Pediatric transplantation, 1994–2003

William E. Harmon[a],[*], Ruth A. McDonald[b], Jorge D. Reyes[c], Nancy D. Bridges[d], Stuart C. Sweet[e], Cindy M. Sommers[f] and Mary K. Guidinger[g]

[a] *Children's Hospital of Boston, Boston, MA*
[b] *Children's Hospital and Regional Medical Center, Seattle, WA*
[c] *University of Pittsburgh Medical Center, Pittsburgh, PA*
[d] *National Institute of Allergy and Infectious Diseases, Bethesda, MD*
[e] *Washington University School of Medicine, St. Louis, MO*
[f] *United Network for Organ Sharing, Richmond, VA*
[g] *Scientific Registry of Transplant Recipients, University Renal Research and Education Association, Ann Arbor, MI*
[*] *Corresponding author: William E. Harmon, william.harmon@TCH.Harvard.edu*

This article uses OPTN/SRTR data to review trends in pediatric transplantation over the last decade. In 2003, children younger than 18 made up 3% of the 82,885 candidates for organ transplantation and 7% of the 25,469 organ transplant recipients. Children accounted for 14% of the 6,455 deceased organ donors. Pediatric organ transplant recipients differ from their adult counterparts in several important aspects, including the underlying etiology of organ failure, the complexity of the surgical procedures, the pharmacokinetic properties of common immunosuppressants, the immune response following transplantation, the number and degree of comorbid conditions, and the susceptibility to post-transplant complications, especially infectious diseases. Specialized pediatric organ transplant programs have been developed to address these special problems, The transplant community has re-sponded to the particular needs of children and has provided them special consideration in the allocation of deceased donor organs. As a result of these programs and protocols, children are now frequently the most successful recipients of organ transplantation; their outcomes following kidney, liver, and heart transplantation rank among the best. This article demonstrates that substantial improvement is needed in several areas: adolescent outcomes, outcomes following intestine transplants, and waiting list mortality among pediatric heart and lung candidates,

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

Introduction

The data and analysis presented in this article provide important information about pediatric organ transplantation. In this report, 'pediatric' refers to all candidates, recipients and donors, aged 17 years and under. Graft and patient survival are reported as unadjusted survival unless otherwise indicated. Unless otherwise noted, the statistics in this article are drawn from the reference tables in the *2004 OPTN/SRTR Annual Report*. Two companion articles in this report, 'Transplant data: sources, collection and research considerations' and 'Analytical approaches for transplant research, 2004', explain the methods of data collection, organization and analysis that serve as the basis for this article (1,2). Additional detail on the methods of analysis 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.

Children represent a distinct group of organ transplant candidates. Pediatric organ transplant recipients differ from their adult counterparts in several important aspects, including the underlying etiology of organ failure, the complexity of the surgical procedures, the pharmacokinetic properties of common immunosuppressants, the immune response following organ transplantation, the measures of success of the transplant procedure, the amount and degree of comorbid conditions and the susceptibility to post-transplant complications, especially infectious diseases. Organ transplantation can never be considered fully successful for children unless they grow and develop as normally as possible following transplantation. Recognizing these special considerations, families have been

particularly willing to be living donors for children and the transplant community has provided special allocation rules to give preference to pediatric candidates.

Pediatric organ transplant programs have been developed to address the requirements specific to children with terminal organ failure. In general, these programs are small and their outcome reports and research protocols are hampered by small numbers. Thus, specialized pediatric registries have been developed to define the requirements and treatments relevant for children. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has been reporting on pediatric kidney transplantation since 1987 (3), and the Studies of Pediatric Liver Transplantation (SPLIT) has been doing so for pediatric liver transplantation since 1995 (4). Similarly, the Pediatric Heart Transplant Study (PHTS) has been a registry since 1993 (5), and the Intestinal Transplant Registry covers pediatric intestinal transplantation (6). Recognizing the specific needs of children, the National Institute of Allergy and Infectious Diseases established the Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) 11 years ago, and it continues to sponsor important trials. The SRTR has contributed to this effort by providing comprehensive data and analysis across all types of pediatric organ transplants and by providing an opportunity to compare the outcomes of children with those of adults. The SRTR has provided many analyses to the OPTN Pediatric and other committees and has developed models to help guide decisions about allocation of organs for pediatric transplantation.
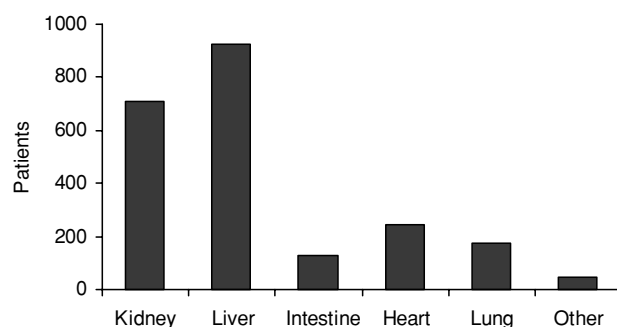
Waiting list

There were 2220 children awaiting all types of organ transplants at the end of 2003, about evenly divided between those <11 years of age and those 11–17 years old (Figure 1). Children account for 3% of all candidates for transplantation. The number of children awaiting transplant has decreased slightly for the past 2 years, with the number of infants <1 year of age decreasing almost 25% since 2000. The organs with the greatest number of children awaiting transplantation were liver (922) and kidney (710) (Figure 2). The number of children awaiting transplant during the past decade has increased by about 70%. However, the proportion of children on the waiting list has decreased from 4% to 3% because of the substantially greater increase of adults during the same time, especially those between 50 and 64 years (a more than threefold increase) and ≥65 years (a more than fivefold increase). The pattern in Figure 1 suggests that the number of children awaiting transplantation may have reached a steady state.

Pediatric organ transplant recipients

In 2003, there were 1802 pediatric transplant recipients, which represented 7% of all recipients. The number of children receiving organ transplants has increased relatively little since 1994 (Figure 3). The number of transplants in children has increased only 16% during the decade while the
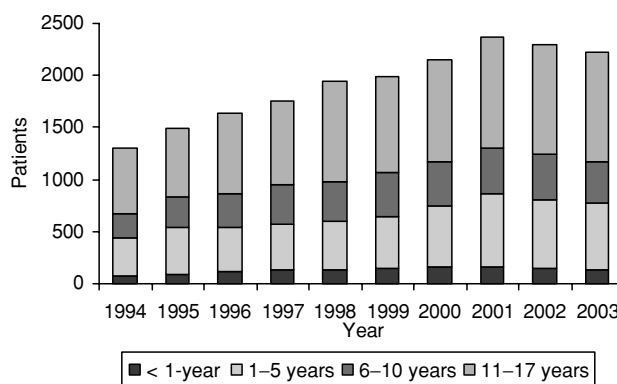
Figure 1: Pediatric transplant waiting list at year-end, 2003. Source: *2004 OPTN/SRTR Annual Report*, Table 1.4.

Figure 2: Number of pediatric patients on waiting list, by organ, 2003. Source: *2004 OPTN/SRTR Annual Report*, Tables 5.1, 6.1, 7.1, 8.1, 9.1, 10.1, 11.1, 12.1, 13.1.
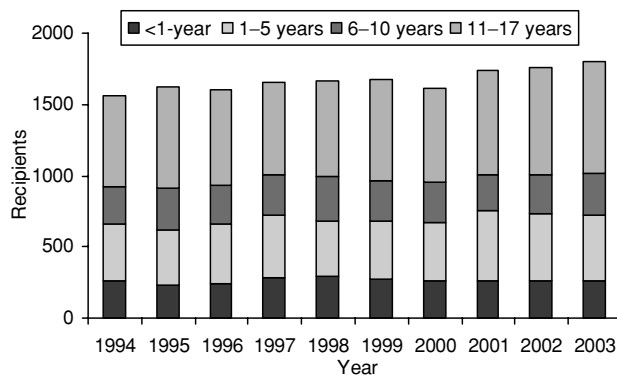
Figure 3: Pediatric transplant recipients, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 1.10.

number of transplants for all ages has grown by 39%. The higher percentage of pediatric candidates who are transplanted reflects the high percentage of living donors for children and the preference provided for children in organ allocation, which is discussed below.
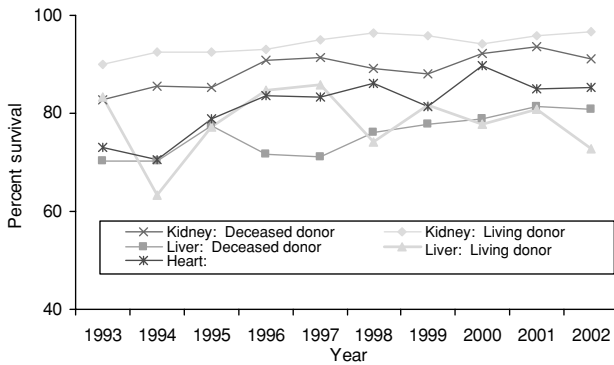
Figure 4: Adjusted 1-year graft survival for pediatric kidney, liver and heart recipients, 1993–2002. Source: SRTR analysis, August 2004.
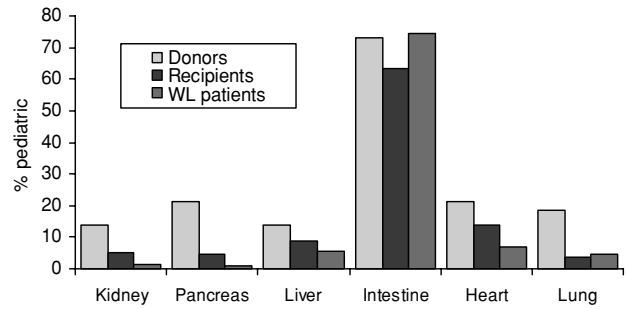

Figure 5: Pediatric as percentage of deceased donors, recipients of deceased donor organs and all wait listed, 2003. Source: *2004 OPTN/SRTR Annual Report*, Tables 2.2–2.7, 5.1, 5.4a, 6.1, 6.4, 7.1, 7.4, 9.1, 9.4a, 10.1, 10.4, 11.1, 11.4, 12.1, 12.4a.

