% of the 7152 deceased organ donors. The transplant community recognizes important differences between pediatric and adult organ transplant recipients, including different etiologies of organ failure, surgical procedures that are more complex or technically challenging, effects of development on the pharmacokinetic properties of common immunosuppressants, unique immunological aspects of transplant in the developing immune system and increased susceptibility to posttransplant complications, particularly infectious diseases. For these reasons, and be-**

*Note on sources:* The articles in this report are based on the reference tables in the 2005 *OPTN/SRTR Annual Report*, which are not included in this publication. Many relevant data appear in the figures and tables included here; other tables from the *Annual Report* that serve as the basis for this article include the following: Tables 1.3, 1.4, 1.5, 1.7, 1.8, 1.10, 1.11a and b, 1.12a and b, 2.1–2.7, 5.1a, 5.3–5.5, 5.9a–c, 5.12a, 5.12c, 5.14, 7.14, 9.1a and b, 9.3–9.5, 9.7a, 9.9a and b, 9.12a and b, 9.14, 10.1–10.7, 10.9, 10.12, 10.14, 10.15, 11.1b, 11.3–11.5, 11.9, 11.12, 11.14, 12.1–12.7, 12.9a and b, 12.14, 13.1b, 13.2, 13.4 and 15.3. All of these tables may be found online at <http://www.ustransplant.org>.

**cause of the impact of end-stage organ failure on growth and development, the transplant community has generally provided pediatric candidates with special consideration in the allocation of deceased donor organs. Outcomes following kidney, liver and heart transplantation in children often rank among the best. This article emphasizes that the prospects for solid organ transplantation in children, especially those aged 1–10 years are excellent. It also identifies themes warranting further consideration, including organ availability, adolescent survival and challenges facing pediatric transplant clinical research.**

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

## Introduction

This article provides important data and analysis regarding pediatric solid organ transplantation in the United States. Unless otherwise noted, the statistics in this article are drawn from the reference tables in the 2005 *Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) Annual Report*. We define 'pediatric' as a candidate, recipient or donor, aged 17 years or less. Graft and patient survival are reported as unadjusted survival unless otherwise indicated. Short-term survival (3 months and 1 year) reflects transplants done from 2002 to 2003; 3-year survival reflects transplants performed from 2000 to 2003; 5-year survival reports on transplants performed from 1998 to 2003. A companion article in this report, 'Analytical Methods and Database Design: Implications for Transplant Researchers, 2005' (1), explains the methods of data collection, organization and analysis that serve as the basis for this article. Additional detail on the methods of analysis employed herein 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>.

Pediatric organ transplant candidates represent a distinct population in comparison with adult candidates because of several important differences. These include different etiologies of organ failure, surgical procedures that are more complex or technically challenging, effects of development on the pharmacokinetic properties of common

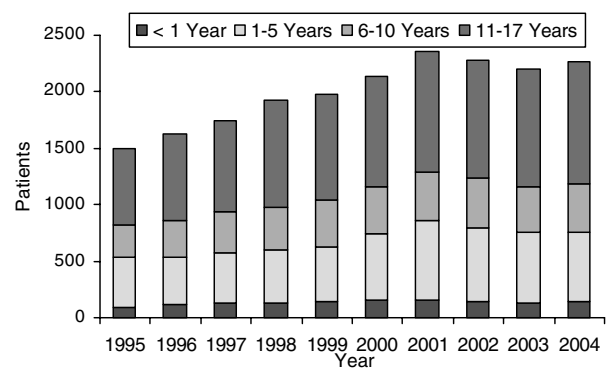
immunosuppressants, unique immunological aspects of transplant in the developing immune system and increased susceptibility to posttransplant complications, particularly infectious diseases. These differences have fostered the development of independent pediatric transplant programs or specialized pediatric expertise within transplant programs that also serve adults. Furthermore, because of the impact of end-stage organ failure on growth and development, the success of pediatric organ transplantation must also be measured by success in facilitating growth and development that is as near normal as possible. Because of these specific challenges, the transplant community has generally provided pediatric candidates with special consideration in the allocation of deceased donor organs. In addition, potential living donors are often more motivated to donate if the recipient is a child (2).

The frequency of transplant in children ranges from 4% to 15% of that in adults for all organs except small intestine (which is the least frequently transplanted organ). For this reason, most centers transplanting pediatric candidates do not accrue adequate numbers of patients to allow meaningful outcomes analysis or sufficiently powered clinical trials or research protocols. Indeed, fewer than 25% of centers reporting pediatric transplants of any organ perform more than 10 per year (OPTN data, 2005). To overcome these barriers, the SRTR provides statistical analyses and models using OPTN/SRTR datasets. These give the OPTN Pediatric and other committees important information to guide decisions about pediatric organ allocation and outcomes assessment. Moreover, the pediatric transplant community has developed several collaborative groups or registries to facilitate analyses not achievable using data collected by the OPTN. These include the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) (3,4), the Studies of Pediatric Liver Transplantation (SPLIT) (5), the Pediatric Heart Transplant Study (PHTS) (6), and the International Pediatric Lung Transplant Collaborative (IPLTC) (7). In addition, the Intestinal Transplant Registry covers pediatric intestinal transplantation (8,9).

The Cooperative Clinical Trials in Pediatric Transplantation (CCTPT), sponsored by the National Institute of Allergy and Infectious Diseases, continues to fund important trials in pediatric renal transplantation; this model should be extended to other pediatric solid organ transplant consortia to develop strategies to answer questions raised in this report.

**Waiting list**

Changes in the waiting list reflect a complex set of interactions. Waiting list additions are driven by the incidence of end-stage organ failure cases amenable to transplant, as well as referral patterns and numbers of transplant programs. Waiting list removals are driven primarily by availability of suitable organs for transplant and the efficacy of organ allocation policy. The contribution of each factor is



Source: 2005 OPTN/SRTR Annual Report, Table 1.4.

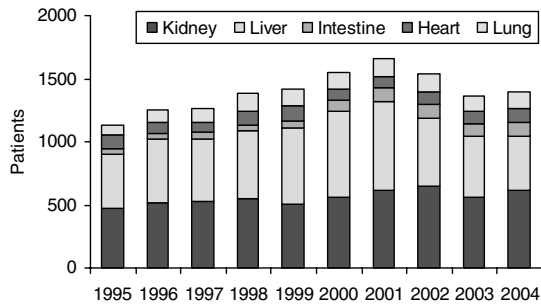
**Figure 1: Pediatric transplant waiting list at year end, 1995–2004.**

different for each organ. For example, kidney transplantation is more likely to be influenced by changes in organ availability and allocation, whereas intestine, a less mature discipline, may be more influenced by program growth. Therefore, interpretation of overall changes in the pediatric waiting list is challenging. Nonetheless, there were 2269 pediatric organ transplant candidates at the end of 2004, reversing a 3-year trend of decreases (Figure 1). There were more candidates in all age groups except 1–5-year-old children. Candidates younger than 11 years continue to account for just over half of pediatric candidates. However, the increase did not reverse the ongoing decline of pediatric candidates as a percentage of all candidates; children currently account for 3% of all transplant candidates. The trend over the past 10 years has been for steady increases in adult candidates, most dramatically in those over 50 years of age. Although the number of pediatric candidates has increased by about 52% over the decade (2276 from 1491), the total number of pediatric candidates at year end has not changed substantially since 2001.

In 2004, liver (428) and kidney (620) pediatric candidates together made up 75% of the active pediatric waiting list candidates (Figure 2). Over the past decade, the largest percentage increase in waiting list activity occurred in intestine (129%, 62 to 142) and lung (79%, 104 to 186) candidates.

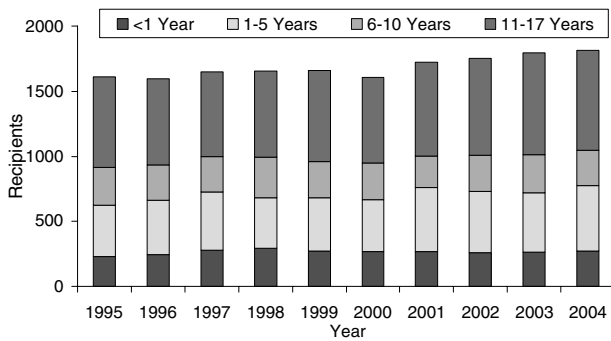
**Transplantation and survival**

**Transplantation:** In 2004, there were 1816 pediatric transplant recipients representing 7% of all recipients. The relative distribution by age groups has stayed constant over the decade (Figure 3). However, as with the waiting list, the combination of a 39% increase in total number of transplants over the decade compared with a 13% increase in the number of pediatric transplants has led to a decline in the percentage of pediatric transplants (Figure 4). In liver, kidney and heart, the percentage of pediatric transplants is higher than that of waiting list candidates. In contrast, for lung and intestine the percentage is lower. This likely



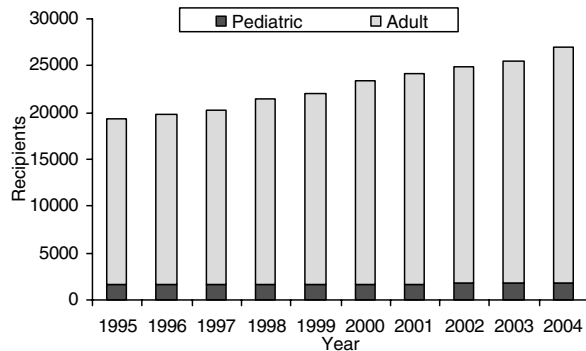
Source: 2005 OPTN/SRTR Annual Report, Table 5.1a, 9.1a, 10.1a, 11.1a, and 12.1a.

**Figure 2: Distribution of active pediatric waiting list candidates by organ, 1995–2004.**



Source: 2005 OPTN/SRTR Annual Report, Table 1.10.

**Figure 3: Pediatric transplant recipients, 1995–2004.**



Source: 2005 OPTN/SRTR Annual Report, Table 1.10.

**Figure 4: Pediatric and adult transplant recipients, 1995–2004.**

reflects a combination of the preference provided for children in organ allocation as well as, for liver and kidney, a higher percentage of living donors for children compared with adults.

**Survival:** Although organ-specific graft and patient survival will be reviewed below, it is worth emphasizing

that the current 3-year graft and patient survival for pediatric recipients are comparable to adult survival for all but intestine (where interpretation is limited by small numbers) (SRTR Center-Specific Reports, available at <http://www.ustransplant.org>). This observation suggests that pediatric transplantation has kept pace with improvements in graft and patient survival for transplantation as a whole seen over the past decade. A few specific pediatric age groups deserve comment. Patients younger than 11 years have the best unadjusted 5-year graft survival rates among all types of renal transplantation. In addition, children aged 6–10 years have the best outcomes among liver transplant recipients. In contrast, infants less than 1 year and adolescents aged 11–17 years tend to have among the lowest unadjusted 5-year graft survival rates across all organs. However, the majority of 5-year unadjusted graft survival rates for these groups in each organ improved compared with previous years. Given these observations, being in the pediatric age group should not be considered a risk factor for poor outcomes following transplantation.

