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Kidney transplantation in children

Vikas R. Dharnidharka
Washington University School of Medicine in St. Louis
Paolo Fiorina
Harvard Medical School
William E. Harmon
Harvard Medical School

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Kidney Transplantation in Children

Vikas R. Dharnidharka, M.D., M.P.H., Paolo Fiorina, M.D., Ph.D., and William E. Harmon, M.D.

From the Division of Pediatric Nephrology, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis (V.R.D.); the Division of Nephrology, Boston Children's Hospital and Harvard Medical School, Boston (P.F., W.E.H.); and the Division of Transplant Medicine, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale San Raffaele, Milan (P.F.). Address reprint requests to Dr. Harmon at the Division of Nephrology, Boston Children's Hospital and Harvard Medical School, 300 Longwood Ave., Boston, MA 02115, or at william.harmon@childrens.harvard.edu.

Drs. Dharnidharka and Fiorina contributed equally to this article.

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Since the first successful kidney transplantation in 1954,[1] kidney transplantation has become the best treatment for adult patients with kidney failure. However, early pediatric kidney transplantation was complicated by technical, immunologic, and logistic problems, all leading to worse patient and graft survival among children than had been observed among adults. Over the past 15 years, a number of advances have greatly improved patient and graft survival among children with kidney transplants.[2,3]

Some aspects of clinical kidney transplantation are similar in children and adults. The immunosuppressive medications and regimens used are similar, creatinine is the major serum biomarker, acute rejection is determined primarily by means of biopsy with the use of the Banff criteria for the classification of rejection (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), and the rejection mechanisms of the kidney graft are generally similar.[4-7] However, many other aspects differ between children and adults — immunologic factors, the primary kidney diseases leading to kidney failure, often with associated urologic issues, and the immunizations that are required before transplantation. Allocation policies regarding kidneys from deceased donors, surgical techniques in small children, and drug metabolism have distinctive aspects in children. The frequency of primary viral infection after transplantation is higher for children than for adults. Furthermore, children are developing so their linear-height growth needs to be optimized and their neurocognitive development fostered. Ultimately, the child with a transplant must be readied for the transition to adult care. This review considers the differences between children and adults undergoing kidney transplantation that necessitate alternative approaches in children and have resulted in innovations and important advances.

THE IMMUNE SYSTEM IN CHILDHOOD

The immune system undergoes profound modification from birth to adulthood, during which period the absolute counts and percentages of circulating T-cell and B-cell subtypes and other immunologic features (Fig. 1)[8,9] slowly yet continuously evolve, accompanied by an increase in alloreactivity. Thymic output is robust during childhood but diminishes during adulthood.[10] In adults, thymic atrophy and continuous antigen exposure shift the composition of the T-cell pool from naive to memory T cells.[10]

As compared with adults, children have an alloimmune response characterized by low expression of the costimulatory ligand CD40L on T cells,[11] fewer antigen-specific T-cell precursors,[12] type 2 helper T-cell (Th2)–skewed immunity with higher peripheral levels of Th2 and lower levels of the type 1 helper T-cell (Th1) cytokines,[13] reduced T-cell effector function,[14] an overall higher percentage of the tolerogenic dendritic-cell subset,[15] and lower titers of anti-HLA antibodies before transplantation[16] (Fig. 1). Younger recipients have better outcomes after transplantation, perhaps suggesting that the more naive immune system provides an advantage (Fig. 2A).

Figure 1 (facing page). Immunologic Mechanisms, Observed in Pediatric Kidney-Transplant Recipients, That May Be Beneficial for Children.

Important features of the naive pediatric immune system can be found in T cells (e.g., reduced CD40L expression, a type 2 helper T-cell–skewed profile, and reduced effector markers; Panel A), macrophages (e.g., reduced HLA-DR expression and reduced costimulatory molecule expression; Panel B), B cells (e.g., fewer mature B cells and reduced anti-HLA antibody production; Panel C), and dendritic cells (e.g., fewer mature dendritic cells; Panel D). T cells in the recipient may be primed by donor-derived antigen-presenting cells, thus initiating rejection of the kidney allograft. Primed T cells release proinflammatory cytokines and facilitate B-cell activation in the recipient. Dendritic cells in the recipient may also activate T cells by means of indirect allorecognition, leading to chronic allograft rejection. Activated macrophages in the recipient sustain inflammation through the release of proinflammatory cytokines. TCR denotes T-cell receptor, TLR4 toll-like receptor 4, and TNF-α tumor necrosis factor α.