As with transplantation in general, pediatric organ transplants are becoming more successful and graft survival shows an increasing positive trend (Figure 4). As noted in previous SRTR annual reports, young children have the best adjusted 5-year graft survival rates among all deceased donor and living donor kidney recipients, although adolescents do not do as well. Similarly, children 6–10 years have the best adjusted 5-year graft survival rates among all deceased donor liver recipients, but infants <1 year of age have the worst. Children ≤10 years undergoing living donor liver transplantation have the best adjusted 5-year graft survival rates of all age groups, with outcomes exceeding those of deceased donor liver transplants. Children 1–17 years old have adjusted 5-year graft survival rates for heart transplants that are comparable to adult recipients 35–64 years old. Children <1 year at the time of a heart transplant have slightly lower long-term graft survival rates than older children, but they are no worse than the 18–34 year group. Meaningful assessment of long-term pediatric living and deceased donor lung and intestine graft survival rates is hampered by the relatively small numbers of such recipients.

Overall, children, especially young children, have excellent long-term graft survival rates, and these rates are often equivalent to or better than the outcomes of transplantation in adults. In general, children can no longer be considered to have excessive risk based solely on their age at the time of transplantation.

Pediatric organ donors
In general, most organ transplant programs do not accept living donors <18 years of age. A recent International Forum on Living Organ Donation proposed a ban on all such transplants (7). A recent review of 40 000 living kidney donors in the United States identified 60 donors who were <18 years at the time of donation (8). Twenty-four of the recipients of these grafts were children, of whom 7 were identical twins; 36 of the recipients were

adults, the oldest of whom was 54 years of age. In 2003, only one living kidney donor was <18 years of age; no living liver or lung segment donors were pediatric.

There were 884 pediatric deceased donors of all organs in 2003, representing 14% of all donors. Almost 60% of pediatric deceased donors were at least 11 years old. The number of pediatric deceased organ donors has been relatively stable over the past 5 years, but the pediatric population has represented a declining percentage of all organ donors over that time span because the number of older adult donors has increased.

As previously described, pediatric deceased donors are more likely to donate each type of organ compared with adult donors (9). The percentage of pediatric deceased donors who donated specific organs was as follows: kidney 89%, liver 90%, heart 52%, pancreas 43%, lung 20% and intestine 10%. The percentage of pediatric deceased donors who donate pancreata, intestines and hearts is substantially higher than adults. The percentage of pediatric deceased donors who donate pancreata and intestines has increased substantially over the past decade.

The percentage of deceased donors who are children substantially exceeds the percentage of children who are either candidates for deceased organ donation or recipients of deceased donor organs for every organ except intestine (Figure 5). For example, children make up more than 20% of the donors of hearts and pancreata but are recipients of only 14% and 5% of those deceased donor grafts, respectively. In general, organs from deceased pediatric donors are more frequently used for adults and more adults receive organs from pediatric donors than children receive organs from deceased adult donors (Figure 6).

A recent SRTR analysis showed that, in 2003, there were 271 instances of donors after cardiac death (DCD), of whom 28 were younger than 18 years of age (10% of total DCD donors). In 2003, there were 394 kidney transplants
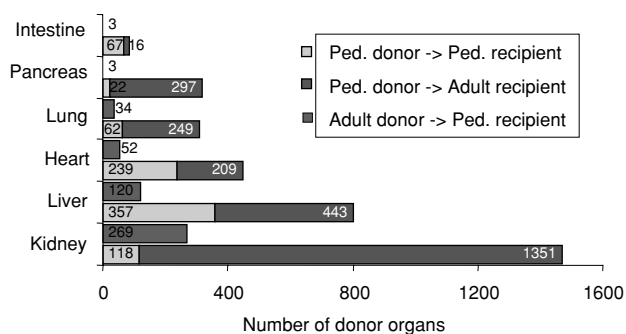
Figure 6: Number of deceased donor organs by age of donor and age of recipient, 2003. Source: SRTR Analysis, August 2004. Organs divided into segments (liver, pancreas, intestine) have each segment counted separately. Multiorgan transplants have each organ counted separately. Adult-to-adult numbers, not shown, are as follows: 24 (intestine), 1040 (pancreas), 1346 (lung), 1582 (heart), 4423 (liver) and 8016 (kidney).

using DCD organs, 9 of which were received by pediatric candidates. During the same time, there were 114 liver transplants performed with DCD donor livers, 5 of which involved a pediatric recipient (SRTR analysis, August 2004).

Pediatric allocation policy overview

This section focuses on organ allocation policy—provisions that determine the order in which available organs are offered to candidates on the waiting list—rather than organ distribution policy, which comprises provisions that govern the composition of the list at the time offers are made. The organ allocation policies summarized in this section reflect policies approved by the OPTN/UNOS Board of Directors as of June 24–25, 2004; implementation of certain policies awaits necessary computer programming. Readers are encouraged to access the OPTN website (www.optn.org) for the most up-to-date policies regarding organ allocation.

Amendments to the National Organ Transplant Act (NOTA), 42 U.S.C. §§ 274 *et seq.*, enacted in 2000 (Title XXI, Children's Health Act of 2000, Public Law 106–310) make clear that as part of its policy development activities, the OPTN is to recognize and address the differences in health and organ transplantation issues between children and adults. Even prior to inclusion of this principle in law, national policies for the allocation of organs took into account the unique challenges for pediatric candidates with end-stage organ failure. For example, since 1990, children have received additional priority for deceased donor kidney offers through assignment of extra points based upon age. This is because young children and adolescents experience age-specific problems associated with dialysis, including disruption of expected growth and development processes due to renal failure. Early reversal of uremia through transplantation can avoid these problems and ameliorate many of the adverse effects of end-stage renal disease (ESRD)

confronting these patients. The intent, therefore, has been to expedite access for these patients to donor kidneys.

In liver, heart and, most recently, lung allocation, the need to recognize differences between children and adults—physiology, disease processes and progression, treatment protocols, morbidity and mortality and growth and development—has been amplified as these respective allocation systems have moved toward greater specificity in defining medical urgency. The intent has been to develop pediatric criteria that are within the framework established for adult candidates and consistent with its principles while addressing conditions and challenges particular to children. Additionally, pediatric candidates receive preference in allocation of adolescent donor organs (heart) and all pediatric donor organs (liver) to take advantage of improved transplant recipient outcomes demonstrated for children but not for adults through donor-to-candidate matching with the younger donors. Pediatric candidates also receive preference in the allocation of pediatric donor lungs to address practical considerations of organ size and suitability for transplant, as well as the relatively high mortality for younger children and adolescents on the lung waiting list.

Kidney allocation

The national system for allocating deceased donor kidneys includes two allocation protocols, one for standard criteria donor (SCD) kidneys (the majority of deceased donor kidneys) and one for expanded criteria donor (ECD) kidneys. Both protocols assign priority for allocation of kidneys nationally to candidates who are a zero mismatch at each of the human leukocyte antigen (HLA) A, B and DR loci before the organs are offered for less well HLA-matched candidates. Both protocols also assign priority based upon blood group identity for donors and candidates, and, in the case of a zero antigen mismatch between donor and blood type candidates, for blood group compatibility. Finally, both SCD and ECD protocols use candidate waiting time as a factor in kidney allocation. For adult candidates, waiting time accrual can begin once they are listed and have either started dialysis or met creatinine clearance/glomerular filtration rate (GFR) criteria. The system for allocating SCD kidneys assigns priority for other characteristics: degree of HLA identity between donor and candidate at the HLA DR locus, relatively high levels of anti-HLA sensitization, prior living organ donation and age for pediatric candidates.

Pediatric-specific elements:
Once a child is placed on the kidney waiting list, waiting time begins to accrue regardless of the candidate's level of renal function. Upon listing, children also receive points for SCD kidney offers based upon their age at time of listing. Children <11 years receive 4 points, and children 11–17 years receive 3 points. The points are assigned in an effort to get pediatric patients transplanted with SCD kidneys within the following time goals: Six months from placement on the waiting list for candidates 0–5 years old at the time of

listing; 12 months from placement on the waiting list for candidates 6–10 years old at the time of listing and 18 months from placement on the waiting list for candidates 11–17 years old at the time of listing.