**Pediatric organ donors**

In 2004, there were 975 pediatric deceased organ donors. Although this represents a 10% increase compared with 2003, there still has been a 19% decrease in pediatric deceased organ donors over the past decade. In contrast, the 11% increase in adult deceased donors over the past year yields a net 48% increase for the past decade. Thus, pediatric donors continue to make up a declining percentage (14%) of all organ donors. Nonetheless, as the majority of pediatric donors are at least 11 years old, and because only 7% of deceased donor recipients are pediatric, it is clear that a considerable number of adults continue to be recipients of pediatric deceased donor organs. Pediatric donors are more likely to donate each type of organ than adult donors. For example, 47% of pediatric donors provided a heart, compared with 26% of adult donors. The average number of organs recovered from a pediatric donor was 3.0 compared with 2.5 for adult deceased donors. These data are consistent with the report that pediatric deceased donors are more likely than adults to donate each type of organ (10).

The past year has shown improvement for pediatric transplantation in terms of waiting list numbers, numbers of transplants and pediatric organ donors. Nonetheless, challenges remain. Despite the recent increase, the number of pediatric organ donors has declined over the past decade. And although there has been some improvement, mortality for infants aged less than 1 year and the adolescent age groups remains a concern. These issues and other organ-specific trends are detailed below. Finally, recent changes in organ allocation policy and the use, in children, of organs from donation after cardiac death (DCD) are reviewed.

### Kidney Transplantation

Although children with end-stage renal disease have the life-sustaining option of dialysis, because kidney transplantation affords superior quality of life, it is considered the optimal modality for these children.

The most recent report (4) from the NAPRTCS database shows steady improvement in the 1-year deceased donor and living donor graft survival rate since its inception in 1987. For the initial cohort period 1987–1990, the living donor and deceased donor 1-year graft survival rates were 89% and 75%, respectively, which improved to 96% and 93%, respectively, for the most recent (1999–2004) period. This improvement paralleled the decreased incidence of acute rejection episodes. For 1987–1990, the living donor and deceased donor 1-year probability of an acute rejection episode was 54% and 69%, respectively, compared with 16% and 21% for 2003–2004. The long-term (7 year) graft survival rate has shown a concomitant increase. For the period 1987–1994, the living donor and deceased donor 7-year graft survival rate was 72% and 55%, respectively, which improved to 76% and 65% for the most recent period (1995–2004). Chronic allograft nephropathy is currently the most frequent (34%) cause of allograft failure in the NAPRTCS database.

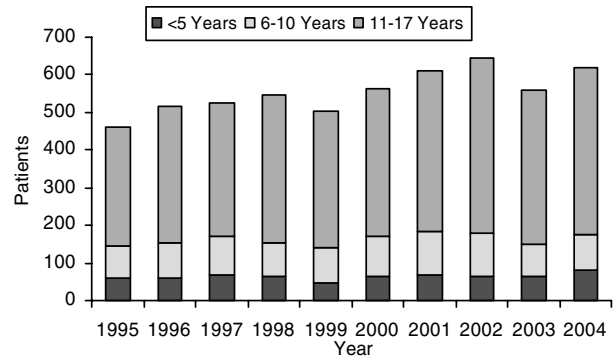
The two most recent reports of the SRTR emphasized the improvement in patient and graft survival rates in pediatric recipients (10,11) dispelling previous concerns that the youngest recipients were at higher risk for graft failure. In actuality, recipients aged less than 11 years had the highest 1- and 5-year graft survival rates compared with all other age groups. A cautionary note was identified in these two reports with respect to the adolescent recipient. The long-term (5 year) graft survival rate for deceased donor and living donor recipients for the 11–17-year-old recipient was inferior to all other age groups except those over 65 years.

Since the number of pediatric recipients transplanted annually is limited and even at a robust pediatric center rarely exceeds 30 transplants, it is imperative that national and international databases exist to identify research efforts to improve outcomes of pediatric recipients.

#### Waiting list

In the pediatric population, there has been a modest increase during the past decade of active candidates on the kidney active waiting list, from 470 in 1995 to 620 in 2004 (Figure 5). However, as a percentage of the total waiting list, which nearly doubled during the past decade, the pediatric population has declined from 1.8% in 1995 to 1.4% in 2004.

The only substantive increase in the pediatric waiting list during the past decade occurred in the adolescent age

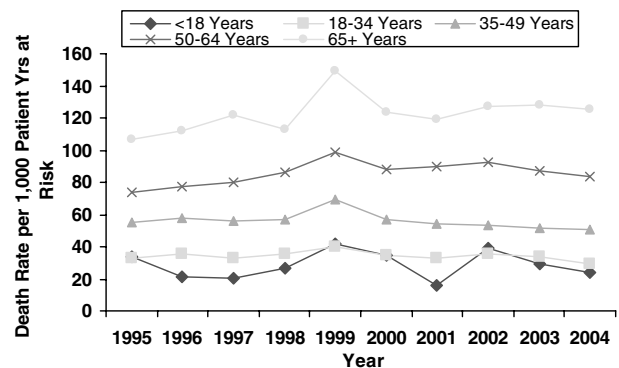


Source: 2005 OPTN/SRTR Annual Report, Table 5.1a.

Figure 5: Pediatric kidney transplant waiting list at year end, 1995–2004.

group (11–17 years), with an increment of 128 patients compared with an increment of nine in the 1–5 year and 10 in the 6–10-year age group. From 2003 to 2004, the number of patients in the 1–5, 6–10 and 11–17-year-old age groups identified on the kidney waiting list increased by 18, 10 and 32, respectively. As the incidence of renal transplant in the pediatric population has not changed appreciably and the median time to transplant for the 11–17-year-old age group has increased from 276 to 450 days, this increase may reflect increased competition for organs from adults.

The mortality rate for children on the kidney waiting list is exceedingly low compared with other age groups (Figure 6). During the past decade, the total number of patient deaths on the kidney waiting list increased from 1625 in 1995 to 4030 in 2004. However, although there were modest fluctuations annually, the deaths in the pediatric population remained unchanged at 17 in both 1995 and 2004,



Source: 2005 OPTN/SRTR Annual Report, Table 5.3.

Figure 6: Annual death rates per 1000 patient-years at risk by age, kidney waiting list, 1995–2004.

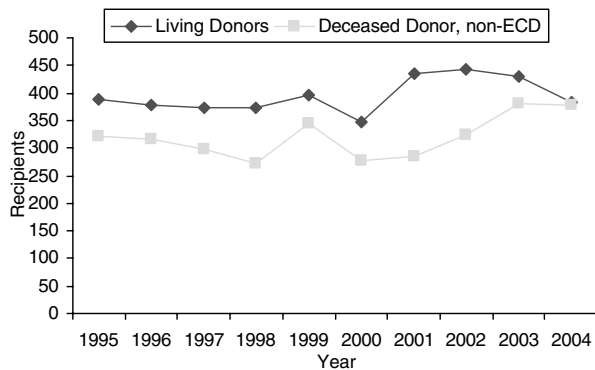
despite a concurrent increase in the pediatric waiting list population.

However, the mortality rate for infants, children and adolescents undergoing dialysis is not inconsequential. One- and two-year patient survival for 853 patients enrolled in the NAPRTCS Dialysis Registry from 2001 to 2004 was 98% and 93%, respectively, with increasing mortality in the younger age groups (4). Recent changes to the pediatric kidney allocation policy, detailed later in this article, preferentially allocate kidneys from deceased donors less than 35 years of age to children. It is expected that this policy will stabilize or reverse waiting list increments seen recently and reduce pediatric mortality on the kidney waiting list.

**Transplantation and survival**

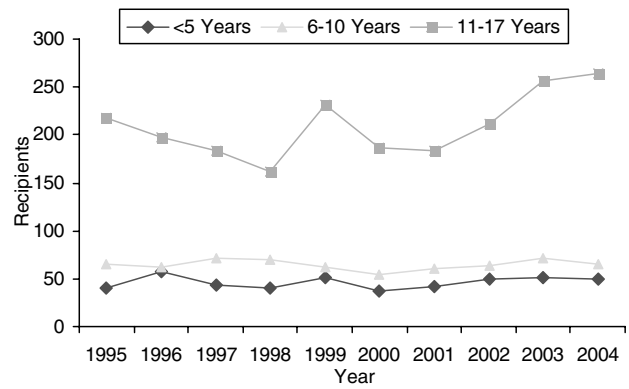
**Transplantation:** In 2004, 765 children received a kidney transplant (384 kidneys from living donors, 378 from deceased donors that were not expanded criteria donors (ECD) and three from ECD deceased donors). This total has minimally increased (8%) from the 719 kidney transplants (389 living donors, 322 deceased donor/non-ECD and eight deceased donor/ECD) performed in children in 1995. However, in contrast to the last two SRTR reports (10,11) where living donor transplants contributed to the increment in pediatric transplants, the increment has abated in 2004 (Figure 7). This is especially notable in the 6–10 year and 11–17-year age groups; these numbers decreased from 93 and 252, respectively, in 2002 to 67 and 210, in 2004.

The number of children receiving a deceased donor kidney (almost entirely non-ECD) has increased modestly (15%) during the past decade, from 330 in 1995 to 381 in 2004 (Figure 8). The number of deceased donor transplants in adolescents has increased modestly, while the number performed in the younger children has remained relatively constant. Across both the pediatric and adult population, the total number of deceased donor/non-ECD kid-



Source: 2005 OPTN/SRTR Annual Report, Table 5.4a and 5.4c.

**Figure 7: Pediatric kidney transplant recipients by donor type, 1995–2004.**

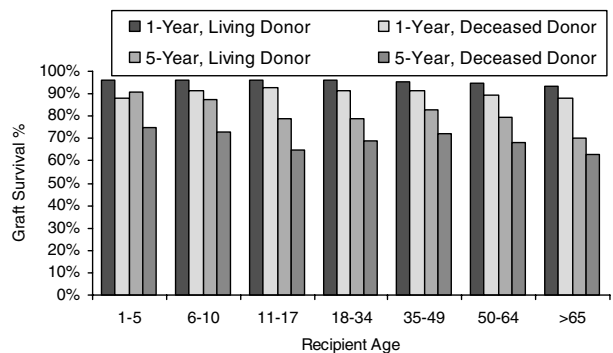


Source: 2005 OPTN/SRTR Annual Report, Table 5.4a.

**Figure 8: Pediatric transplant recipients of non-ECD deceased donor kidneys, by age, 1995–2004.**

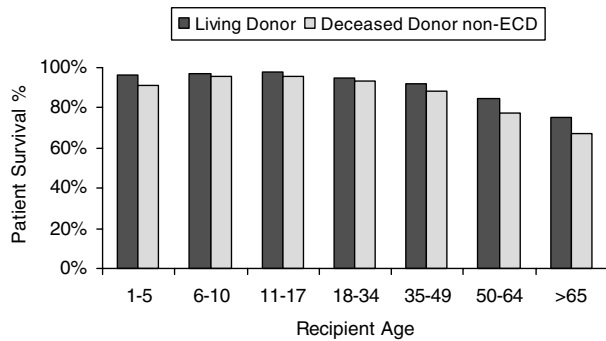
neys transplanted showed a gradual increase during the past decade, from 6679 in 1995 to 7270 in 2003; however, there was a substantial (9%) increase to 7915 in 2004.