CONSIDERATIONS BEFORE TRANSPLANTATION

CAUSES OF KIDNEY FAILURE

The most common primary causes of kidney failure are congenital or inherited disorders such as renal dysplasia, obstructive uropathies, or reflux nephropathy in young children[19] and acquired glomerular diseases such as focal segmental glomerulosclerosis and lupus nephritis in older children. In contrast, the most common primary renal diseases that lead to end-stage kidney disease in adults are diabetic nephropathy, hypertension, and autosomal dominant polycystic kidney disease, which rarely cause end-stage kidney disease in children.

UROLOGIC ISSUES

Abnormal bladder function may accompany kidney failure in children. In patients with a posterior urethral valve, an open vesicostomy may need to be performed early in life to decompress a dysfunctional bladder. An open vesicostomy may be kept in place for many months after transplantation.[20] Children with small bladder capacity may benefit from a bladder augmentation in which segments of ileum, stomach, or appendix are used to create a permanent cutaneous conduit that enables the child to be continent and to have clean, intermittent catheterization.[20] Children with obstructive uropathy have a higher rate of urinary tract infection after transplantation than children with other causes of end-stage kidney disease,[21] possibly necessitating lifelong antimicrobial prophylaxis.

IMMUNIZATIONS

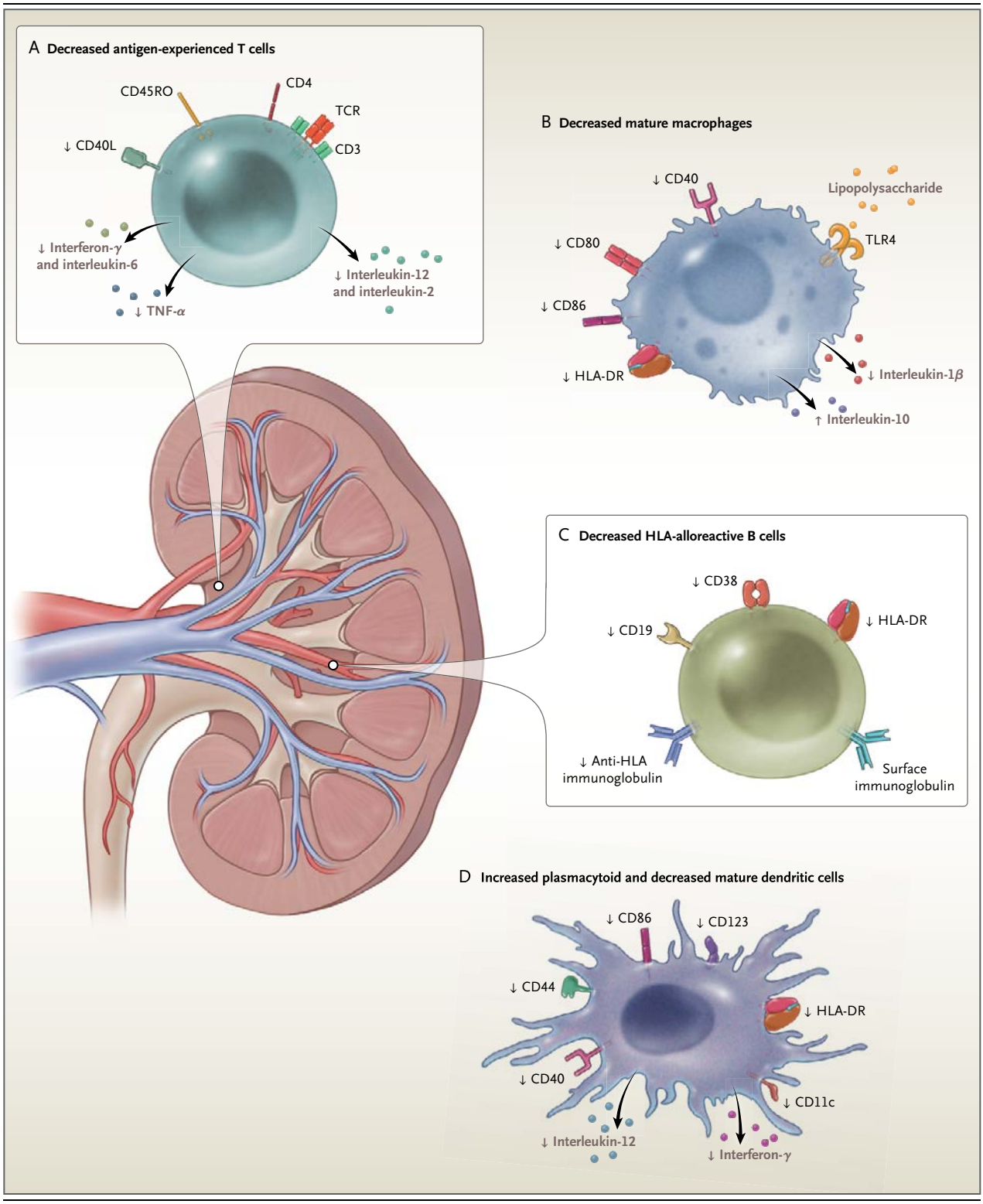
Children require multiple vaccinations during early childhood to protect them from preventable infectious diseases. However, vaccines may not be effective if administered to an immunocompromised patient. Therefore, a vigorous effort to immunize children completely before transplantation is critical. Because children with end-stage kidney disease often have a suboptimal immune response and reduced duration of immunity, higher initial doses, extra doses, and antibody titer monitoring with booster doses of vaccines may be needed. In the period after transplantation, the administration of live vaccines is generally avoided,[22] but other immunizations may be given after immunosuppressive medications have reached low maintenance levels, typically at 6 to 12 months after transplantation. Injectable influenza vaccine should be given annually.