Any child who is not transplanted within these time goals receives maximum priority for subsequent SCD kidney offers. This priority is superseded by candidates with relatively high anti-HLA sensitization who otherwise would have been prioritized for the organ offer, candidates who are zero antigen mismatched with the donor and in need of combined kidney/non-renal organ transplantation, or prior living organ donors. This additional priority for SCD kidney offers, as well as the points assigned at the time of listing, is not applied in the allocation of ECD kidneys, recognizing that children generally are not good candidates for ECD kidneys because of the risk of reduced long-term graft survival associated with these organs and possibilities for sensitization following transplant. Finally, pediatric patients receive preference in the allocation of zero antigen mismatched donor kidneys after such organs have been offered to candidates wait-listed within the donation service area of the organ procurement organization that procured the organ and highly sensitized candidates with panel reactive antibody (PRA) $\geq$80% (Table 1).

Liver allocation

The pediatric end-stage liver disease (PELD) model, the national system for allocating deceased donor livers, attempts to assign priority to candidates based upon medical urgency. The highest urgency level, Status 1, defines candidates who are expected to live for less than 7 days without a liver transplant. For adult patients, this includes only candidates with fulminant liver failure who meet enumerated criteria. For pediatric candidates, this includes candidates located in an intensive care unit (ICU) with acute or chronic liver failure who meet enumerated criteria. Following Status 1, candidates are prioritized based upon their probability

of death on the waiting list as determined by formulas that assess various prognostic factors. Exceptions are established for candidates not appropriately addressed by the protocols for determining medical urgency, including, for example, candidates with hepatocellular carcinoma (HCC), pediatric candidates with metabolic diseases or hepatoblastoma and candidates with other unique considerations. Deceased donor livers are allocated first to Status 1 candidates on a regional level before being offered for less urgent candidates at the local level of organ distribution, and second to other candidates with medical urgency scores $\geq$15 on a regional level before being offered for less urgent candidates at the local level of organ distribution.

Within Status 1, points are assigned based upon identical or compatible ABO types between donor and candidate. All other candidates are assigned priority within each level of urgency based upon ABO identity, then ABO compatibility (with limitations upon allocating blood type O donor livers to other than blood type O candidates), and then ABO incompatibility with the donor. Waiting time also is used to prioritize candidates within Status 1 or other designated urgency levels. Status 1 candidates receive waiting time points based only upon waiting time accrued while in Status 1. Other candidates receive waiting time points based upon waiting time accrued while listed at their current or a higher (more critical) urgency level.

Pediatric-specific elements: Pediatric candidates in Status 1 include those with fulminant liver failure, as defined for adult Status 1 candidates, as well as other acute and chronic pediatric patients expected to live <7 days and meeting additional criteria, e.g. on a mechanical ventilator, or with upper gastrointestinal bleeding, hepatorenal syndrome, Stages III or IV encephalopathy, refractory ascites/hepato-hydrothorax or biliary sepsis requiring or unresponsive to specified therapies.

The formulas determining priority for liver candidates not listed as Status 1 also differ for adult and pediatric candidates. The PELD model was developed by the EMMES Corporation using the SPLIT registry to provide a pediatric-specific version of model for end-stage liver disease (MELD). PELD was developed after assessing prognostic factors applicable specifically to children (moving to the ICU and death pre-transplant). Factors presently used include albumin, bilirubin, INR, growth failure and age <1 year. Based on recent studies showing that adolescent candidates (i.e. candidates 12–17 years old), in general, would receive a higher priority for liver offers if assigned a score calculated by the adult candidate formula rather than the pediatric candidate formula, adolescent candidates are now assigned scores using the adult formula. Additionally, because the adult candidate formula for predicting mortality on the waiting list results in a minimum score of 6 while the pediatric formula has no minimum score, pediatric candidates with medical urgency scores $\leq$6 are considered with adult candidates with medical urgency scores of 6.

Table 1: Summary of pediatric priority in kidney allocation

Factor	Priority
Waiting time	Accrual begins once placed on waiting list; time goals to transplant established for candidates 0–5 years old (6 months from listing), 6–10 years old (12 months from listing), and 11–17 years old (18 months from listing)
Points	Up to 4 points assigned at wait-listing based upon age; children not transplanted within time goals to transplant are assigned maximum priority, regardless of total points, with exceptions for candidates based upon, for example, level of anti-HLA sensitization and HLA mismatch
Zero Antigen Mismatch Offers	Preference assigned to children (first within blood group identical categories, and then within blood group compatible categories) after allocation for candidates wait-listed at local level of organ distribution and candidates with high anti-HLA sensitization

Table 2: Summary of pediatric priority in liver allocation

Factor	Priority
Status 1	Includes candidates with fulminant liver failure + other acute and chronic pediatric candidates who meet enumerated criteria
Equation predicting medical urgency	Separate equation developed for pediatric candidates using prognostic factors applicable specifically to children
Pediatric donor liver allocation	Pediatric candidates are assigned preference in the allocation of pediatric donor livers within Status 1 and by medical urgency score both above and below medical urgency thresholds
Pediatric candidates with metabolic diseases & non-metastatic hepatoblastoma	Assigned to Status 1 or medical urgency score deemed appropriate by candidate's physician and applicable regional review board

Table 3: Summary of pediatric priority in heart allocation

Factor	Priority
Medical urgency status	Medical urgency status codes are defined separately for pediatric candidates to address conditions & challenges unique to pediatric candidates; pediatric definitions continue to apply for children from the time of listing until transplant
Adolescent donor heart allocation	Pediatric candidates are assigned preference in the allocation of adolescent donor hearts within each medical urgency status; this preference continues to apply for children from the time of listing until transplant

Pediatric candidates receive preference ahead of adult candidates in the allocation of pediatric donor livers within the group of Status 1 candidates, as well as by medical urgency score, first, above a threshold of medical urgency defined as $\geq 50\%$ risk of a 3-month candidate mortality, then below it. Finally, pediatric candidates with metabolic diseases (e.g. ornithine transcarbamylase deficiency or Crigler–Najjar disease Type I) or non-metastatic hepatoblastoma are assigned to Status 1 or a medical urgency score, as deemed appropriate by the candidate's transplant physician and applicable Regional Review Board (RRB). Pediatric candidates with metabolic diseases are eligible for Status 1 without the need for RRB review once hospitalized (Table 2).

Heart allocation

The national system for allocating deceased donor hearts assigns priority to candidates based upon medical urgency (i.e. the likelihood of a candidate dying while waiting for a heart transplant). Priority is assigned within each heart medical urgency status category for blood type or for compatibility in the case of blood type B patients (blood type O donor hearts) and blood type AB patients (ABO A and B donor hearts). Following allocation for all born transplant candidates with compatible blood types, donor hearts are allocated by heart status category to pediatric candidates <1 year who have incompatible blood types and have indicated they will accept a heart from a donor of any blood type. Waiting time also is used to prioritize candidates within their designated urgency status. Candidates accrue waiting time within each heart status; priority is assigned based upon waiting time accumulated while listed at their current or a higher (more critical) urgency status.

Pediatric-specific elements: Medical urgency status codes are defined separately for adult and pediatric candidates, addressing differences in, for example, therapies and severity of illness among pediatric candidates. Additionally, pediatric candidates receive preference ahead of adult candidates in the allocation of adolescent (i.e. 11–17 years old) donor hearts within each medical urgency status. Children retain the pediatric priority assignments for heart allocation from the time of listing until they are transplanted. The system allows transplantation across blood groups in the case of very young pediatric candidates (i.e. <1 year old). This accomplishes two purposes: it provides for listing *in utero* candidates when blood type is unknown and it permits placement of otherwise unusable pediatric donor hearts in candidates who, based upon available evidence, can be safely transplanted with ABO incompatible donor hearts (Table 3).

Lung allocation

The national system for allocating deceased donor lungs assigns priority to candidates age 12 years and older based on a calculation of their medical urgency and the projected benefit of transplantation. Waiting list urgency is measured by the expected days of life during the next year that would result if the candidate did not receive a transplant (i.e. remained on the waiting list). Post-transplant survival is measured by the expected days lived during the first year post-transplant. The candidate's priority for receiving lung offers, defined by a lung allocation score, is calculated from the difference between the candidate's transplant benefit measure (post-transplant survival measure minus waiting list urgency measure) and the candidate's waiting list urgency measure. Candidates <12 years old are allocated lungs based on time on the waiting list. Candidates with blood type identical to the donor receive preference in lung allocation ahead of candidates with compatible (but not identical) blood types.