**Survival:** Short-term graft survival for pediatric recipients of both deceased donor and living donor kidneys has improved over the past decade; the difference in the 1-year graft survival rate between the two donor categories has diminished markedly (4). The 1-year unadjusted graft survival rate of deceased donor/non-ECD kidneys in 2004 was 91% for all recipients and ranged from 88% to 92% for pediatric recipients (Figure 9). The 1-year unadjusted graft survival rate for all living donors in 2004 was 95% and ranged from 96% to 100% for pediatric recipients (9). The superb short-term graft survival rate probably reflects substantive advances in clinical management, as well as emergence of new immunosuppressive therapeutic regimens.



Source: 2005 OPTN/SRTR Annual Report, Table 5.9a and 5.9c.

**Figure 9: Unadjusted 1- and 5-year graft survival of living and deceased donor non-ECD kidney transplants by recipient age.**



Source: 2005 OPTN/SRTR Annual Report, Table 5.12a and 5.12c.

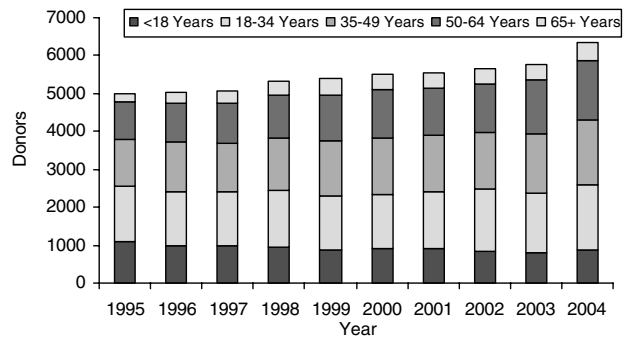
**Figure 10: Unadjusted 5-year patient survival of living and deceased donor non-ECD kidney transplants by recipient age.**

Long-term graft survival rates in pediatric recipients continue to improve; however, annual attrition primarily from chronic allograft nephropathy continues unabated with the current clinical management. The decreasing disparity in short-term graft survival rates between deceased donor and living donor kidneys is not perpetuated for long-term rates. The 5-year unadjusted graft survival rate in 2004 for 1–5 year, 6–10 year, and 11–17-year age groups from deceased donor/non-ECD and living donors were 75%, 73%, 65%, and 91%, 87% and 79%, respectively. Numbers for the entire kidney waiting list in 2004 are similar: graft survival was 69% for deceased donor organs versus 80% for living donor kidneys. The limited number of infants under 1 year who received grafts from a deceased donor (n = 1) or living donor (n = 25) obviated the ability to include this age group in the analysis. However, the excellent long-term survival of the youngest recipients (1–5 years) of both deceased donor and living donor grafts as reported previously (10, 11) justifies continued preferential allocation for the pediatric age recipient. Most disturbing is the continued poor long-term graft survival rates in the adolescent recipient, which also has been identified previously (10, 11). The etiology of this phenomenon is speculative, with nonadherence a potential major contributor (12).

As expected, the unadjusted survival of pediatric recipients receiving either a deceased donor/non-ECD or living donor kidney transplant is excellent and substantively better than the adult age groups (Figure 10). The unadjusted 5-year patient survival rates in 2004 for all deceased donor/non-ECD and living donor recipients were 83% and 90%, respectively. Pediatric recipients have better long-term survival: among 1–5-year-old children, these rates were 92% and 95%, respectively, 95% and 97% among 6–10-year olds, and 97% and 98% among 11–17-year olds.

**Organ donation**

The number of deceased donor kidneys from pediatric donors has continued to decrease during the past decade,



Source: 2005 OPTN/SRTR Annual Report, Table 2.2.

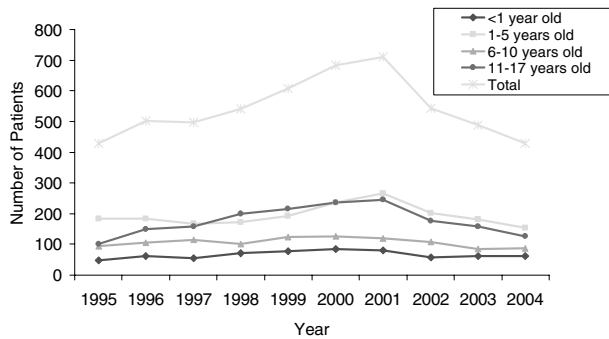
**Figure 11: Deceased kidney donors by age, 1995–2004.**

both in absolute numbers and as a percentage of the total number transplanted (Figure 11). Between 1995 and 2004, the total number of deceased kidney donors increased from 5003 to 6327; pediatric deceased kidney donors decreased from 1083 to 867. In 1995, 22% of the deceased donors were pediatric; in 2004 this number decreased to 14%. Some of the decrease could be attributable to the reluctance to transplant kidneys from young pediatric donors into young pediatric recipients because of poorer outcomes primarily attributable to an increased incidence of vascular thrombosis (13). However, in 1995, 14% of deceased kidney donors were aged 11–17 years; in 2004, this decreased to 8%. Multiple factors probably contributed to this reduction. An assessment of the factors is indicated, especially because recent data show that en bloc transplantation of kidneys from young pediatric donors into adult recipients is efficacious (14).

Although the graft survival rate of kidneys transplanted into pediatric recipients has improved during the past decade, nonadherence in adolescents (12) and chronic allograft nephropathy (4) must be addressed if long-term pediatric kidney allograft survival rates are to continue to improve in infants, children and adolescents.

**Liver Transplantation**

Pediatric liver transplant recipients differ from their adult counterparts with respect to the relative distribution of etiologies of liver disease and indication for transplantation. Additionally, the impact of end-stage liver disease on growth and development leads to a distinct morbidity in this population. In addition to ongoing pediatric analyses by the SRTR, the SPLIT registry provides a rich source of pre- and posttransplant outcomes in this population (5, 15). The SPLIT consortium has recently secured NIH funding, which should further its abilities to ask important questions in this population. Other NIH initiatives, including the Biliary Atresia Research Consortium (BARC) and Cholestatic



Source: 2005 OPTN/SRTR Annual Report, Table 9.1a.

**Figure 12: Active pediatric patients on the liver transplant waiting list, 1995–2004.**

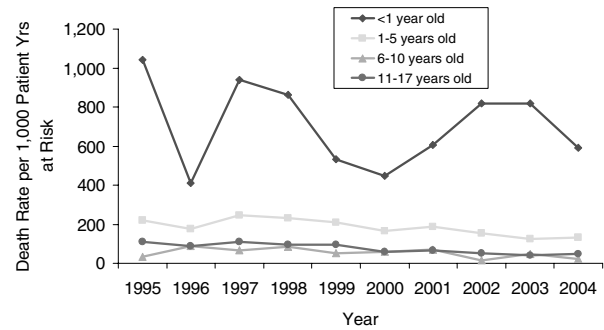
Liver Disease Consortium, will add to our understanding of liver disease in the pediatric population.

### Waiting list

At the end of 2004, 428 of the 12 744 candidates actively awaiting liver transplantation were pediatric patients. Of these children, 61 were less than 1 year of age, 154 were aged 1–5 years, 88 were aged 6–11 years and 125 were 11–17 years of age. The relative distribution of these age groups has not changed noticeably over the decade (Figure 12).

Over the last decade, the large increase in the numbers of adult candidates awaiting liver transplantation has led to a decline in the overall proportion of pediatric candidates represented on the waiting list, from 9% in 1995 to 3% in 2004. The absolute number of children awaiting transplantation at year end grew steadily from 1995 to 2001 (Figure 12). However, over the last 3 years, there has been an appreciable decline in the number of pediatric candidates awaiting transplantation, a decrease seen, too, in adult candidates. Absent any major change in the incidence or management of end-stage liver disease, or changes in indications for transplantation or numbers of transplants performed, it is likely this decrease reflects a change in listing practices attributable to the implementation of the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores in 2002. Because these allocation strategies emphasize disease severity over waiting time, it is no longer necessary to list candidates for the purpose of accruing priority for organ allocation.

In addition to 428 active candidates, another 409 children were listed but inactive at year end. The relative percentage of active patients compared with the total listed is lower in the pediatric population (51%) compared with adults, where 76% of all listed patients were active.

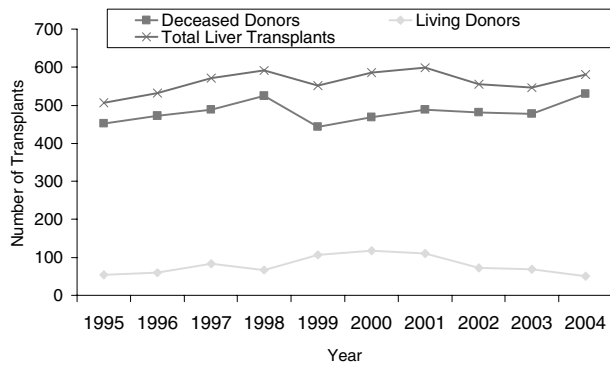


Source: 2005 OPTN/SRTR Annual Report, Table 9.3.

**Figure 13: Annual death rate per 1000 patient-years at risk for pediatric patients on liver waiting list, 1995–2004.**

In 2004, 80 pediatric candidates died while on the waiting list. Of note, 36 of these deaths were in patients listed for multiorgan transplants, including 29 children listed for liver-intestine transplantation (SRTR analysis, August 2005). The death rate in children listed for multiorgan transplant is disproportionately high compared with children listed for liver alone. Over the last 10 years, the death rate for patients awaiting liver transplantation across all pediatric and adult ranges has declined, with the notable exception of children less than 1 year of age (Figure 13). These infants still have the highest death rate of any age range, with a rate of 591 per 1000 patient-years at risk. Children aged 6–10 years and 11–17 years have the lowest death rates of any age group (23 and 49 per 1000 patient-years at risk, respectively), while children in the 1–5-year age group had an intermediate rate of 132 per 1000 patient-years at risk.

Since implementation in 2002, it has been possible to stratify patient outcomes based on MELD or PELD scores. When waiting list mortality rates are analyzed by PELD score, candidates with a PELD <11 had a death rate of 26, while those with a PELD of 11–20, 21–30 and >30 had rates of 225, 308 and 224 per 1000 patient-years at risk, respectively. While the utility of direct comparison of PELD to MELD is limited, it is worthwhile to note that adult candidates with a MELD of 11–20 had a death rate of 137; this rate dramatically increases with higher MELD scores. The observed relative plateau in death rates with higher PELD scores is not in itself an indication that PELD does not reflect disease severity. Rather, this plateau reflects, at least in part, a higher rate of transplantation in children with higher PELD scores which limits waiting list deaths. Additionally, a substantial portion of children with high PELD scores are changed to Status 1, which may also act to limit the deaths observed at higher PELD scores. The impact of the recent changes in allocation policy limiting the practice of upgrading children to Status 1 remains to be determined.



Source: 2005 OPTN/SRTR Annual Report, Tables 9.4a and 9.4b.