PRIORITIZED ALLOCATION OF KIDNEYS TO CHILDREN

The allocation of kidneys from deceased donors involves a complex algorithm that includes the degree of anti-HLA sensitization, the need for multiple donor organs, the blood-group match, the relative HLA match, and the waiting time accrued by the candidate recipient. Children make up a small fraction of persons awaiting kidney transplantation, and they have been afforded exceptional societal benefits in many countries. Thus, allocation policies regarding organ transplants have preferentially allocated higher-quality kidneys from deceased donors to children in relatively prompt fashion,[23] with resultant mean waiting times as short as 3 months in some regions.[24] However, such policies have led to a decline in the donation of kidneys from living donors and to a greater proportion of poorly HLA-matched kidney transplants from deceased donors in children.[25]

SURGICAL ISSUES AT TRANSPLANTATION

Unlike heart and liver allografts, the kidney allograft is placed in a different location from the failed native organ, and the native organ is often



left in place. Thus, size and age matching is generally not required in kidney transplantation. In fact, matching very young donors to very young recipients was associated previously with a very high rate of graft loss, often due to thrombosis.[26] On the basis of those adverse results, pediatric

Figure 2 (facing page). Graft and Patient Survival and Rates of Rejection and Post-Transplantation Lymphoproliferative Disorder (PTLD).

The rates of graft survival at 10 years after receipt of a transplant from a living donor are lowest among recipients older than 65 years of age and adolescents and are highest among the youngest recipients (Panel A). The data are from the Scientific Registry of Transplant Recipients 2012 annual report.[17] Graft survival has improved for transplants from living donors and deceased donors, but a gap between the two sources remains (Panel B). The data, which are based on 11,603 renal transplantations in 10,632 children, are from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS).[18] Rates of acute rejection within the first 6 months have decreased in each more-recent cohort, but the slope of the rate of acute rejection at later time points has remained the same (Panel C). The graph for transplants from deceased donors (data not shown) is similar to the graph shown for transplants from living donors. The data are from NAPRTCS.[18] As compared with survival among adult recipients of kidney transplants, patient survival among children is very high, regardless of whether the transplant was from a living or deceased donor (Panel D). The data are from NAPRTCS.[18] Rates of PTLD rose dramatically in the mid-1990s and early 2000s, primarily driven by a rise in early PTLD that may have been related to the effects of more-potent immunosuppressive medications (Panel E) (Martz K, EMMES: personal communication).