The system also assigns preference in the allocation of pediatric donor lungs to pediatric candidates. Adolescent (i.e. age 12–17 years) donor lungs are allocated first to adolescent candidates based on lung allocation score, then to candidates age 0–11 years based on waiting time, and

Table 4: Summary of pediatric priority in lung allocation

Factor	Priority
Transplant benefit/medical urgency score	Adolescent candidates are assigned priority based upon transplant benefit measure and waiting list urgency; young (age 0–11) pediatric candidates are assigned priority based upon time on waiting list
Pediatric donor lung allocation	Pediatric candidates receive preference ahead of adult candidates in the allocation of all pediatric donor lungs

Figure 7: New pediatric registrants on the kidney waiting list, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 5.2.

finally to adult candidates (age 18 years and older) based on lung allocation score. Lungs from young pediatric donors (age 0–11 years) are allocated first to candidates aged 0–11 years by waiting time, then to adolescent candidates based on lung allocation score, and finally to adult candidates based on lung allocation score. Lungs from donors age 18 years and older are allocated first to candidates 12 years and older based on lung allocation score and then to younger pediatric candidates 0–11 years based on waiting time.

Pediatric-specific elements: That young pediatric candidates (0–11 years) are allocated lungs based on waiting time rather than on lung allocation score acknowledges differences in diagnoses and outcomes from older lung candidates (≥12 years). Pediatric candidates receive preference ahead of adult candidates in the allocation of all pediatric donor lungs. Young pediatric candidates receive first preference for young pediatric (0–11 years) donor lungs, followed by adolescent candidates, and then adult candidates. Adolescent candidates receive first preference for adolescent donor lungs, followed by young pediatric candidates, and then adult candidates (Table 4).

Kidney transplantation

In the past, children under the age of 10 were considered to be the highest-risk patients with poorest graft survival. Although some hypothesized that this was due to an elevated immune response, other factors such as graft thrombosis and adverse donor selection proved to be more significant (10,11). In the modern era of surgical techniques and immunosuppression, these children now have the best long-term outcomes (12,13). Unfortunately, the teenage pediatric population has worse long-term outcomes (14), but they are improving (12). Research efforts need to identify the causes of poor outcomes for this age group and identify strategies to improve long-term graft survival.

Waiting list
Children do not contribute to the problem of increasing donor-recipient imbalance. The number of children entering the waiting list per year has increased relatively slowly over the past decade (Figure 7). In 2003, there were 773
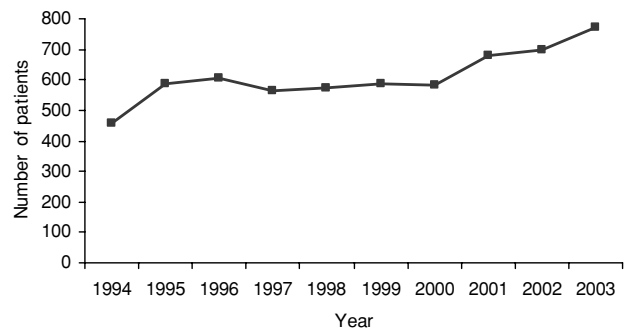
new pediatric registrants to the waiting list compared with 458 new registrants in 1994. There has been significant growth in the number of new adult registrants; 23 720 new registrants in 2003 compared with 16 075 in 1994. The greatest growth in new registrants in the pediatric population were those 11–17 years (536 new registrants in 2003 compared with 297 in 1994). In the adult population, the greatest growth has been in those aged 50–54 years (9552 new registrants in 2003 compared with 4844 in 1994) and those aged 65 years or greater (2924 new registrants in 2003 compared with 877 in 1994).

The percentage of children on the waiting list has declined. In 1994, children made up 1.8% of the waiting list; this dropped to 1.3% in 2003. In 1994, there were 467 children on the list compared with 25 360 adults. In 2003, there were only 710 children on the list compared with 53 521 adults. Again, the greatest growth was seen in registrants over 50 years old.

The mortality rates for children on the waiting list remained low, as they do not have the same comorbidity factors that result in increased mortality for adults. There were only seven deaths in children younger than 10 years and 12 deaths in those aged 11–17 years. The annual death rate per 1000 patient years at risk has declined by 50% over the past decade for children aged 1–5 years, from 110 in 1994 to 55 in 2003. For those 6–10 years, the annual death rate has ranged between 9 and 74 per 1000 patient years at risk over the past decade and currently is at 28. Similarly, the annual rate has fluctuated for those aged 11–17 years and currently is at 26 per 1000 patient years at risk.

Transplantation and survival
In 2003, 812 children received a kidney transplant compared with 672 in 1994. However, the increase seen over the years results primarily from a rise in living donor transplants, with 430 living donor recipients in 2003 compared with 303 in 1994 (Figure 8). Since 1995, more than half of all pediatric transplants have come from living donors.
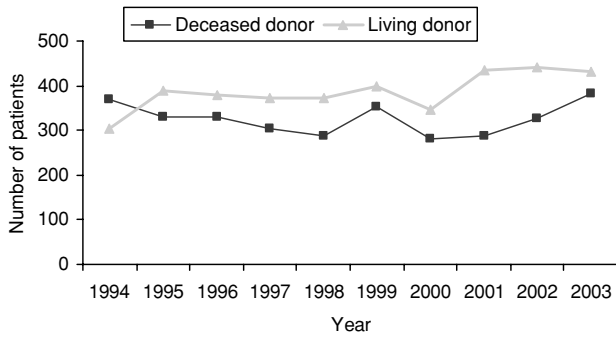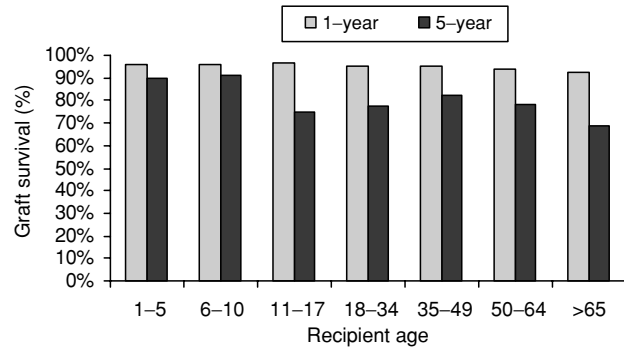
Figure 8: Pediatric recipients of deceased and living donor kidney transplants, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Tables 5.4a–5.4c.
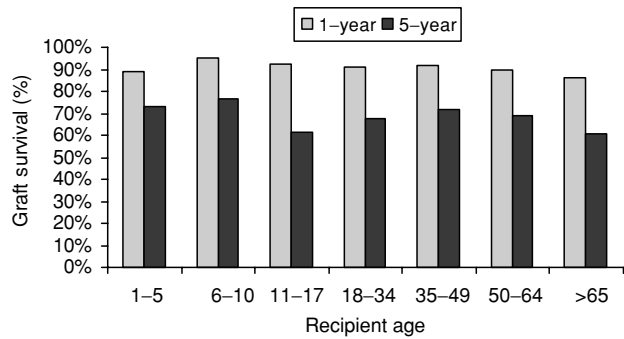
Figure 9: Adjusted 1- and 5-year graft survival of deceased donor non-ECD kidney transplants by recipient age. Source: *2004 OPTN/SRTR Annual Report*, Table 5.8a.

Figure 10: Adjusted 1- and 5-year graft survival of living donor kidney transplants by recipient age. Source: *2004 OPTN/SRTR Annual Report*, Table 5.8c.

The number of children who received a deceased donor renal allograft has been essentially stable over the past decade: 382 in 2003 versus 369 in 1994 (Figure 8). The number of adults receiving a deceased donor organ increased by 1013 over the past decade: 8283 in 2003 versus 7270 in 1994. Consistent with the aging of the waiting list, almost all of this increase has resulted from the higher number of deceased donor transplants being done in groups aged 50–64 years (1177 transplants) and 65 years and greater (710 transplants). The number of deceased donor transplants in the young and middle adult age groups has actually declined over the past decade, a decrease of 524 transplants in those aged 18–34 years and a decrease of 350 transplants in the group aged 35–49 years.

The ECD allocation policy for kidneys went into effect in October 2002. The system was designed to maximize procurement and placement of ECD organs while minimizing cold ischemia time. Patients are to be informed of the increased risk of graft failure associated with these organs and to give consent prior to being placed on the ECD list concurrent with their placement on the list for SCD kidneys. Prior to enactment of this policy, children were receiving ECD kidneys (14 in 1994), and African American children had a significantly higher likelihood of receiving an organ that met today's definition of an ECD kidney (15). In 2003, however, only one child was allocated an ECD kidney. It is worth noting that a review of the waiting list shows that a substantial percentage of pediatric patients were placed on the ECD list.

The short-term graft survival for pediatric recipients of both deceased and living donor kidneys is improving, and the difference in graft survival between the two categories of allografts is diminishing (16). One-year adjusted graft survival in children ≥1 year ranged from 89% to 95% for deceased donor non-ECD recipients (Figure 9) and was 96% in living donor recipients (Figure 10). This probably reflects advances in overall management, as well as improved selection of deceased kidney donors. In addition, these ex-

cellent short-term graft survival rates included teenaged children, with an adjusted graft survival rate of 96% at 3 months and 92% at 1 year for deceased donor non-ECD recipients and a rate of 98% at 3 months and 96% at 1 year for living donor recipients.