**Figure 14: Pediatric recipients of deceased and living donor liver transplants, 1995–2004.**

**Transplantation and survival**

**Transplantation:** In 2004, there were 529 deceased donor liver transplants into pediatric recipients, an increase of 51 more transplants compared with 2003 (Figure 14). Pediatric recipients accounted for 9% of the 5845 deceased donor liver transplants performed in 2004. While the total number of deceased donor transplants performed across all ages has dramatically increased over the decade, from 3880 in 1995 to 5845 in 2004 (a 51% increase), the number of pediatric deceased donor liver transplants has increased modestly from 452 to 529 (17%).

Living donor liver transplantation was first performed in 1989. In 2004, living donation accounted for 50 transplants in the pediatric population (Figure 14). Notably, this represents the smallest number of living donor liver transplants performed in children over the last decade and is a marked decrease from a peak of 117 such transplants in 2000. Of the living donor liver transplants performed in 2004, 43 were in children 5 years of age and younger, while the remaining seven were performed in children between ages 11 and 17 years.

It is interesting to reflect on the practice pattern of living donor liver transplantation over the last 10 years. In 1995, all 54 living donor liver transplants were performed in pediatric recipients. In 2004, there were 50 living donor transplants performed in children and 273 such transplants in adults. The number of adult-to-adult living donor liver transplants has remained relatively stable for the last 3 years (range: 253–289), but it is substantially less than the 408 such transplants performed in 2001.

While the relative contributions of deceased donor and living donor transplantation have changed over the years, the total number of pediatric liver transplants performed has been relatively stable (Figure 14). The incidence of transplantation, expressed as the number of transplants per one million population, has also stayed relatively constant across the pediatric population for the last 10 years,

**Table 1: PELD score at transplant, 2004**

	Deceased donor	Living donor
PELD <11	87	10
PELD 11–20	53	7
PELD 21–30	40	3
PELD >30	10	1
Total PELD	190	21
Total non-PELD	339	29

Source: 2005 OPTN/SRTR Annual Report, Tables 9.4a and 9.4b.

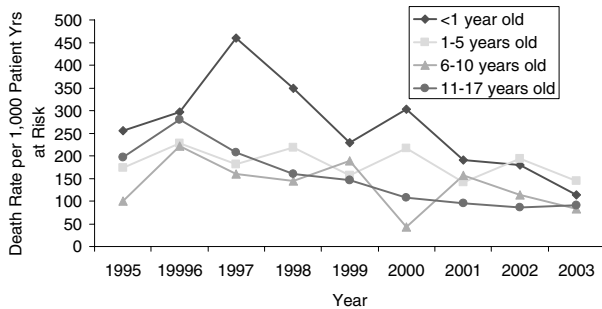
but has increased 1.5- to 2-fold in adults older than 50 years. For pediatric recipients, incidence of transplantation is highest in infants less than 1 year (39.7 per million), followed by the 1–5-year age group (10.39 per million). Children in the 6–10 year range have the lowest incidence of transplant of any age group at 3.78 per million.

For pediatric recipients allocated a deceased donor liver by their PELD score, the majority had a score  $\leq 20$  (Table 1) and many had a PELD <11. A similar trend is noted for recipients of living donors. The PELD score was only used in 190 of the 529 deceased donor transplants (36%). The majority of the other such transplants were performed in children with chronic liver disease, either awarded a PELD score based on exception or made a Status 1. There appears to be marked regional variation of the use of such mechanisms (16–18). Steps being taken to make listing practices less subjective include establishing detailed Status 1 criteria for pediatric patients with chronic liver disease and consideration of the role of regional review boards in the exception process.

**Survival:** Annual death rates in the first year following deceased donor liver transplantation across the pediatric age ranges have generally improved over the last decade (Figure 15). This improvement has been most marked among infants aged less than 1 year. Pediatric recipients currently have lower death rates in the first year following transplantation compared with adult recipients. When these death rates are examined as a function of PELD score at time of transplant, in 2003 children with a PELD <11 had a death rate of 68.1 per 1000 patient-years at risk. Children with a PELD of 11–20 at time of transplant had a rate of 70.9 per 1000 patient-years at risk, while the rate for those with a PELD of 21–30 was 161.1.

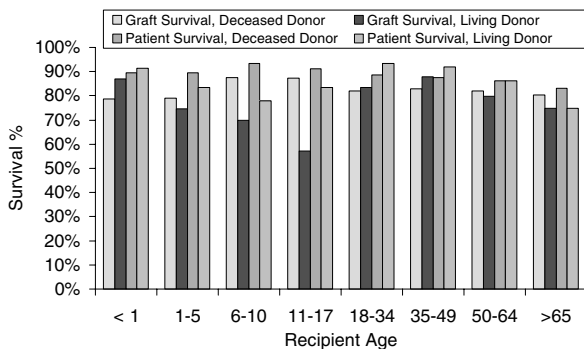
Children aged 6–10 years and 11–17 years who receive a deceased donor transplant have the best 1-year graft survival across all age ranges, but the poorest graft survival following the living donor transplantation (Figure 16). For infants less than 1 year, living donor graft survival exceeds that observed from deceased donors. Unadjusted patient survival at 1 year following deceased donor liver transplantation is excellent across all ages (Figure 16), though survival following living donor liver transplantation in children





Source: 2005 OPTN/SRTR Annual Report, Table 9.7a.

**Figure 15: Annual death rate per 1000 patient-years at risk for pediatric recipients in first year after deceased donor liver transplantation, 1995–2003.**



Source: 2005 OPTN/SRTR Annual Report, Tables 9.9a, 9.9b, 9.12a and 9.12b

**Figure 16: Unadjusted 1-year graft and patient survival of deceased donor and living donor liver transplants by recipient age.**

1 year of age and older is below that observed for deceased donors. Patient survival at 5 years after deceased donor liver transplantation in the pediatric population ranges from 79% to 87%, which exceeds the survival observed in adult recipients. The reason for notably poorer outcomes following living donor liver transplantation in children 6–17 years of age is unknown, though technical factors including graft to recipient volume, severity of illness and etiology of liver failure may all contribute.

In assessing the decision when to transplant a child, an appreciation of the real risk of posttransplant mortality is vital. Recently, Merion and colleagues demonstrated that adult candidates with a MELD <15 faced a higher risk of mortality in the first year after transplantation compared with remaining on the waiting list (19). For pediatric patients, the data are less clear. While children with end-stage liver disease face additional risks of morbidity related to growth and development, it is intuitive that there is some level of liver disease for which the risk of transplantation exceeds the risk of remaining on the waiting list. It remains unclear,

however, where that level of disease is (20). The challenge for the pediatric community is to better understand these specific risks and benefits in order to make the optimal decisions.

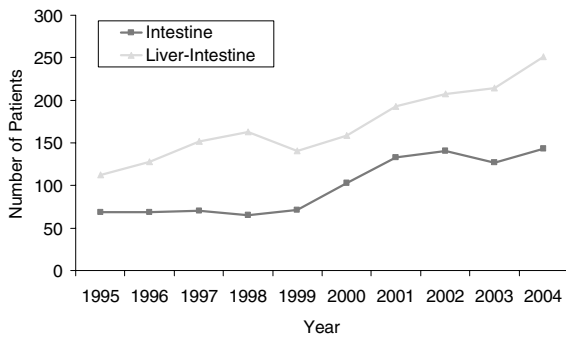
## Intestinal Transplantation

The worldwide experience in intestinal transplantation now exceeds 1000 patients (21), and its place as accepted therapy for patients with intestinal failure and life-threatening complications in the United States was established in 2001 when the federal government approved Medicare funding for this procedure. Previous SRTR reports and single-center publications have documented improving outcomes (10,11,22,23). Increasing numbers of centers have been establishing intestinal transplant programs. The international Intestine Transplantation Society has been established in the last 2 years and this year, the 9th International Small Bowel Transplant Symposium was held. Despite the growing maturity of intestine transplantation, problems still relate to the difficulty in obtaining suitable composite allografts for patients with intestinal failure and associated end-stage liver disease. This is reflected in high waiting list mortality rates for intestinal transplant candidates. The postoperative care is intensive and complex, and infection due to over-immunosuppression and rejection due to inadequate immunosuppression yield limited short-term outcomes. This has resulted historically in graft and patient survivals that have been less successful than those seen for liver, kidney or heart transplantation.

### Waiting list

The intestinal waiting list has two active categories, urgent and nonurgent, and within these categories, organs are allocated based on waiting time. Allocation from this list is primarily to candidates listed for isolated intestine transplantation, though it is acceptable for an organ procurement organization to allocate a combined liver-small intestine allograft from this list, provided there are no Status 1 liver patients waiting in that region (24, OPTN Policy 3.11.4). In practice, the majority of combined liver and small intestine allografts are allocated according to the patients' MELD or PELD score, i.e. according to liver allocation policy. It has long been recognized that waiting list mortality is high, particularly for small infants waiting for liver-small intestine transplantation and that waiting list mortality is higher for any given PELD score when compared with isolated liver candidates. Based on the limited data available shortly after the introduction of PELD, the SRTR calculated the size of the difference in mortality rate between the liver-only patients and liver-intestine candidates. Based on these estimates, OPTN allocation policy was changed to include an additional 10% mortality risk above that predicted by their calculated PELD or MELD score (24, OPTN Policy 3.6.4.7). The same SRTR analysis demonstrated that there was no interaction between waiting list mortality for liver-intestine candidates and PELD, suggesting that PELD

## Pediatric Transplantation, 1995–2004



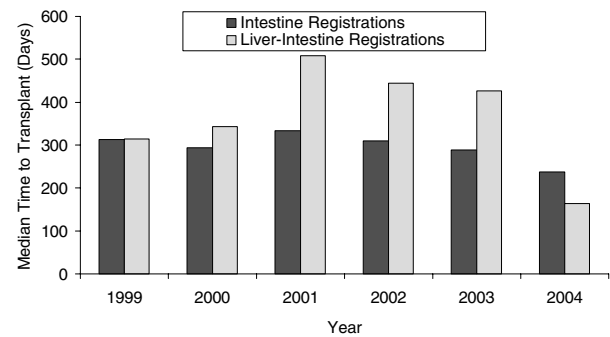
Source: SRTR Analysis, May 2005 and 2005 OPTN/SRTR Annual Report, Table 1.3.

**Figure 17: Differential growth of the waiting list, intestine and liver-intestine, 1995–2004.**

was equally predictive for increasing waiting list mortality for both liver-alone candidates and liver intestine candidates, but, for the latter group, at a higher level (25). Updated analysis with an additional 2 years of data suggest, at least for children, that this increased mortality risk on the waiting list may be still greater than the 10% presently allowed. These findings have yet to be discussed in the appropriate OPTN committees; it would be premature to predict whether this latest analysis will lead to further alteration in allocation policy.