programs now transplant adult kidneys into small children once the recipient has reached a sufficient size, typically 6.5 to 10.0 kg of body weight. An infant's peritoneal cavity has enough space to accommodate an adult kidney without compressing the allograft.[27,28] However, the youngest pediatric recipients have an allograft-size mismatch that leads to a high glomerular filtration rate and makes interpretation of serum creatinine results more difficult, since acute rejection may initially occur without an elevation of the serum creatinine level. Kidneys from deceased donors who were very small children are no longer allocated to small children but are, in fact, now transplanted en bloc (both kidneys together, attached to a single segment of the aorta and vena cava) into adults with excellent results.[29]

The surgical procedure for a kidney transplantation in a child with a body weight of more than 30 kg is identical to that in an adult. However, in a child with a body weight of less than 10 kg, a midline longitudinal abdominal incision is needed. Space between the peritoneum and subcutaneous fascia is limited, so the kidney is placed intraperitoneally, with a small risk that it will migrate to another part of the abdominal cavity. Blood vessels from the donor are connected to the recipient's aorta and inferior vena cava. In children with a body weight of 10 to 30 kg, surgeons individualize the incision and allograft sites and blood-vessel anastomoses on the basis of the child's anatomy. In small children, strict attention must be paid to maintenance of the intravascular volume during the operation and in the early postoperative period.[30,31] Some children may require native nephrectomies, either to prevent blood-flow steal by the native kidneys or to eliminate excess urine volume or protein losses. Additional surgical details are described elsewhere.[30]

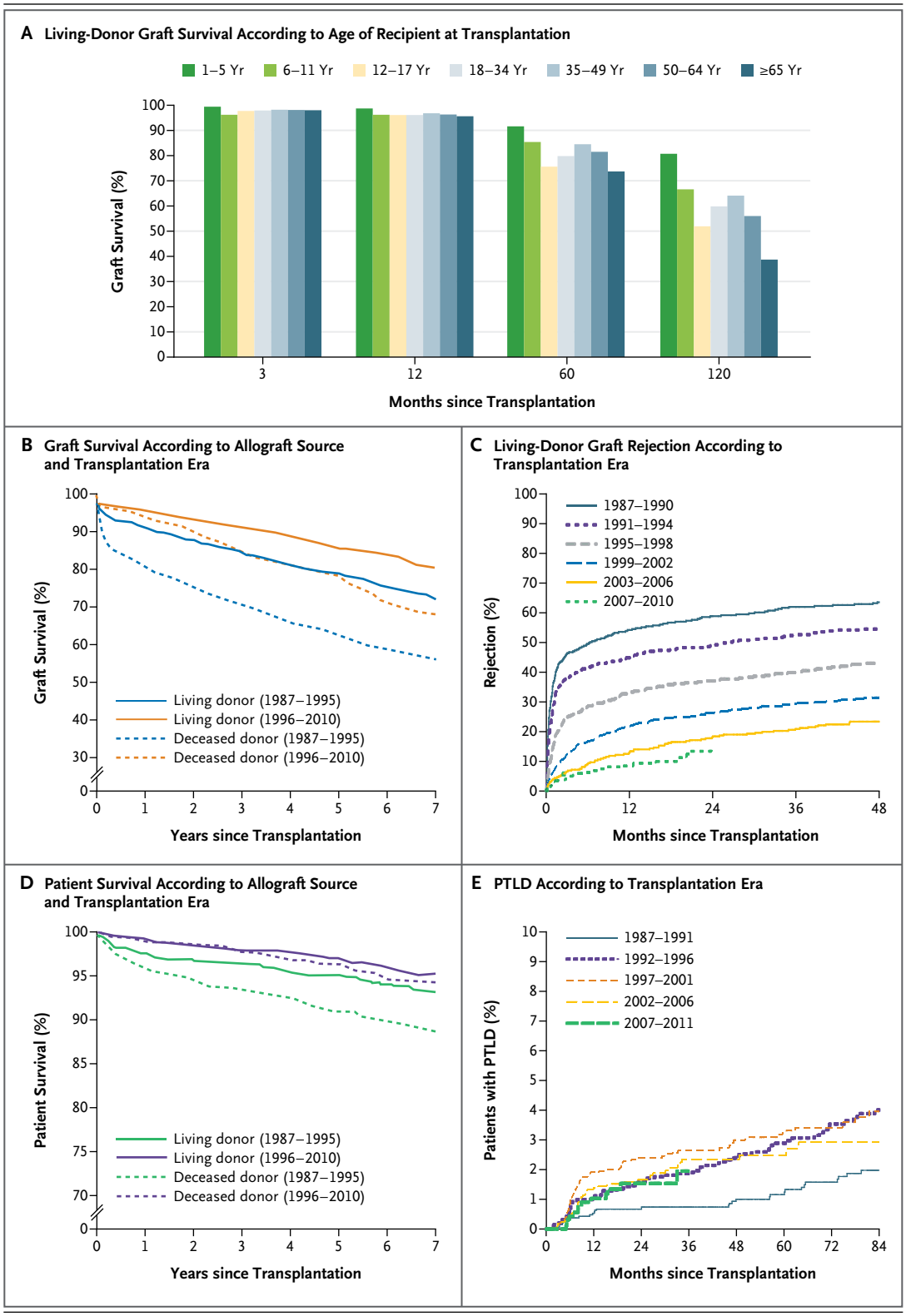
Temporary ureteral stenting is commonly used in adult kidney-transplant recipients,[32] but whether stenting is truly helpful in children is not known. Recommendations to stent became common before the association of ureteral stenting with BK virus nephropathy was known.[33,34] Some pediatric kidney-transplant recipients require specialized ureteral reimplantation, bladder augmentation, or urinary diversion procedures.[35]