Improvement also has been impressive in long-term graft survival rates for young pediatric recipients of either living or deceased donor allografts. A decade ago, it was believed that children had the worst graft survival rates. But a recent analysis of the OPTN/SRTR data showed that young children have the best long-term graft survival of any age group (12,13). For living donor recipients, adjusted 5-year graft survival rates are the highest in children 1–10 years (90% for 1–5 years and 91% for 6–10 years). The next highest long-term graft survival rate is seen in the adult group aged 35–49 years. After the age group ≥65 years, teenagers have the next poorest 5-year graft survival rate at 75%, and young adults aged 18–34 years are at 78%.

Children ≤10 years have the best adjusted 5-year deceased donor non-ECD graft survival: 73% for those 1–5 years and 77% for those 6–10 years. Teenagers had a rate of 62%.
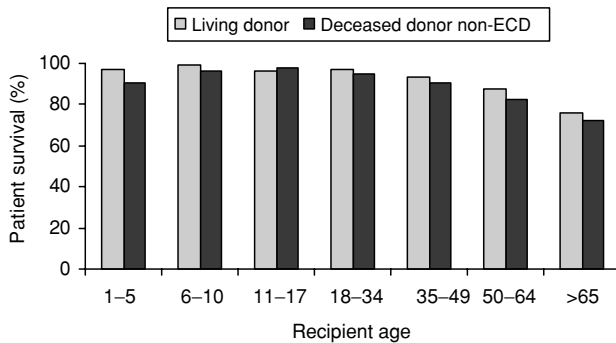
Figure 11: 5-year patient survival of living and deceased donor non-ECD kidney transplants by recipient age. Source: *2004 OPTN/SRTR Annual Report*, Tables 5.11a and 5.11c.

Adults with the best long-term graft survival were those aged 35–49 years (72%).

It is unfortunate that the superb long-term graft survival rates seen in young children are not seen in adolescent recipients. As mentioned above, teenagers have excellent graft survival rates at 3 months, 1 year and even 2 years, but their graft survival rate declines precipitously after that. The reasons for this decline are not entirely known, but contributing factors may include poor compliance with immunosuppressive regimens (17) and the high incidence of recurrence of focal segmental glomerulosclerosis seen in this patient population (18). However, the long-term graft survival rates for adolescents are improving. In the most recent report, the 5-year adjusted graft survival rate had increased to 75% in living donor recipients and to 62% in deceased donor non-ECD recipients. This improving trend was also shown in an SRTR analysis presented at the American Transplant Congress in 2003 (12).

As expected, the death rates of pediatric kidney transplant recipients at 3 months, 1 year and 3 years were generally lower than those of adults, and the 5-year patient survival rates were better (Figure 11). The adjusted 5-year patient survival rate of pediatric deceased donor non-ECD recipients ≥1 year ranged from 90% in children aged 1–5 years to 98% in teenagers. The adjusted 5-year patient survival rates were higher for living donor recipients, ranging from 97% in children aged 1–5 years to 99% in children aged 6–10 years.

The number of pediatric deceased donors continued to decline. However, the percentage of pediatric deceased donors (14%) is substantially greater than the percentage of pediatric candidates on the waiting list (1%) and greater than the percentage of pediatric recipients who receive a deceased donor kidney (4%). Kidneys from donors aged 11–17 years generally have the best graft survival rates of all donors, 73% at 5 years.

Graft survival has improved for kidneys from younger donors. The 5-year graft survival rates from deceased donors aged <1 year has risen to 60%, equal to that of donors aged 50 years or greater. More impressive is the continued improvement in 5-year graft survival from donors aged 1–5 years at 70%, which is approaching the long-term graft survival seen with adolescent donors at 73%. Therefore, the use of kidneys from those very young donors should be encouraged in selected recipients (19,20).

During the past decade, graft survival has improved substantially, with children under 10 years demonstrating the best long-term patient and graft survival rates among all transplant recipients. Adolescents have not fared as well; they have the worst long-term graft survival of any group, though it is improving. Studies are needed to determine which factors contribute to poor graft survival in adolescents and how they can be remedied. Children wait less time on the list than do adults, but this is appropriate, given the morbidities of delayed growth and development associated with ESRD, as well as with the difficulty children have with vascular access for dialysis.

Liver transplantation

Pediatric liver transplant recipients are a distinct population because of their unique distribution of diagnoses and indications for transplantation. There are also important age-related manifestations of end-stage liver disease that are reflected in different patterns of pre-transplant morbidity and mortality. These differences also affect short and long-term post-transplant survival. More importantly, given the longer expected useful life of a liver graft in this patient population, issues regarding quality of life and benefit from transplantation are key factors in assessing success of pediatric liver transplantation. Consequently, entities such as the SPLIT registry (4) and the National Institutes of Health-sponsored Biliary Atresia Research Consortium (BARC) have been developed to address the impact of these issues in children and to participate in the development of proposed allocation policies to serve this vulnerable patient population. As in past years, pediatric organ allocation and care processes are discussed and contrasted with adult counterparts, and the specific needs and outcomes of pediatric liver candidates and recipients are described in this section.

Waiting list
The incidence of end-stage liver disease requiring transplantation, as reflected in candidates listed for transplant, has demonstrated a significant increase from 1994, when there were 492 patients under 18 years listed for liver transplantation, to 2000 when 969 were listed (Figure 12). Since 2001, however, the number of listed pediatric candidates has remained relatively stable, with 922 patients listed in 2003, representing 5% of the entire liver transplant waiting list of 17 171 patients. The percentage of pediatric
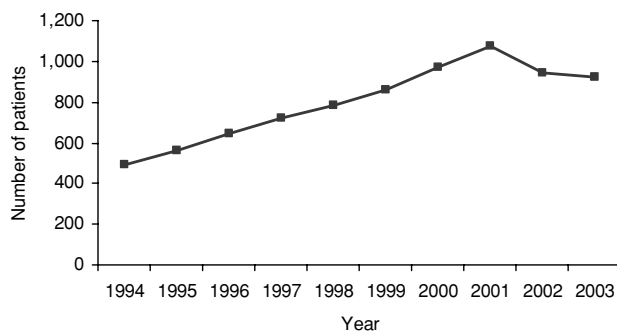
Figure 12: Pediatric patients on the liver waiting list, 1994–2003. Source: 2004 OPTN/SRTR Annual Report, Table 9.1.

patients on the waiting list has remained fairly stable since 1998, varying from 5% to 7% over the course of those years. The development of medical severity scoring systems (MELD and PELD) has led to the collection of data concerning severity of liver failure since 2002.

The annual incidence of patients with PELD meriting placement on the waiting list can be ascertained by noting the number of new registrants placed on the liver transplant waiting list. This has remained stable with 881 new pediatric registrants in 2003, compared with 880 in 2002. Previous reports had described a notable decrease in registrations in the adolescent age group (11–17 years). Stability in the proportions of pediatric candidates across age groups may reflect the impact of the PELD scoring system over the course of the most recent 2 years. Because allocation is based on the medical severity scoring system, listing prior to clinical deterioration plays a less important role in practice patterns.

The median time to transplant for pediatric registrants has not changed substantially according to age groups since 1993. In 2003, the median time to transplant for children age 1–5 years was comparatively longer (277 days) than times to transplant for infants (140 days) and longer than for the older pediatric age groups of 6–10 and 11–17 years (144 and 168 days, respectively).

Since the inception of MELD/PELD on February 27, 2002, the median time to transplant for pediatric registrants has remained relatively stable in the subgroups of patients with PELD scores of <11 (204 days), 11–20 (117 days) and 21–30 (237 days). However, for patients with PELD scores of >30, the median time to transplant was much longer in 2003, 118 days compared with 15 days in 2002. Speculation regarding the cause for this discrepancy resides in the use of exception points and varying criteria for Status 1 listing among different regions.

Although the absolute number of deaths generally increased throughout the decade, annual death rates have decreased steadily from 1994 (225 deaths per 1000 patient years) to 2001 (124 deaths per 1000 patient years). There has been a corresponding decline in the number of deaths of the pediatric candidates on the waiting list, with 86 patients dying in 2003 compared with 103 patients in 2002. This decline parallels the overall decline in death rate. The annual death rate per 1000 patient years generally has decreased throughout the decade for all pediatric waiting list candidates over age 1 year; however, for children younger than 1 year, the death rate in 2003 was 818 per 1000 patient years, much higher than the overall death rate for all candidates and reflecting a persistent rise for this group in the past several years. This higher death rate in infants has previously been ascribed to a relative increase in mortality due to medical management issues and the availability of finding suitable grafts for this size patients. The appropriate PELD score for these small infants may not adequately reflect their risk of dying, particularly when awaiting combination organs such as liver and intestine transplants, for which most of the patients are in the <5-year age group.

Transplantation and survival

There were 478 children under the age of 18 years who received a deceased donor liver transplant in 2003, which is comparable to the 492 children under the age of 18 years transplanted in 1994 (Figure 13). However, this represents a progressive proportional decrease in the deceased donor liver transplants allocated to children, from 14% in 1994 to 9% in 2003. The proportion of patients within each age group has been consistent since 1998, ranging between 1% and 4%.