Examining the number of candidates on the waiting list reveals increasing demand for intestinal transplantation over the last 10 years (Figure 17). At the end of 1995, 82 candidates were listed for intestine transplant; in 2004, this figure was 196. The waiting list for isolated intestinal transplantation (from 22 patients in 1995 to 105 in 2004) has grown more rapidly than listings for combined liver and intestine transplantation (from 60 in 1995 to 91 in 2004) and may be related to earlier referral of patients for intestine transplant (SRTR analysis, May 2005). Of these 196 candidates, 142 were less than 18 years old and approximately 49% of the listed candidates were younger than 6 years. The ratio of adults to children does not appear to be changing over time. In terms of race/ethnicity, the majority of candidates are white and non-Hispanic, although the proportion of whites has fallen over the 10-year period, from 75% to less than 60% of the intestine list. The proportion of African American candidates has not changed noticeably. Hispanics have increased from 7% in 1995 to 17% in 2004. Greater demand can also be seen in the number of new registrants to the intestine list, which increased from 91 in 1995 to 250 in 2004.

In 2004, the median time to transplant for all intestine registrants was 238 days, the lowest level in 10 years (Figure 18). Still, the longest waits are those of infants aged less than 1 year. The most dramatic reduction is seen in the candidates for combined liver and intestine transplant,



Source: SRTR Analysis, May 2005 and 2005 OPTN/SRTR Annual Report, Table 1.5.

**Figure 18: Median time to transplant for intestine and liver-intestine registrations, 1999–2004.**

whose median waiting time is 163 days (SRTR analysis, May 2005). This finding may result from changes in liver allocation policy as it relates to candidates for combined liver and intestine transplant. However, noticeable reductions in waiting list mortality in this group are not being seen.

The annual death rate on the intestine waiting list is 306 per 1000 patient-years at risk for all intestinal candidates, which is by far the highest for any solid organ transplant group and has not shown any substantial changes in 10 years. To put this in perspective, the annual death rate for intestinal transplant recipients is twice that of the next highest risk group (combined heart and lung candidates). Infants less than 1-year old have consistently high death rates, about double those seen in the intestinal group as a whole. High death rates in the youngest children probably relate to the combination of a number of factors, including severity and rapid progression of liver disease, higher incidence of sepsis, and the inherent difficulty in obtaining size-matched allografts. Candidates 6–17 years old have considerably lower waiting list death rates; this probably reflects that these children do not have advanced liver disease and are more likely to be listed for isolated intestinal transplant. Of the patients who died awaiting intestine transplantation over the period from 1995 to 2004, 92% of deaths were in patients also listed for a liver transplant (SRTR analysis, May 2004). This is not unexpected; even if a candidate is initially listed for intestine transplant only, as their disease progresses they also are likely to become candidates for a liver transplant. These data, however, show that patients with intestinal failure are not dying in large numbers prior to transplant in the absence of advanced liver disease.

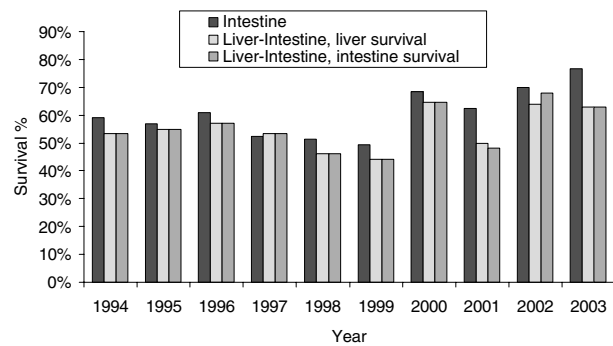
Previous SRTR annual reports have examined the number of potential donors that ultimately become small intestine donors. There were 7152 deceased donors in 2004; 297 were less than 6 years and 97 were younger than 1 year. But of these, only 87 and 43 of those younger than 6 years

and 1 year, respectively, became small intestine donors. If we look at the same donors in terms of livers procured, 262 donors younger than 6 years and 86 donors younger than 1 year became liver donors. Perhaps infant intestinal candidates should receive preferential access to these donor organs, given that liver-only candidates have a number of other options, including reduced-size split and living-related livers.

### Transplantation and survival

**Transplantation:** In 2004, 152 intestinal transplants were carried out in 17 U.S. centers, compared with 46 transplants in 10 centers in 1995. Fifty-two patients received isolated intestinal transplants and 100 received intestinal transplants in combination with other abdominal organs; all but five included a liver. Children made up 61% of recipients; 50% were children in the 0–5-year age group. Similarly, in the last 10 years, 61% have been in the pediatric age group. The incidence of intestinal transplantation remains low but increased in 2004 to 0.52 transplants per million population compared with 0.18 transplants per million in 1995. The highest rates were among the youngest children, with an incidence of 5.71 per million in infants aged less than 1 year and 2.67 per million in children aged 1–5 years. The incidence in the 6–17-year age group was essentially unchanged over the 10-year period. These figures can be compared with the incidence of kidney transplantation of 54 per million and liver transplantation of 21 per million population. The incidence of intestine transplantation appears to be equal between racial and ethnic groups, and by sex. The low incidence of intestinal transplantation is, in part, due to the relative rarity of intestinal failure compared with renal or liver disease. But the contribution of lack of access to organs and experienced transplant programs cannot be estimated.

**Survival:** Graft survival following intestine transplantation has improved over the 10-year period, with 1-year unadjusted graft survival at 77% in 2003 compared with 59% in 1994; the most notable improvements occurred over the last 4 years (Figure 19). This period of time has seen increased use of antibody induction therapies including IL2 receptor inhibitors (basiliximab or daclizumab), rabbit antithymocyte globulin and alemtuzumab. Unadjusted graft survival rates for the most recent cohorts are 87% at 3 months, 73% at 1 year, 52% at 3 years and 43% at 5 years. Patient survival also has shown improvement; the annual death rate per 1000 patient-years at risk for recipients in the first year after intestinal transplants has fallen over the last 5 years from 515 in 1999 to 208 in 2003. Unadjusted patient survival at 3 months, 1 year, 3 years and 5 years, now stands at 90%, 79%, 61% and 52%, respectively. Death rates are highest for the youngest children, ranging from 1222 per 1000 patient-years at risk in 2000 to 331 in 2003. Conversely, the lowest death rates were observed in 11–17-year-old recipients, with 99.1 deaths per



Source: SRTR Analysis, May 2005 and 2005 OPTN/SRTR Annual Report, Table 1.11b.

**Figure 19: One-year unadjusted graft survival of deceased donor intestine and liver-intestine transplants, 1994–2003.**

1000 patient-years at risk in 2003. These differences most likely relate to the number of isolated intestinal transplants in relatively healthy teenagers, whereas the sicker infants require combined intestine and liver transplants.

An update from the Intestinal Transplant Registry was recently published (9). Up until May 2003, the total world experience in human intestine transplantation amounted to 989 transplants in 923 patients. Furthermore, 61% of patients were less than 18 years of age and 75% of transplants were done in the United States. In the most recent cohort from the database (1998–2003), 1-year graft survival was 65%, with patient survival at 77% for isolated intestine transplantation; graft and patient survival for liver and intestine recipients were 59% and 60%, respectively. The OPTN/SRTR data for 2004 suggest still further improvements in survival following intestine transplantation. The reasons for improved outcomes are multifactorial but include greater experience and refinement of surgical techniques, patient selection and changes in immunosuppressive regimens (including increased popularity of antibody induction regimens). Changes have also been implemented in the management and surveillance of infectious complications, such as routine surveillance for Epstein-Barr virus and treatment of PTLD.

Short-term survival rates have been improving and may now be approaching rates seen for other solid organ transplant groups. Attention is currently being given to issues related to long-term survival, quality of life and growth and development. Immunosuppressive minimization is being approached from a number of angles to reduce complications associated with long-term use and side effects of immunosuppressant therapies. Antilymphocyte antibody induction regimens without maintenance corticosteroids have been introduced in a number of centers with promising early results (9,23,26) The priority for intestine transplant candidates is to examine whether further

changes in organ allocation policy can reduce high waiting list death rates, particularly for those awaiting combined liver and intestinal transplantation.

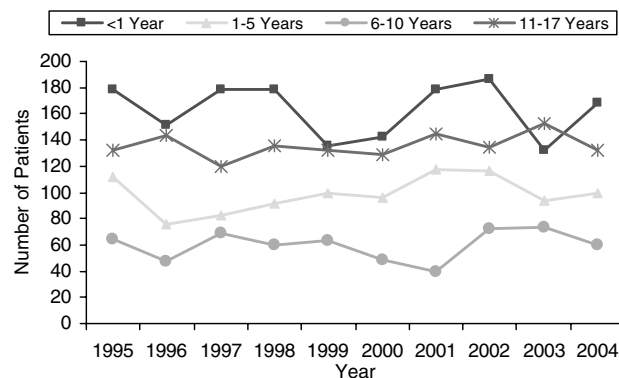
## Heart Transplantation

Compared with adults, pediatric heart transplantation is characterized by the striking number of infants and children with congenital cardiac anomalies. Challenges include higher waiting list mortality (due to limited access to ventricular assist devices), coronary vasculopathy and long-term immunosuppression complications.

### Waiting list

The number of pediatric patients awaiting heart transplantation has been relatively steady over the past 5 years; the number awaiting transplantation at the end of 2004 was 256, while the 5-year average is 243. Children consistently account for 5–7% of all of those awaiting heart transplants. As in prior years, the largest age group among children waiting for a heart transplant is aged 1–5 years, followed by adolescents aged 11–17 years. However, for a single 1-year age group, infants (0–1 year) make up by far the largest group of candidates. Infants represented 168 of 459 (37%) of new pediatric registrations in 2004 (Figure 20).

The diagnoses leading to listing for transplantation vary by age. For infant candidates, the indication for placement on the waiting list is a congenital heart anomaly in over two-thirds of patients (27). In older children and adolescents, cardiomyopathy is the leading indication for transplantation; the dilated form is most common. Congenital cardiac anomalies do, however, continue to account for a substantial minority of transplants even in older age groups. This observation is important because complex cardiac anatomy, in addition to small size, precludes the use of ventricular assist devices for many children with end-stage cardiac failure. Difficulty supporting these young patients



Source: 2005 OPTN/SRTR Annual Report, Table 15.3.

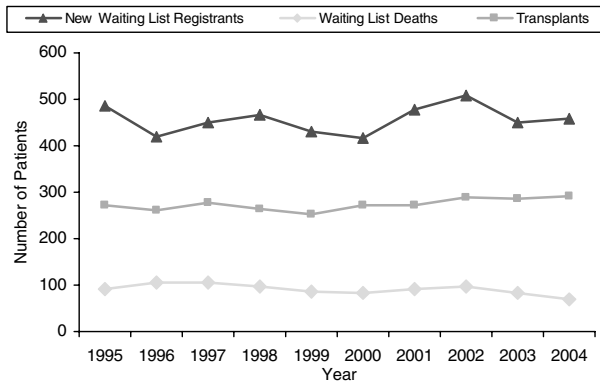
**Figure 20: New pediatric registrants on the heart waiting list by age, 1995–2004.**

with complex congenital heart disease undoubtedly contributes to their high waiting list mortality.