CONSIDERATIONS AFTER TRANSPLANTATION

GRAFT SURVIVAL

Kidney-allograft survival has improved tremendously over time in successive cohorts of pediatric recipients,[18] regardless of whether the transplant was from a living or deceased donor (Fig. 2B). Such progress can be attributed to multiple factors — refinements in pretransplantation preparation, enhanced surgical techniques, better choice of donors, more potent immunosuppressive medications, greater understanding of pediatric-specific pharmacokinetics, and use of evidence-based medication protocols. In addition, overall rates of acute rejection among children have declined; the acute-rejection rate at 1 year among recipients of allografts from living donors decreased from 55% in the late 1980s to 10 to 15% in the most recent cohorts (Fig. 2C).[18] Although developing countries have lower rates of transplantation than developed countries, in addition to limited resources for acquiring the newer, more expensive immunosuppressive agents, they have had similar improvements.[36]

Kidneys transplanted into children 5 years of



age or younger have shown the most dramatic improvement (Fig. 2A). Unfortunately, adolescents now have the worst long-term graft survival among all pediatric-recipient age groups and represent the highest-risk recipients. Many reasons are postulated for this outcome, of which

poor adherence to medication therapy is believed to be a major factor.[37,38] The early mortality among pediatric kidney-transplant recipients is very low (Fig. 2D), and death results mostly from infection or cancer,[18] whereas mortality after transplantation is much higher among adults, and deaths are largely due to cardiovascular disease.

VIRAL INFECTIONS

Opportunistic viruses have emerged as great challenges to clinical management after kidney transplantation, probably related to the immunosuppressive regimens used currently, which are more potent than those used in the past. Since the mid-1990s, the incidence of the Epstein–Barr virus (EBV)–driven cancer known as post-transplantation lymphoproliferative disorder (PTLD) has dramatically increased (Fig. 2E), and BK virus has emerged as a new cause of infection. These two viruses typically infect people early in life, when they are immunocompetent, and cause mild disease but leave behind a pool of latent virus in the reticulothelium or urothelium. Since kidneys transplanted in children are usually from adult donors, there is an increased chance that a kidney from a seropositive donor (with latent virus) will be transplanted into a seronegative recipient. Thus, as compared with adults, children are at higher relative risk for severe disease from cytomegalovirus, EBV, or BK virus,[39] with higher rates of complications, graft loss, and death.[40,41]