Living donor liver transplantation has been performed in children since 1989; the introduction of living donor transplantation to adults occurred on a consistent basis after 1998. The utilization of this modality in children has remained relatively stable since 1994 (Figure 13), whereas in adults it has shown clear growth. In 2003, 67 children received living donor liver transplants, accounting for 21% of all living donor transplant procedures performed. The majority of these procedures (87%) were performed in children under 5 years old. There has been a decrease in the number of total pediatric living donor procedures performed since 2001 (107 in 2001and 72 in 2002). This may be a reflection of the increased utilization of split liver grafts satisfying some of the demand for donor organs. The utilization of living donor liver segments has occurred over a wide range of both MELD and PELD scores, as well as patients with HCC stage T1 and T2.

Annual death rates per 1000 patient years in the first year after transplant increase with age in the adult subcategories. There have been general but inconsistent decreases over time in the death rates in the pediatric age ranges. The drop in annual post-transplant death rates in pediatric patients has been especially notable in the <1-year age group since 2001.
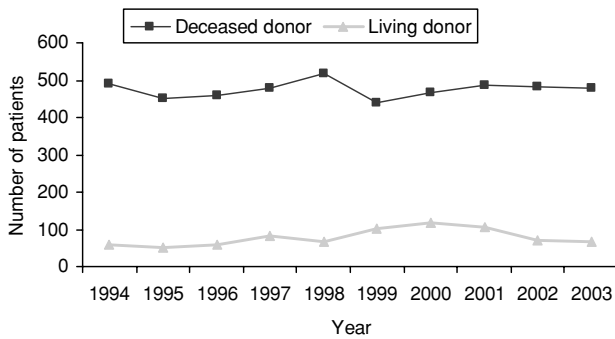
Figure 13: Pediatric recipients of deceased and living donor liver transplants, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Tables 9.4a and 9.4b.
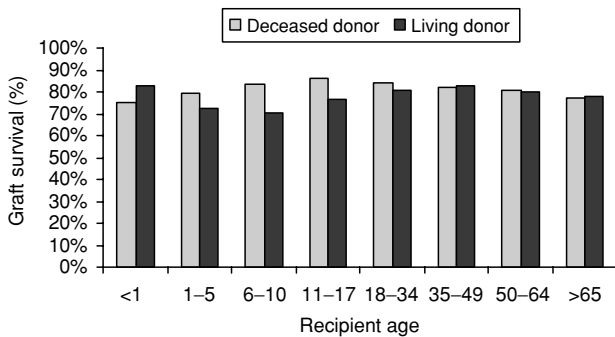
Figure 14: Adjusted 1-year graft survival of deceased donor and living donor liver transplants by recipient age. Source: *2004 OPTN/SRTR Annual Report*, Tables 9.8a and 9.8b.

Adjusted deceased donor liver allograft survival at 3 months, 1 year, 3 years and 5 years was lower in transplant recipients <1 year old compared with older pediatric recipients. The best short- and long-term graft survival among all adult and pediatric patient age subgroups was observed in the 6–10 and 11–17 age groups, where graft survival was superior across all time points. Analysis of survival as a function of donor type revealed superior patient and graft survival for children younger than 1 year with an allograft from a living donor compared with a deceased donor; this trend was not detected for any other age group (Figure 14). Similar patient and graft loss trends in this younger pediatric cohort from either a living donor or a deceased donor have been reported previously (4,21).

Intestine transplantation

There have been dramatic improvements in intestinal transplantation since the early 1990s in terms of surgical technique, immunosuppression and survival. Currently, intestinal transplantation is indicated for patients with short gut syndrome who have had serious complications of their total parenteral nutrition (TPN). Historical limitations

to success have been infection and rejection, principally due to complications of systemic immunosuppression. However, recent advances in immunosuppressive management have gradually improved both patient and graft survival. Another challenge has been the lack of availability of suitable organs for this patient population, since they may require intestines together with other intra-abdominal organs, principally the liver, due to TPN-induced cirrhosis. Both adult and pediatric candidates who develop TPN-induced cholestatic liver disease have a high mortality rate on the waiting list when compared with patients awaiting liver transplantation alone. Modifications of surgical techniques have allowed for increased utilization of intestinal organs alone or in combination with other organs in this patient population.

Waiting list

From 1994 to 2000, there was a gradual increase in the total number of adult and pediatric patients listed for intestinal transplantation. However, this number remained relatively stable between 2001 (168 candidates) and 2003 (172 candidates). The proportions of candidates by age group have also been unchanged since 2001, with more pediatric patients than adults listed. This difference may reflect referral standards as well as reimbursement standards. Intestinal transplantation has been reimbursed at a higher rate in pediatric patients, although most of these transplants may be performed at a financial loss. It was only after Medicare approved intestinal transplantation as a covered procedure in 2001 that substantial adult access to intestinal transplant procedures occurred. As of 2003, for candidates awaiting intestine-only transplantation, there had been no major changes in listing status with regard to how they are assigned urgent, non-urgent or inactive status. For patients awaiting the intestine in combination with a liver graft, significant allocation changes followed the introduction of MELD/PELD based allocation. The initial MELD/PELD allocation policy did not adequately address the incremental severity of pre-transplant death rates for patients with intestinal failure and associated end-stage liver disease. In-depth analysis performed by the SRTR in pediatric intestinal failure patients awaiting the intestine plus a liver graft revealed that, though the PELD scoring system was predictive of mortality in patients awaiting intestine plus a liver graft, this mortality risk was significantly higher when compared with patients awaiting a liver or intestine transplant. Recently approved changes in organ allocation policy reflecting this new information have allowed patients awaiting liver and intestine transplants to receive an increased PELD score equivalent to a 10% higher risk of the 3-month mortality. Additional guidelines regarding Status 1 listing for patients meeting criteria who are awaiting liver and intestine grafts are currently under discussion.

The number of new intestinal transplant registrants in the various adult and pediatric age ranges has remained relatively stable since 2000 and may reflect actual referral

patterns, as well as the limited number of centers performing this procedure as of 2003. For similar reasons, the median time to transplant, which reflects the difficulty facing these candidates awaiting intestinal transplantation, has remained high, and for some age groups, it has been over 300 days. Children of all ages wait longer for intestine transplants than do adults.

These long waiting times for intestinal transplantation with the added liver disease severity translate into very high waiting list mortality. In 2003, the annual death rate per 1000 patient years at risk was 295 for the total candidate group. These death rates were even higher in the <1 year and 1–5 year age groups (635 and 327, respectively). It is evident that these smaller subgroups of pediatric patients have a higher risk of mortality due to inadequacy in securing appropriate-sized deceased donors before clinical deterioration occurs. In 2003, there were 6455 deceased donors, of whom 257 were <6 years of age. However, only 60 donors in this age group became intestine donors. Changes in allocation and improvements in technical considerations regarding reduced-sized grafts may have contributed to the slight decrease in the waiting list death rate in this subgroup. The discrepancy between the number of deceased donors, candidate waiting times and candidate waiting list mortality reflect present allocation rules that have prompted changes in the PELD scoring system; however, further changes may be required in order to address this high mortality.

Transplantation and survival

In 2003, there were 112 intestinal transplant recipients, of whom 71 were pediatric recipients. This accounted for 63% of all intestinal transplant procedures performed that year. Within the pediatric population, 75% of these patients were <6 years of age. The incidence of intestinal transplants per 1 million population has remained relatively stable since 2001 for the entire group of patients and was 0.40 in 2003. Comparative rates for 2003 for liver transplantation (19 per 1 million population) and kidney transplantation (52 per 1 million population) are much higher. This may be because of a combination of limited access to organs, limited numbers of centers performing the procedure and a smaller number of eligible candidates.

Over the past 10 years, the outcomes after intestinal transplantation have been gradually improving, particularly in the last year: in 2003, the overall first year post-transplant death rate per 1000 patient years at risk was 310, a marked drop from 2002 (404). Post-transplant death rates tend to be higher in pediatric patients <10 years old than in older children. Graft survival rates after intestinal transplantation for all age groups at 3 months, 1 year, 3 years and 5 years were 81%, 66%, 48% and 34%, respectively.

Overall, adjusted patient survival rates for the most recent cohorts following intestinal transplantation at 3 months,

1 year, 3 years and 5 years were 89%, 77%, 61% and 49%, respectively.

The most recent publication from the International Intestinal Transplant Registry shows a total of 606 transplants performed in 560 pediatric recipients in 42 centers, with survivors accumulated at 290 (6). Though there had been a gradual increase in transplants performed, this has stabilized since 2001 at about 80 transplants per year, with most recipients being within the 1–13 year age group. Half (50%) of patients required a liver in association with their intestinal graft, and 37% of the patients required an isolated intestinal graft. Variations of the multiorgan intra-abdominal procedure were performed in 13% of the recipients. Outcomes have improved since 2000, with improvement factors related to center volumes and also to improvements in immunosuppressive regimen. Consequently, the findings of this registry mirror data presented in this report, as well as reports from large single-center studies.

The reasons for improvement have been multifactorial and include better access to organs, which is reflective of changes in organ allocation policy; experience with overall management of these patients in larger centers; and introduction of additional immunosuppressive medications including rapamycin, thymoglobulin and the interleukin-2 receptor antibodies. These changes have led not only to a decrease in incidence and severity of rejection due to graft loss, but also to a decrease in patient morbidity from opportunistic infections and to reduced early and late toxicities from immunosuppressive medications. Early treatment with preemptive management of both cytomegalovirus and Epstein–Barr virus likewise have reduced mortality due to infections with these viruses after intestinal transplantation.