Although children in all age groups have substantially shorter waiting times (median waiting times range from 57 to 154 days) than do adults, they have a substantially greater risk of death while on the waiting list. The annual waiting list death rate (expressed per 1000 patient-years at risk) is higher in all pediatric age groups compared with all adult candidates less than 65 years. The highest death rate is among infants aged less than 1 year. An informative way to view pretransplant outcomes is with competing outcomes analysis (28). This approach provides a time-related prediction of simultaneous mutually exclusive events (e.g. death while waiting, transplantation, still waiting, etc.). Analysis of all 2375 patients listed for transplantation from January 1, 1993 through December 31, 2003 in the PHTS, a North American multi-institutional study of outcomes after listing for heart transplant, demonstrates that the proportion of patients transplanted increases over time to 68% by 1 year after listing, while the proportion who die on the waiting list increases to a maximum of 17% by 1 year (29). The same data set shows evidence for a decrease in waiting list mortality in pediatric heart transplant candidates over the last 5 years compared with earlier eras. It should be noted that most deaths on the waiting list occurred in Status 1A patients (most urgent status), with a very low 1-year waiting list mortality for Status 2 patients (approximately 5%). These data suggest that the OPTN urgency status system appears to be meeting its primary objective of prioritizing those patients most likely to die soon without transplantation.

### Transplantation and survival

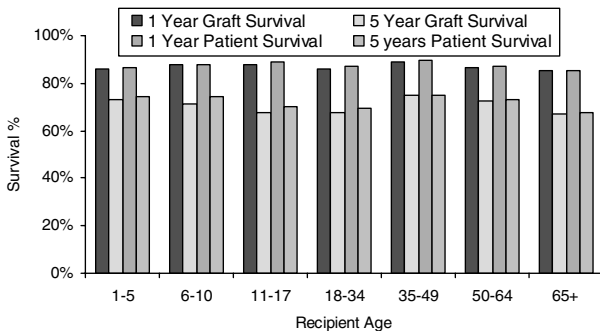
**Transplantation:** Over the past 10 years, children have accounted for approximately 12% of all heart transplant recipients and the number of transplants has remained stable at around 250–290 per year (Figure 21). Prior to 1998, infants were generally the largest pediatric group receiving transplants on an annual basis; since then, adolescents constituted the largest group. This change likely reflects widespread adoption of staged reconstruction (Norwood procedure) for initial palliation of hypoplastic left heart syndrome (HLHS) in most centers. Because of the scarcity of donor organs and consequent long waiting list times for newborns, only a few centers continue to offer transplantation as primary therapy for newborns with HLHS. Despite these trends, the rate of transplantation per 1 million population remains higher for infants than for any other age group, except adults between 50 and 64 years, among whom it is slightly higher. The high rate of transplantation in these very young children reflects the high incidence of severe symptomatic congenital heart disease in the first year of life and the relatively high incidence of cardiomyopathy in this age group (30,31). Currently, approximately 60–80 heart transplants are performed each year in the United States in infants.



Source: 2005 OPTN/SRTR Annual Report, Tables 11.3, 11.4, and 15.3.

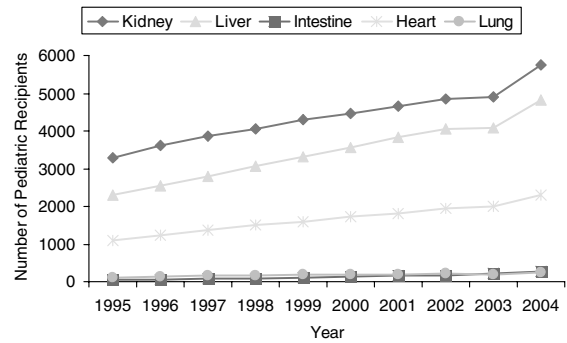
**Figure 21: New pediatric heart waiting list registrants, deaths on the waiting list, and transplants, 1995–2004.**

**Survival:** Retransplantation is rare in the early years after heart transplantation; therefore, graft survival rates and patient survival are very similar (Figure 22). One-year unadjusted patient survival rates in childhood are similar across all ages, with only slightly lower survival in infants compared with older children (1-year unadjusted patient survival of 85% in infants vs. 89% in the 11–17-year age group). These results are also comparable with those in adults less than 65 years old. However, at 5 years, infant survival exceeds that of all other age groups including most adult groups (5-year survival for infant recipients is 75% vs. 70% for recipients in the 11–17-year age group.) This likely reflects the higher perioperative mortality associated with transplantation for congenital heart disease in young infants, but a lower late mortality in the same population. The latter finding is most likely because of a lower incidence of posttransplant coronary artery disease in young transplant recipients (6). Regardless of age at transplant, those transplanted for congenital heart disease have worse patient survival (27,30). In contrast to adults, there is evidence that graft and patient survival have improved for children



Source: 2005 OPTN/SRTR Annual Report, Table 11.9.

**Figure 22: Unadjusted 1- and 5-year graft and patient survival of heart transplants by recipient age.**



Source: 2005 OPTN/SRTR Annual Report, Tables 5.14, 7.14, 9.14, 10.14, 11.14, and 12.14.

**Figure 23: Prevalence of pediatric recipients living with a functioning transplant at end of year, 1995–2004.**

transplanted in the most recent era. Data from the PHTS demonstrate that urgency status at listing is not predictive of posttransplant survival, nor is the requirement for a ventricular assist device as bridge to transplant (29,32). For survivors of pediatric heart transplantation (approximately 2300 pediatric recipients in the United States at the end of 2004) (Figure 23), the principal challenges involve prevention of graft vasculopathy (6), prevention and treatment of infection and malignancy (most notably PTLD) (33), and minimization of end-organ toxicities secondary to immunosuppressive medications. Perhaps of greatest concern in the latter category is the decline in renal function seen late after heart transplantation with current calcineurin inhibitor-based regimens (34,35). Increasing numbers of children will require kidney transplantation over the next decade following extrarenal solid organ transplantation in childhood. Finally, strategies to improve adherence to therapy are also key to long-term survival, since adolescent nonadherence appears to be a principal cause of death among teenagers and young adults after heart transplantation (12,36).

### Heart-Lung Transplantation

Heart-lung transplantation continues to be a relatively rare procedure. The reasons are likely multifactorial and may include current use of bilateral lung transplantation as the procedure of choice for children with parenchymal lung disease as well as most cases of primary pulmonary hypertension. The relatively high death rate on the waiting list (perhaps related to an inherent bias in the allocation system against heart-lung transplants) and poor long-term survival following transplantation may also discourage referral for consideration of transplantation.

#### Waiting list

During the past 10 years, the number of new heart-lung registrants of all ages has been steadily decreasing. In 2004, there were only 78 new registrations nationwide across all age groups. This has resulted in a gradual decline

in the number of patients on the waiting list. In children, the number of new registrants and active waiting list candidates has always been extremely low. At the end of 2004, only 25 children were on the heart-lung waiting list (active and inactive); 15 of these 25 (60%) were in the 11–17-year age group.

**Transplantation and survival**

**Transplantation:** The total number of heart-lung transplants performed each year in the United States is very small and has gradually declined over the last decade. In 2004, only 39 procedures were performed across all age groups. During the past 5 years, the annual number of pediatric heart-lung transplants performed has ranged from five to eight per year, representing 15–22% of all heart-lung transplants. In 2004, there were only six procedures in children nationwide.

**Survival:** Data available on long-term pediatric heart-lung graft and patient survival are limited; it is difficult to analyze outcomes for so rare a procedure. Survival analyses within the *OPTN/SRTR Annual Report* reflect transplants performed over a small number of years only. While this suffices for a description of survival for almost all other organs across all age groups, it does not allow for appropriate description of patient and graft survival for pediatric heart-lung recipients. The registry of the International Society for Heart and Lung Transplantation provides data on a larger cohort of pediatric recipients transplanted over a long period of time. For the period 1982–2002, probability of survival at 1 and 5 years after heart-lung transplantation in children is approximately 65% and 40%, respectively (37). Lack of improvement in survival over the last two decades is of particular concern. The short-term results are somewhat inferior to those of isolated lung transplantation, but the long-term outcomes are comparable to those for bilateral lung transplantation. This likely reflects the fact that the lung allograft is the primary determinant of long-term survival after heart-lung transplantation and that obliterative bronchiolitis (chronic rejection) and its complications are the leading cause of death late after both lung and heart-lung transplantation.

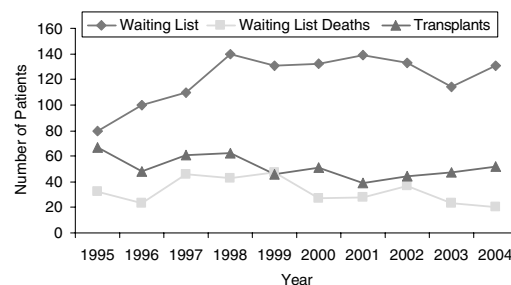
**Lung Transplantation**

As in previous years, the population of pediatric patients undergoing lung transplantation remains quite different than that of adults. In 2004, 36 of 54 (67%) pediatric lung transplants were for cystic fibrosis (CF), compared with 178 of 1118 (16%) in adults. CF accounted for 5 of 10 (50%) patients receiving lung transplants between the ages of 1 and 10 years and 31 of 40 (78%) patients aged 11–17 years (SRTR analysis, August 2005). These percentages are similar to those seen in international reports (27,37). Lung transplant in the infant and toddler population continues to be an infrequent occurrence (five transplants in 2004). Although these patients carry diagnoses seen in

adults, such as alveolar proteinosis and interstitial lung disease, genetic studies of these infants have revealed etiologies distinct from adults including disorders of surfactant protein B and C and the ABCA3 transporter (38–41). Other indications for transplant unique to infancy include irreparable congenital cardiac or pulmonary vascular abnormalities and pulmonary hypertension/hypoplasia associated with congenital diaphragmatic hernia. Given that pediatric lung transplants make up less than 5% of the total lung transplant population, these differences make extrapolation of models for waiting list mortality and posttransplant survival from adults to children challenging. These models are increasingly important components of allocation policy, as well as benchmarks for evaluation of transplant center outcomes. Therefore, careful consideration will continue to be necessary when applying these models to pediatric candidates.

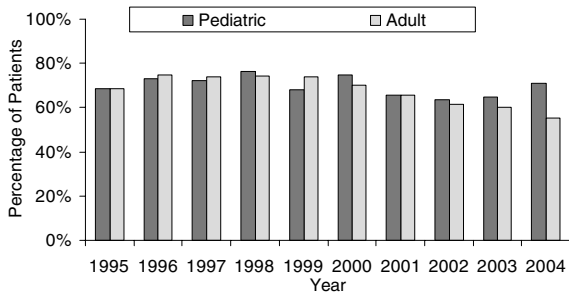
**Waiting list**

In comparison with 2003 and reversing a trend over the prior 2 years, the total number of active pediatric lung transplant candidates increased (Figure 24). This change resulted primarily from increased numbers in the groups of patients 1–5 and 6–10 years of age (from 2 to 15 and 20 to 25, respectively). It is unclear whether this reflects a shift in referral patterns; there have been no major changes in therapy for CF or pulmonary hypertension during the past year. Moreover, the percentage of active pediatric candidates among all active lung transplant candidates has increased from 5% in 2003 to 7% in 2004. In addition, this also reflects a rather sharp decline in the percentage of active adult candidates (Figure 25). This disparity should continue in the coming year, as the virtual elimination of waiting time from the lung allocation system for patients 12 years and older (implemented in May 2005) will likely lead to a sharp decline in the percentage of active patients in the 12 years and older age group (reflecting listing practice changes similar to those seen in liver transplantation following implementation of MELD/PELD). The percentage of active patients in the 11 year and under age



Source: 2005 OPTN/SRTR Annual Report, Tables 12.1a, 12.3, 12.4a and 12.4b.