Transplantation physicians typically reduce immunosuppression as a first response to each infection, with varied results. Ganciclovir is generally effective both as prophylaxis against and as treatment for cytomegalovirus infection, and antiviral prophylaxis has been associated with reduced rates of PTLD.[42,43] For BK virus infection, no antiviral treatment strategies have been validated, although cidofovir and leflunomide have been used in both adults and children.[41,44] Many pediatric kidney-transplantation centers perform serial monitoring for viruses with the use of a polymerase-chain-reaction (PCR) assay in the first 12 months after transplantation, in order to detect infections early.[45]

GROWTH CONCERNS

Children are in a state of active growth. Chronic kidney failure can lead to severe growth failure, often with associated loss of self-esteem.[46] Children with kidney failure were once approximately 2.5 SD below the expected height for their age at the time of transplantation. Improved nutrition before transplantation and aggressive use of recombinant human growth hormone have reduced, although not eliminated, this height deficit.[46] Renal transplantation generally improves linear growth but does not completely restore it.[47] The greatest recovery in growth is seen in the youngest children, and the least is seen in adolescents. The use of glucocorticoid withdrawal or avoidance protocols and the administration of growth hormone after transplantation may further improve growth recovery.[48]

TRANSITION OF CARE

Adolescents must eventually graduate to adult care — a transition that can be stressful for both the patient and the caregiver. A gradual transition rather than an abrupt transfer, early preparation of the patient and family, and the use of checklists to document maturing transition skills in the patient have been recommended to ensure a successful transition.[49]

PEDIATRIC IMMUNOSUPPRESSION — LESSONS FROM CLINICAL TRIALS

An important advance in pediatric kidney transplantation over the past two decades has been the emergence of prospective trial groups in the United States, Europe, Australia, and Asia. With relatively low patient volumes (10 to 30 transplantations per year) at most centers, meaningful results can be obtained through multicenter collaboration. Retrospective data registries such as the North American Pediatric Renal Trials and Collaborative Studies, combined adult and pediatric registries such as the United Network for Organ Sharing, the United States Renal Data System, the Collaborative Transplant Study, the Australia and New Zealand Dialysis and Transplant Registry, and the newly formed Cooperative European Pediatric Renal Transplant Initiative Registry in Europe[50] have provided important, but limited, information (Table S2 in the Supplementary Appendix). The results of prospective, randomized, multicenter clinical trials conducted in the United States or Europe are summarized in Table S3 in the Supplementary Appendix, and the results of nonrandomized, multicenter trials are summarized in Table S4 in the Supplementary Appendix. These trials have shown that high doses of immunosuppressive drugs to compensate for gluco-

corticoid withdrawal can lead to unacceptable rates of PTLD, that glucocorticoid avoidance is not immunologically detrimental,[51] although it does not ameliorate chronic histologic damage,[52] and that tacrolimus is associated with a significantly lower rate of acute rejection at 6 months than is cyclosporine.[53]

The children enrolled in these trials had a high rate of adherence to the trial requirements, including protocol-specified graft biopsies. However, pilot trials of immunosuppression in children should be conducted only if there are at least preliminary safety and perhaps efficacy data from studies involving adults, unless the studies apply uniquely to children (e.g., studies of growth strategies). Because only 700 to 800 kidney transplantations are performed in children in the United States annually, cooperation among pediatric research consortia is critical for full enrollment and study completion.

Pharmacokinetic and mechanistic studies have been coupled to many of these prospective studies. Pharmacokinetic studies showed that cyclosporine has a shorter half-life in children than in adults and requires dosing three times daily.[54] Similarly, sirolimus has a shorter half-life in children than in adults and often requires twice-daily dosing.[55,56] The area under the curve of dose-normalized mycophenolic acid is higher in children than has been commonly observed in adults.[56] These differences in metabolism are believed to be due to developmental changes in biliary transporters and metabolic enzymes such as cytochrome P-450 and glucuronosyltransferases.[56] In glucocorticoid-free protocols as compared with protocols that include glucocorticoids, the use of mycophenolate mofetil is associated with more frequent and severe leukopenia, anemia, and gastrointestinal disturbances.[57,58]