These data demonstrate that, although the population of wait-listed candidates and recipients is stable, the benefit from transplantation has improved as reflected in improved patient and graft survival. The majority of these patients have been transplanted in a limited number of centers in the United States, and this may contribute to high pre-transplant waiting list mortality given that the organ allocation policies have not allowed for wider sharing of these pediatric donor organs. It remains to be seen if further allocation policies will change this pre-transplant outcome. Overall outcomes for intestine transplantation, both short- and long-term, appear to be improving.

Heart transplantation

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 2003 was 244, 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 the group aged 1–5 years, followed by adolescents aged 11–17 years. There were fewer infants on the list this year compared with previous years (16 versus an average of 32 in the preceding 4 years). This decline may reflect an increase in palliative surgical reconstruction as initial therapy for complex heart lesions such as hypoplastic left heart syndrome, rather than transplantation (22).

Although children in all age groups have substantially shorter waiting times (median waiting times range from 59 to 107 days) than do adults, they have a substantially greater risk of death while on the waiting list. The highest death rate is among infants <1 year, in 75% of whom the indication for placement on the waiting list is a congenital heart anomaly (23). In older children and adolescents, cardiomyopathy is the leading indication for transplantation; however, congenital cardiac anomalies continue to account for a substantial minority of transplants even in this older group. This observation is important because cardiac anatomy, in addition to size, precludes the use of ventricular assist devices for many children with end-stage cardiac failure. This, in addition to scarcity of organs and the inherent hemodynamic instability of complex congenital heart disease, undoubtedly contributes to their high waiting list mortality.

Transplantation and survival

Over the past 10 years, children have accounted for approximately 12% of all heart transplant recipients. 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 may be related to changes in the surgical management of newborns with congenital heart disease, as noted above; to changes in heart allocation policy that favor adolescents; and to other unidentified causes. 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 youngest children likely reflects the high incidence of moderate-to-severe congenital heart disease in infants (6 per 1000 live births) (24), which is the indication for transplantation in 66% of recipients in this age group (25).

Over the past 10 years, recipients younger than 1 year have generally had a higher annual death rate in the first year after heart transplantation. An analysis performed by the PHTS suggests that this high early mortality is linked to the diagnosis of congenital heart disease and specifically to the diagnosis of hypoplastic left heart syndrome (5). Adjusted patient survival at 3 and 5 years continues to be slightly worse among those transplanted as infants (Figure 15). Regardless of age at transplant, those trans-
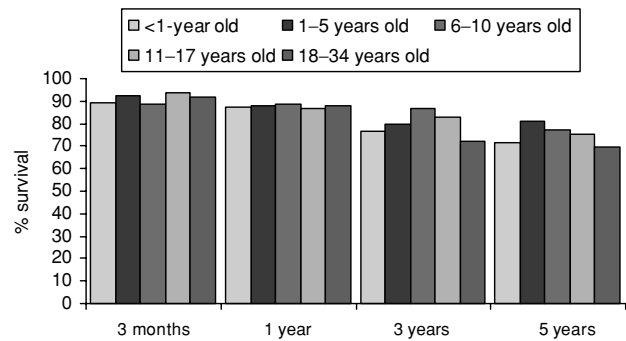
Figure 15: Adjusted patient survival for children and young adult recipients of heart transplants. Source: *2004 OPTN/SRTR Annual Report*, Table 11.11.

planted for congenital heart disease have worse patient survival.

These data suggest many avenues for efforts that might decrease pre- and post-transplant mortality among children with end-stage cardiovascular disease. There are several priorities, among them increasing organ availability through increased donation and recovery, developing techniques to circumvent immunologic barriers to transplantation, and perhaps an increased use of DCD organs. The development of circulatory support devices suitable for infants and small children, as well as devices suitable for those with abnormal cardiac anatomy or abnormal circulatory physiology, could contribute to improved outcomes at every step in the transplant process. The potential impact of these devices is far-ranging; they would increase the number of candidates who could be bridged to recovery and so avoid transplantation; increase the number of recipients who, in the absence of recovery, survive until an organ becomes available; improve the health status of those who come to transplantation by preventing the end-organ damage that results from circulatory insufficiency; and support heart recipients through a period of early graft dysfunction. Finally, improvement of the long-term outcome of pediatric heart transplantation will depend upon the development of more effective and less toxic medical regimens to protect the transplanted heart from chronic immunologic injury.
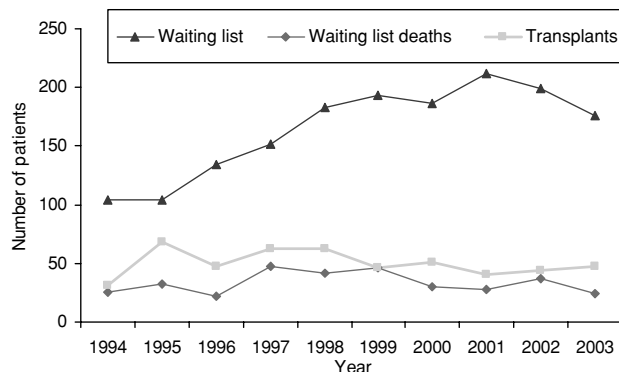
Lung transplantation

The population of pediatric patients undergoing lung transplantation is somewhat different than that of adults. According to SRTR analyses, from 2000 to 2003, cystic fibrosis (CF) accounted for nearly 44% of patients receiving lung transplants between the ages of 1 and 10 years and 77% of patients ages 11–17 years. These percentages are similar to those seen in international reports (23). In comparison, in 2003, CF made up only 16% of the total population of deceased donor lung transplant recipients. In addition, the infant and toddler population of lung transplant recipients includes many disease processes unique to infancy,

including surfactant protein B and C disorders (26,27), irreparable congenital cardiac or pulmonary vascular abnormalities and interstitial lung diseases (ILD) with histologies distinct from adult ILD (28,29). When considered in light of the relatively small numbers of patients coming to lung transplant in the pediatric population, these differences make comparisons with waiting list mortality and post-transplant survival in adults challenging. This has been particularly difficult with recent attempts to model these outcomes for organ allocation purposes.
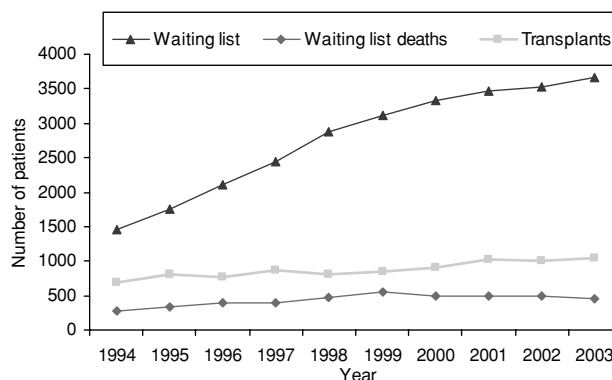
Waiting list

In comparison with 2002, the total number of pediatric lung transplant candidates continued to decline in 2003 (Figure 16). In addition, the percentage of pediatric candidates among all lung transplant candidates has declined over the past 10 years from 7% in 1994 to 5% in 2003. Over the past 5 years, this decline can be accounted for both by decreases in the number of children 6–10 years old awaiting lung transplant and by increases in the number of adults, particularly in the 50–64 year age group, waiting for transplant (Figure 17). There are several possible reasons for this decline. One likely factor is improvement in therapy for CF and pulmonary hypertension. Data from the Cystic Fibrosis Foundation registry indicates that both lung function and survival as a function of age have improved over the past 10 years (30). The advent of pulmonary vasodilators such as prostacyclin, bosentan and sildenafil have improved the survival of pediatric patients with pulmonary hypertension (31). It is also possible that referrals for lung transplant in pediatric age groups have been influenced by the recognition that lung transplant remains a treatment rather than a curative procedure.

Evaluation of the time to transplant for lung is difficult, as median values are not available for the majority of age groups in the past 5 years; this is likely because of long waiting times and relatively high waiting list mortality. However, the 25th percentile of time to transplant is available for all age groups in the cohort of patients listed for trans-

Figure 17: Adults listed for lung transplant, dying on the waiting list, and transplanted, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Tables 12.1, 12.3 and 12.4.

plant in 2002. With the exception of the 11–17 age group, values for other pediatric recipients were lower than those for adult age groups. In contrast, the values for the 11–17 age group were among the highest, probably reflecting competition with adult candidates. Nonetheless, caution is required when drawing conclusions from these data, as the values over time are quite variable across all age groups. This is likely due, in part, to substantial regional variability in waiting times (32).

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 (Figures 16 and 17). However, in 2003, waiting list mortality for the 1–5 and 6–10 year age groups was 61 and 38 deaths per 1000 patient years at risk, respectively. These are the lowest values among any age group and the lowest values for these pediatric age groups over the past 10 years. Recognizing that these data are based on a relatively small number of patients, the slight increase in the number of lung donors under age 11 years over the past 4 years may have contributed to improved organ availability. In contrast with other pediatric candidates, however, the death rate for adolescent lung transplant candidates remained higher than that of any other age group, with the exception of candidates aged 65 years or older. Contributing factors include the unpredictability of the course of CF lung disease, coupled with competition with adults for deceased donor organs.