**Figure 24: Pediatric patients listed for lung transplant, dying on the waiting list and transplanted, 1995–2004.**



Source: 2005 OPTN/SRTR Annual Report, Tables 12.1a and 12.1b and 2004 OPTN/SRTR Annual Report, Table 12.1.

**Figure 25: Percentage of patients listed for lung transplant with active status, 1995–2004.**

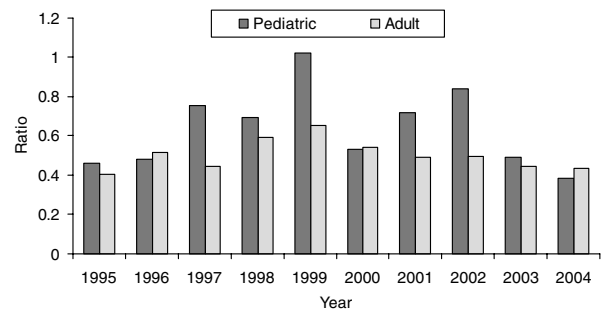
groups is unlikely to change because allocation remains based on waiting time for this age group.

Determining median values for time to lung transplant is not possible for the majority of age groups in the past 5 years because more than half of the patients in these groups have yet to be transplanted. This likely reflects the practice of listing patients early in order to accumulate enough waiting time to be offered organs when their disease progresses. Based on the 10th and 25th percentile data, median waiting times will be at least 3–4 months for patients less than 5 years of age, and at least 1–2 years for patients 6 years and older.

Although waiting list mortality in the pediatric population historically has been above the mean, and the number of waiting list deaths compared with transplants has generally been high for pediatric candidates compared with adults (Figure 26), in the past 2 years this trend shows some evidence of reversing. This is reflected in decreases in total waiting list deaths (Figure 24) as well as waiting list mortality which, in 2004, for the 6–10 year and 11–17-year age groups, was below the mean at 103 and 108 deaths per 1000 patient-years at risk, respectively. These are the lowest values among any age group and among the lowest values for these pediatric age groups over the past 10 years. Although interpretation of these data must be tempered by the small number of patients they are based on, the improved death rate observed for adolescent lung transplant candidates is encouraging. In light of the large percentage of CF patients in the adolescent age group and the unpredictability of the course of this disease, we hope that the adolescent preference incorporated into the modifications to the lung allocation policy adopted in May 2005 will allow this trend to continue.

### **Transplantation and survival**

**Transplantation:** In 2003, there were 54 pediatric lung transplants (both deceased and living donor). This represents 4% of all lung transplants and has continued to in-



Source: 2005 OPTN/SRTR Annual Report, Tables 12.3, 12.4a and 12.4b.

**Figure 26: Ratio of waiting list deaths to transplants, pediatric and adult, 1995–2004.**

crease slightly since 2002 (Figure 24). These numbers still represent a decline over the past decade from peaks of 67 transplants and 8% of all transplants in 1995. Given that the waiting list for pediatric lung candidates (both active and total) has nearly doubled over the past 10 years, the factors contributing to this decline most likely include decreasing numbers of pediatric donors coupled with steady increases in the number of adults listed for lung transplant. Living donor lobar lung transplants (LDLLT) continued to make up a very small percentage of transplants in 2004, representing less than 2% of total transplants. CF remained, by far, the most common diagnosis in patients receiving LDLLT. Two LDLLT recipients in 2004 had received a prior lung transplant; there were three pediatric LDLLT recipients compared with five in 2003. This is probably not an important difference, though over the decade, there appear to be fewer LDLLT being done in both children and adults. In addition to the relatively few programs willing to tackle the technical and ethical complexities of a LDLLT program, this decline may be due in part to recent data from the University of Southern California program suggesting that short- and long-term survival may be lower than that of deceased donor recipients (42). However, promising results from the program at Okayama University in Japan balance this concern (43).

There were no major differences in the incidence of lung transplantation in all pediatric age groups in comparison with 2003. In general, the incidence of pediatric lung transplant is less than half that in adults. Granting the small numbers, the only pediatric age groups with substantial change in the past decade have been infants less than 1-year old and children aged 1–5 years. Both have declined by more than 50% from peak values. The reasons for and import of this observation are unclear.

**Survival:** Patients with a history of prior transplant, on mechanical support or hospitalized in an intensive care unit continued to have the highest annual death rates per 1000 patient-years at risk. However, as a whole, death rates in deceased donor recipients, including all pediatric age

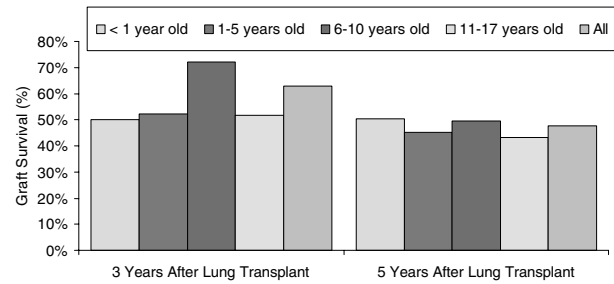
groups, have continued to decrease between 1995 and 2003, including a 31% decline over the past 2 years. For pediatric recipients transplanted in 2003, only two deaths occurred in the 11–17-year age group, yielding a rate of 74. This is the lowest value in the past decade, though the numbers are quite variable. Although there are likely to be multiple contributing factors, two relevant trends are notable; decreased induction use of T-cell directed antibodies in favor of IL-2 receptor antagonists, perhaps leading to a lower risk for early infection and a reduced death rate in patients with long ischemic times, perhaps a result of lower incidence or severity of early graft dysfunction. These two trends may be important because infection and early graft dysfunction are the two most common causes of death in the first year following transplantation (37).

The annual death rate in the first year after LDLLT also has been comparable to that for deceased donor transplants for the past 2 years after several years of being consistently higher. Death rates in pediatric LDLLT recipients over the past decade have been comparable to those of adults.

Although better than intestinal transplantation, long-term survival after lung transplantation across all age groups remains poor compared with heart, liver and kidney transplantation. Unadjusted 5-year graft survival is 48% compared with 69%, 67%, 72% and 32% for deceased donor kidney, liver, heart and intestine transplant recipients, respectively.

Subgroup analysis of lung transplant recipients again showed that previous lung transplantation was a strong predictor of poor graft survival. Although the numbers are small, comparison of different age groups revealed the following: (1) Infants less than 1 year of age have worse early unadjusted survival than other age groups, but comparable 5-year survival. (2) At 5 years, all pediatric age groups have unadjusted survival comparable to adults (Figure 27). Similar to previous observations (10,11), in the cohorts used for this analysis, 5-year outcomes in adolescents appear to be worse than in other children or adults younger than 65 years. Five-year unadjusted graft survival in all LDLLT recipients is 41% compared with 48% in deceased donor recipients. Unadjusted graft survival of pediatric LDLLT recipients aged 6–10 years is 55% comparable to 50% in adult LDLLT recipients aged 18–34 years.

An increasing percentage of pediatric lung transplants are being performed in transplant programs that predominantly serve adults (Figure 28). In the past 4 years, this has comprised roughly 40% of pediatric transplants and 20% of transplants in recipients younger than 11 years. In contrast to the growth of pediatric transplant programs overall, this likely reflects that the number of active pediatric lung transplant programs has not increased during the past decade (Figure 29). Finally, only 5% of programs perform more than 10 pediatric lung transplants per year. Lack of program growth, coupled with small numbers of experienced pro-



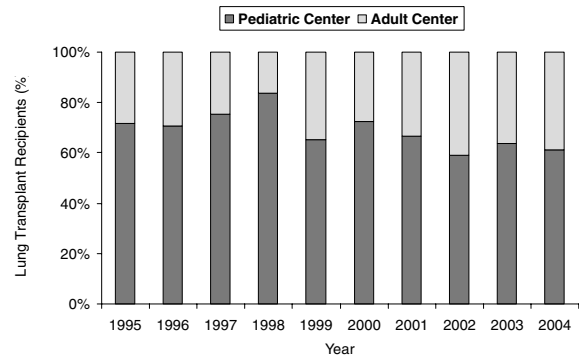
Source: 2005 OPTN/SRTR Annual Report, Table 12.9a.

Figure 27: Unadjusted graft survival at 3 and 5 years for deceased donor lung transplant recipients, by age.

grams, makes learning from experience and prospective studies a considerable challenge. Nonetheless, lung transplantation remains a viable therapy for end-stage pediatric pulmonary parenchymal and pulmonary vascular disease in pediatric patients, with outcomes comparable to those seen in adults. Bronchiolitis obliterans and other late complications remain as barriers to the long-term success of pediatric lung transplantation. We look forward to the development of multicenter collaborations and basic science partnerships that take advantage of emerging technologies such as gene array technology, molecular genomics and proteomics in order to dissect the basic processes required to prevent chronic graft dysfunction and lead to robust tolerance.

### Allocation Policy Update

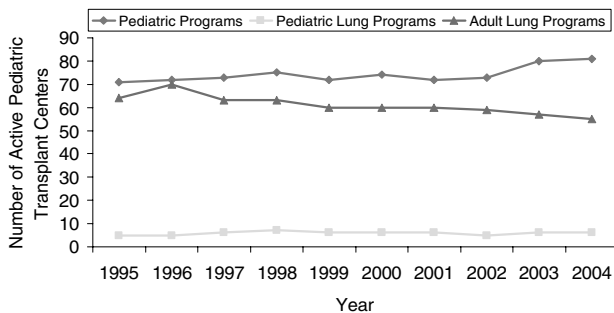
This section summarizes the pediatric-specific aspects of organ allocation. Changes during the past year involved preferentially directing organs from pediatric and younger donors to pediatric candidates.



Source: SRTR Analysis, August 2005.

Figure 28: Distribution of lung transplant recipients between centers serving primarily pediatric or adult recipients for recipients aged 0–17 years.





Source: OPTN, 2005.

**Figure 29: Number of active pediatric transplant centers (reporting 1 or more transplant per year).**

### Kidney

To minimize the harmful developmental effects of end-stage kidney failure, kidney allocation policy previously gave pediatric candidates maximum priority after exceeding preset waiting time goals. Despite this added advantage, many children were not being transplanted quickly after exceeding their time goals. Moreover, this policy also created inefficiencies in the allocation system because a significant percentage of kidneys offered under the policy were being turned down because of donor age or organ quality.

**New kidney allocation policies:** To address these concerns, the policy of allocating kidneys to pediatric candidates was revised so that kidneys from donors less than 35 years old are now offered preferentially to pediatric candidates. Only patients with 0 HLA mismatches and those who are highly sensitized have higher priority. Pediatric candidates less than 11 years old are given additional point priority because of their younger age and the greater impact of kidney failure on development.