Some of the most important results from these trials were obtained from mechanistic studies, particularly those that may account for the replenishment of the immune system after lymphocyte depletion — homeostatic proliferation of peripheral memory T cells in adult recipients and thymopoiesis in pediatric recipients.[59] In children, CD8+ naive cells were shown to be more resistant to alemtuzumab-mediated depletion, and their recovery, albeit greater than that of CD4+ cells, remained low at 24 months,[60] whereas CD8+ cells in adults were fully recovered at 6 months after transplantation.[61,62] The prolonged depletion obtained with alemtuzumab (a potent monoclonal anti-CD52 antibody) in children is in conflict with the general theory that depletion would be more transient in children, owing to more active lymphopoiesis, than in adults.[63] Induction therapy with rabbit antithymocyte globulin (ATG), a polyclonal depleting agent, promotes long-term graft survival in pediatric kidney-transplant recipients,[64] with depletion of naive T cells and central memory T cells and little effect on effector memory T cells.[65] In addition, regulatory T cells (Tregs) were spared with alemtuzumab and expanded with ATG,[65] conferring an additional immunologic benefit by helping to accommodate the graft.

B-cell depletion with the lytic chimeric mouse–human anti-CD20 antibody rituximab is used increasingly in pediatric kidney-transplant recipients.[66] Data have shown full recovery of the B-cell pool 15 months after rituximab treatment in children, whereas recovery began only at 24 months in adults and was never complete.[67] Reemerging B cells appeared to be naive, immature, and more regulatory in children than in adults.[66] By 3 to 5 years after transplantation, new antibodies directed against HLA antigens developed in 25% of children,[68] as compared with only 10% of adults.[69]

Identification of relatively noninvasive biomarkers of acute rejection that might replace transplant biopsy is important. PCR-based panels of candidate markers such as interferon-inducible protein 10 and forkhead box P3 from urine have been tested.[70,71] Recently, several of these markers have been validated for acute rejection in adult kidney-transplant recipients, although BK virus infection also elevates these markers.[70] A PCR-based five-gene panel was tested in pediatric kidney-transplant recipients and validated as highly sensitive for the prediction of acute rejection.[72] The panels in these two studies[70,72] have no markers in common with each other or with the AlloMap panel[73] used to predict acute rejection in cardiac-transplant recipients, raising the question of whether the mechanisms of acute rejection are fundamentally different in different organ systems or patient populations or are influenced by differences in immunosuppression protocols.

FUTURE THERAPEUTIC DEVELOPMENTS

Inducing tolerance to a kidney allograft (tolerogenic strategies) holds the promise of immunosuppressive-free management. Different tolerogenic strategies have been explored primarily in the

preclinical setting but could have important benefits for children. For example, a phase 3 study of belatacept-based immunosuppression regimens versus cyclosporine in renal-transplant recipients (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial [BENEFIT]) showed a better average glomerular filtration rate at month 60 in the belatacept group than in the cyclosporine group.[74] Belatacept, a selective T-cell (lymphocyte) costimulation blocker, is being studied cautiously in children owing to concern about the risk of PTLD. Abatacept, another selective costimulatory agent, may have positive effects beyond the potential for tolerogenicity, because it has decreased proteinuria in kidney-transplant recipients with recurrent focal segmental glomerulosclerosis.[75]

Treatment with stem cells and Tregs, which is being studied in adult kidney-transplant recipients, may become feasible for pediatric recipients as well.[76] Mesenchymal stem cells are poorly immunogenic bone marrow–derived stem cells that inhibit T-cell proliferation and induce Tregs.[77] A recent study evaluated mesenchymal stem cells as an alternative to antibody induction therapy in adult kidney-transplant recipients.[78] However, mesenchymal stem cells have triggered concerns, given their oncogenic potential.[79]

SUMMARY

Transplantation in children with kidney failure once presented many technical, immunologic, and logistic problems that led to worse patient and allograft survival, as compared with adults. Advances in all these areas and the development of pediatric-trial groups have resulted in dramatic improvements, such that young children now have the best long-term graft survival among all age groups, including adults.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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