Transplantation and survival

In 2003, there were 47 pediatric lung transplants (both deceased and living donor). This represents 4% of all lung transplants and is increased slightly compared with 2002. However, it remains well below the peaks of 68 transplants and 8% of all transplants in 1995. This decline cannot be accounted for by changes in any one age group and is most likely because of steady increases in the number of adults

Figure 16: Children listed for lung transplant, dying on the waiting list and transplanted, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Tables 12.1, 12.3 and 12.4.

listed for lung transplant coupled with stable to declining pediatric listings.

The number of pediatric living donor lobar lung transplants (LDLLT) remained stable in 2003, as did the number of LDLLT in adults. CF remained, by far, the most common diagnosis in patients receiving LDLLT. Overall, the number of LDLLT remains well below the peak of 30 in 1998. In addition, for the first time since 1994, none of the LDLLT recipients had a prior lung or heart–lung transplant. The decrease in LDLLT is likely related, in part, to the technical and ethical complexities of the operation, coupled with the recognition that short- and long-term survival may be lower than that of deceased donor recipients. The incidence of lung transplantation in all pediatric age groups remained stable and well below the incidence in the adult population.

The annual death rate in the first year after deceased donor lung transplantation in 2002 was 215 per 1000 patient years at risk, an 18% decrease compared with 2001. Patients with a history of prior transplant, on life support, or hospitalized in intensive care continued to have the highest death rates. Overall, death rates in deceased donor recipients, including all pediatric age groups, have decreased between 1994 and 2002. For pediatric recipients transplanted in 2002, deaths occurred in the 11–17 year age group with a rate of 197 per 1000 patient years at risk; this is down from 241 in 2001. Over the past 4 years, there have been only 18 deaths in the first year after deceased donor transplants in the 109 pediatric recipients aged less than 11 years. Possible contributing factors for this change include decreased early graft dysfunction related to improvements in preservation solutions and prevention of acute rejection, perhaps because of increased use of IL-2 receptor antagonists as induction agents. The annual death rate in the first year after LDLLT also decreased recently, dropping from 456 per 1000 patient years at risk in 2001 to 184 in 2002. The relatively small numbers of patients make interpretation difficult.

Long-term survival after lung transplantation across all age groups remains poor compared with heart, liver and kidney transplantation. Unadjusted 10-year graft survival is 22% compared with 47% for deceased donor heart transplant recipients. Graft survival after lung retransplantation remains worse than primary transplantation. Small numbers mandate caution in interpreting data for pediatric age groups in this context. However, at 3 years, all pediatric age groups had adjusted graft survival rates for deceased donor recipients comparable to those of adults. Five-year adjusted graft survival, however, appears to be lower for all except the 1–5 year age group (Figure 18). This observation is consistent with worse outcomes for other solid organs in the adolescent age group. Five-year adjusted graft survival in all LDLLT recipients is 25% compared with 44% in deceased donor recipients, but adjusted graft survival of pediatric LDLLT recipients is comparable to that of pediatric deceased donor recipients at 5 years.
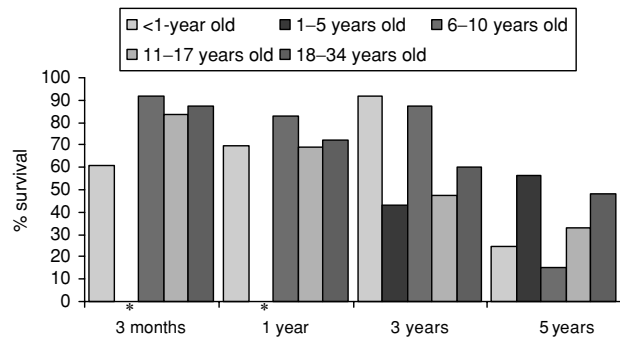
Figure 18: Adjusted lung graft survival for children and young adults. * Values not determined due to insufficient follow-up. Source: *2004 OPTN/SRTR Annual Report*, Table 12.8a.

Lung transplantation remains a viable therapy for end-stage pediatric pulmonary parenchymal and pulmonary vascular disease. A decline over the past few years in the number of pediatric patients listed for transplant likely reflects a combination of improved therapy for these diseases, coupled with recognition that long-term survival remains poor (31). Waiting list mortality for adolescent candidates remains higher than most other age groups. The benefit given to pediatric recipients in the recently approved revision to the lung allocation policy should help reduce this disparity. Five-year adjusted graft survival in the majority of pediatric age groups was lower than that of adult deceased donor recipients. Although the relative numbers are small, exploration of possible causes is warranted. Living donor lobar transplant remains an option for patients requiring lung transplantation. In contrast to adults, the 1-year death rates and 5-year adjusted graft survival rates for pediatric LDLLT recipients were comparable to cadaveric organ recipients. However, it is likely that the technical and ethical challenges associated with LDLLT will limit significant expansion of its use. Finally, although short-term survival after lung transplantation has improved over the past 10 years, bronchiolitis obliterans and other late complications continue to prevent lung transplantation from achieving long-term survival comparable to other solid organ transplants. Because relatively few pediatric lung transplants are done each year, learning from clinical experience will mandate multicenter collaborations and standardization of care protocols. This approach, combined with the development of basic science partnerships to leverage emerging technologies such as molecular genomics and proteomics, should increase our understanding of the basic processes involved in long-term graft acceptance or failure and ultimately lead to improved therapies and outcomes.

Heart–lung transplantation

Waiting list
During the past 6 years the number of heart–lung waiting list patients of all ages has been steadily decreasing, from

a peak of 250 registrants in 1998 to 189 registrants in 2003. Consistent with this trend is the steady decline in the number of pediatric heart-lung patients on the waiting list during this time period, from 51 (20% of total) in 1998 to 27 (14% of total) in 2003. Of the 27 pediatric patients on the waiting list in 2003, there were no infants (age <1 year), and children between 11 and 17 years made up the largest age group (n = 13). In 2003, there were only 15 new pediatric heart-lung registrants, down from 20 such registrants in 2002 and the lowest number in 10 years. It is unlikely that this can be attributed wholly to the changing preference for the use of lung over heart-lung transplantation in patients with CF, as the number of new pediatric lung waiting list registrations has also decreased over recent years. There may be a connection between this decrease and the small number of centers performing pediatric heart-lung transplant procedures; high death rates on the waiting list and poor long-term survival post-transplant may also discourage potential registrants.

As in years past, children on the heart-lung waiting list had higher annual death rates per 1000 patient years at risk compared with adults. In 2003, the overall waiting list death rate among all heart-lung transplant candidates was 101 per 1000 patient years at risk. For children aged 11–17 years (the only pediatric age group for whom these data are available), this rate was higher (217) compared with all adult age groups (for whom the rate ranged from 60 to 139). The increased death in children while waiting may be related to several factors. Children awaiting thoracic organ transplant are more likely to be in on life support in the ICU (33); suitable cardiac assist devices are lacking for smaller children; and possibly pediatric candidates are in competition with adults for organs.

Transplantation and survival

During the past 10 years, the annual number of pediatric heart-lung transplants performed has ranged from 5 to 15, representing 8–26% of all heart-lung transplants. Of the 29 heart-lung transplants performed in 2003, 6 (21%) were in children, with the majority (n = 5) performed in children aged 11–17 years. Because of the small number of pediatric heart-lung transplants, time to transplant and annual death rates after transplant cannot be calculated.

There are limited data on long-term pediatric heart-lung graft and patient survival, and it is difficult to analyze outcomes for so rare a procedure. Heart-lung recipients in the 11–17 years age group have lower adjusted graft and patient survival at 3 months and 1 year compared with the overall heart-lung transplant population; however, they have higher graft survival rates (63% versus 45%) and patient survival rates (67% versus 46%) at 3 years. These data suggest that for this pediatric age group, although there is substantial early mortality, the decline in survival beyond 3 months is minimal to at least 3 years. Five-year data are available only in the 1–5 year age group, with ad-

justed graft and patient survival of 40%. This is probably comparable to the 37% adjusted graft and patient survival in the overall heart–lung transplant population.

Summary

Overall, children, especially young children, have excellent long-term graft survival rates. These rates are often equivalent to or exceed the outcomes of transplantation in adults. In general, children can no longer be considered to have excessive risk based solely on their age at the time of transplantation. That said, the transplant community recognizes the unique challenges faced by pediatric candidates with end-stage organ failure. In liver, heart and, most recently, lung allocation, the need to recognize differences between children and adults has been amplified as these respective allocation systems have moved toward greater specificity in defining medical urgency. Pediatric kidney recipients under the age of 10 years now have the best long-term outcomes. But graft survival rates for teenage kidney recipients are not as encouraging, and more research is needed to understand this trend. The numbers of pediatric patients on the waiting lists for liver and heart are relatively stable. Annual death rates have decreased steadily for liver recipients, but infant heart recipients experience high mortality in the year after transplant, suggesting the need to increase donation and develop circulatory support devices.

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