Analyses presented to the OPTN Board of Directors showed that this change will have a minimal impact on the allocation system. Many pediatric recipients were already receiving organs from donors less than 35 years old and the total number (381) of pediatric recipients of deceased donor kidneys is small compared with the 2595 deceased kidney donors under 35 years of age in 2004.

### Liver

Three major changes were made in organ allocation policies for pediatric liver candidates.

**New liver policies:** In 2004, approximately 37% of pediatric liver recipients were transplanted at Status 1. The previous pediatric Status 1 criteria were broad and included variables that were subject to interpretation. This, coupled with the 'Status 1 by exception' category, resulted in a large

percentage of pediatric candidates being listed at Status 1. The revised Status 1 criteria are much more stringent, remove 'Status 1 by exception', and subdivide Status 1 into two categories, 1A and 1B, that reflect different risks of waiting list mortality (Table 2).

To address any potentially harmful consequence of the new, more stringent Status 1 criteria, allocation of pediatric livers was also revised to further favor pediatric candidates. Previously, only pediatric candidates at >50% risk of 3-month waiting list mortality (corresponding to a PELD score >46) would be offered a pediatric donor liver before any adult with a MELD score >30 (the 50% risk of 3-month waiting list mortality for adult candidates).

The new pediatric preference algorithm shares pediatric donor livers regionally to pediatric candidates based on a PELD/MELD score rather than on a waiting list mortality risk. After Status 1 patients are offered the pediatric donor liver, the liver will be offered regionally to pediatric candidates aged 0–11 years, then locally to pediatric candidates aged 12–17 years with a MELD score  $\geq 15$ , before being offered locally to adult candidates with a MELD score  $\geq 15$ . The revised algorithm is intended to promote broader sharing of pediatric donor livers to pediatric candidates (especially to the youngest ones) and to encourage the splitting of young, healthy livers from adolescent donors. Simulation modeling for this revised algorithm also showed an increase in pediatric transplants adequate enough to offset the anticipated decrease in pediatric transplants from an earlier policy, where adult donor livers are shared regionally at a MELD score >15 (SRTR analysis, July 2004).

The other policy change during the past year involved listing pediatric candidates 12–17 years old using MELD scores. MELD was felt to be a better predictor of mortality than PELD because PELD does not consider the effect of kidney failure.

### Lung

Details of allocation policy for lung transplant patients can be found elsewhere in this report (44). Most important, pediatric donor lungs are now offered preferentially to pediatric candidates before being offered to adult candidates. Pediatric candidates 0–11 years old are assigned priority based on waiting time, whereas pediatric candidates older than 12 years are assigned a lung allocation score. Lungs from donors 0–11 years old will be offered first to pediatric candidates 0–11 years old, then to candidates 12–17 years old, before being offered to adult candidates. Lungs from donors 12–17 years old will be first offered to candidates 12–17 years old, then to candidates 0–11 years old, before being offered to adult candidates.

**Table 2:** Allocation criteria for pediatric liver candidates

Pediatric Status 1A criteria	
Fulminant hepatic failure	Onset of hepatic encephalopathy within 8 weeks of first symptoms of liver disease One of three criteria met (1) ventilator dependence (2) requiring hemodialysis/hemofiltration (3) INR >2.0
Primary nonfunction	Diagnosis within 7 days of transplantation Must include two of the following (1) ALT $\geq$ 2000 (2) INR >2.5 (3) Total bilirubin $\geq$ 10 mg/dL (4) Acidosis, defined as pH $\leq$ 7.3 and/or lactate $\geq$ 2 $\times$ normal
Hepatic artery thrombosis	Diagnosis within 14 days of implantation
Acute decompensated Wilson's disease	
Pediatric Status 1B criteria	
Chronic liver disease	In the ICU Calculated PELD or MELD >25 One of the following criteria are met (1) On a mechanical ventilator (2) GI bleeding requiring at least 30 cc/kg of RBC replacement with past 24 h (3) Renal failure requiring hemodialysis/hemofiltration (4) Glasgow coma score <10
Metabolic disease, Hepatoblastoma	Pediatric candidates with urea cycle disorders or organic acidemias or hepatoblastomas may receive a PELD/MELD score of 30. If candidate has not been transplanted within 30 days, then may be listed as Status 1B

Source: OPTN (24).

### Heart

There have been no changes to the national system for allocating deceased donor hearts. Candidates continue to be assigned priority based upon medical urgency, blood type, and waiting time. Pediatric candidates are assigned medical urgency status codes based on criteria that take into account differences in diseases, therapies and severity of illness among pediatric candidates. They also receive preference ahead of adult candidates in the allocation of adolescent (i.e., 11–17 years old) donor hearts within each medical urgency status.

Organ allocation policy includes pediatric-specific aspects to preferentially direct pediatric donor organs to pediatric candidates. The above revisions should yield better outcomes and more efficient allocation of organs to pediatric candidates. Details of the actual allocation policies can be found at the OPTN web site (24).

### Further Challenges in the Pediatric Transplant Population

The data presented above support the conclusion that pediatric organ transplantation has achieved levels of success, in terms of both graft and patient survival that are comparable overall to adults. The overarching success of pediatric transplantation is well represented by the pediatric recipients alive at the end of 2004 (Figure 23). Nonetheless, three important themes—resulting in part because of

this success—warrant further consideration: organ availability, adolescent survival and challenges facing clinical research.

The discussion above suggests that pediatric organ transplant candidates will continue to face increasing competition from adults. This, coupled with decreasing numbers of pediatric donors, will diminish access for pediatric candidates, particularly for those organs with donor size constraints. Organ donation initiatives and favorable allocation policies will not completely mitigate this problem. One area drawing increased attention is DCD. A recent SRTR analysis showed that, in 2004, there were 391 instances of DCD, of which 41 donors were younger than 18 years of age (10% of total DCD events). In 2004, there were 530 kidney transplants using DCD organs, six of which were received by pediatric candidates. During the same time, 177 liver transplants were performed with DCD livers, three of which involved a pediatric recipient (SRTR analysis, August 2005). Expanded use of DCD organs is an exciting possibility. However, the observed substantial increase in delayed graft function (Table 3) associated with DCD in kidney recipients must be assessed carefully before DCD organs are routinely accepted for use in children.

A second focus is the perennial concern about adolescent graft and patient survival. Although commonly ascribed to nonadherence, prospective validations of this assumption—in spite of anecdotal experiences common to all centers—are difficult to obtain (45). Other

**Table 3:** Donation after cardiac death, 1995–2004: incidence of delayed graft function

	Year									
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
No. of delayed graft function										
Total	1884	1990	1874	1980	1974	1885	1964	1943	2028	2144
DCD	52	45	54	44	64	68	101	106	164	226
ECD (not DCD)	371	428	393	456	406	356	406	429	455	411
SCD	1461	1517	1427	1480	1504	1461	1457	1408	1409	1507
No. of Transplants										
Total	7599	7595	7636	7893	7914	7958	8065	8287	8388	9025
DCD	103	94	117	105	142	163	246	287	393	530
ECD (not DCD)	990	1061	1123	1207	1209	1160	1165	1216	1315	1341
SCD	6506	6440	6396	6581	6563	6635	6654	6784	6680	7154
% Delayed graft function										
Total	24.8%	26.2%	24.5%	25.1%	24.9%	23.7%	24.4%	23.4%	24.2%	23.8%
DCD	50.5%	47.9%	46.2%	41.9%	45.1%	41.7%	41.1%	36.9%	41.7%	42.6%
ECD (not DCD)	37.5%	40.3%	35.0%	37.8%	33.6%	30.7%	34.8%	35.3%	34.6%	30.6%
SCD	22.5%	23.6%	22.3%	22.5%	22.9%	22.0%	21.9%	20.8%	21.1%	21.1%

Source: SRTR Analysis, May 2005.

Note: DCD = donation after cardiac death, ECD = expanded criteria donor and SCD = standard criteria donor.

unexplored factors include the impact of adolescent development on the pharmacodynamics and efficacy of immunosuppressant medications, the effect of adolescence on the immune response and the effect of transitions between pediatric and adult caregivers. Although the transition of pediatric transplant recipients from pediatric transplant centers to adult transplant centers is an area of current focus (American Society of Transplantation adolescent transition conference, Chicago, 2005), another unexplored transition is that which occurs when pediatric candidates cared for by pediatric subspecialists undergo transplant and receive posttransplant care from a center primarily caring for adults. Review of OPTN data indicates that more than 60% of recipients 11–17 years old receive transplants in centers that transplant more adults than children (OPTN data, 2005). It is difficult to determine from the data set whether such centers have a different spectrum of caregivers compared with pediatric centers. However, this observation invites exploration of the pediatric services available in *all centers*, particularly relating to adolescent development and monitoring/prevention of nonadherence. Indeed, the Pediatric and Membership committees of the OPTN recently have discussed including specific criteria for programs serving pediatric candidates as part of an overall review of the OPTN requirements for transplant programs.

The final challenge facing pediatric transplantation relates to clinical research. Although research cooperatives (NAPRTCS, SPLIT, PHTS, IPLTC and the intestinal transplant registry) have been successful to varying degrees in reporting results of retrospective analyses, with the exception of NAPRTCS and the CCTPT, these groups have been less successful in implementing prospective trials. It is worth emphasizing that only 24% of centers performing pediatric transplants of *any organ* performed more than 10 total pediatric transplants in 2004. Furthermore, 42% of

pediatric transplants were performed in centers transplanting more adults than children (OPTN data, 2005). Given these observations, one must consider whether the majority of pediatric transplants occur in places where pediatric transplantation is not a research priority. The importance of prospective studies is underscored by an observation resulting from a CCTPT-sponsored steroid withdrawal trial showing that the incidence of PTLD was increased (46). It is unlikely that single-center studies would have made this important observation. To ensure that we learn as much from each pediatric transplant recipient as possible, the pediatric transplant community must overcome the collaborative barriers of such a fragmented population.

## Summary

Overall, the prospects for solid organ transplantation in children, especially those aged 1–10 years, are excellent. Organ allocation policies typically grant preference to these patients, and long-term graft survival rates for this age group are often equivalent to or exceed the outcomes of transplantation in adults. Adolescents also receive preference in allocation and have excellent short-term survival in general. However, long-term outcomes in adolescents continue to be suboptimal. Infants also remain a challenging population, with higher waiting list mortality and poorer outcomes. However, evidence that long-term complications in infants may be lower (6,47), raises the question whether outcomes for these patients could be improved by shortening time to transplant.

The success of pediatric transplantation is in part responsible for the ongoing challenges the pediatric transplant community now faces. Larger waiting lists require consideration of other sources of organs, such as DCD. Successful

transplantation of adolescents requires more effective management of their transition to adult caregivers. Finally, although overall pediatric outcomes are now comparable to those of adults, more effective collaborations for clinical research are necessary to keep pace with improvements in the adult world.

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This study was approved by HRSA's SRTR project officer. HRSA has determined that this study satisfies the criteria for the IRB exemption described in the "Public Benefit and Service Program" provisions of 45 CFR 46.101(b)(5) and HRSA Circular 03.

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