Outcomes After Pediatric Kidney Transplantation Improving: How Can We Do Even Better?

Kidney transplant is the treatment of choice for children and adolescents with end-stage renal disease because transplantation improves quality of life and survival to a far greater extent than chronic dialysis.¹ Unfortunately, however, transplantation does not completely normalize the excess risks associated with end-stage renal disease nor do transplanted allografts function indefinitely. In this issue of *Pediatrics*, Van Arendonk et al² provide valuable information on national trends in outcomes among pediatric kidney transplant recipients. Over a 25-year period, the authors observed remarkable improvements in patient and allograft survival following kidney transplantation after accounting for many changes in donor and recipient characteristics. The greatest improvements for both patient and allograft survival were within the first year, highlighting the need for ongoing improvements in long-term outcomes.

How will additional improvements in overall survival be achieved? The causes of death were not specified in the study by Van Arendonk et al,² precluding greater insight into the reasons for improved survival. Whether improvements were related to reductions in cardiovascular causes, infection, or malignancy are not known but are important to better understand how to achieve greater improvements. Increases in survival were mirrored by trends observed in the general population.³ However, the reasons for better survival in the general populations were more likely related to reductions in infant mortality.

Despite the advances in both populations, further improvements may be gained from greater attention to cardiovascular risk factors. Among those with kidney transplants, more proactive preventive care may reduce the high risk of future cardiovascular mortality observed in early adulthood.⁴ Among those in the general population, similar strategies that encourage cardiovascular health behaviors are likely to be important for longer term gains in survival.⁵ For all children and adolescents, additional increases in longer term survival will likely require more system-wide approaches to cardiovascular risk management.⁴⁻⁶

How will additional improvements in allograft survival be achieved? Although primary nonfunction and delayed graft function declined substantially over time,² it is not clear whether these decreases mediated the corresponding increases in death-censored graft survival. Nonetheless, with little room for further benefit from additional reductions in either primary nonfunction or delayed graft function, the optimal prevention and management of chronic allograft nephropathy remains one of the critical challenges that must be surmounted to improve long-term kidney transplant outcomes.

Chronic allograft nephropathy is the most common cause of graft failure after the first year, likely the result of both immunologic and nonimmunologic factors.⁷ Although a number of immunologic factors

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contribute to chronic allograft loss, acute rejection episodes are particularly important and have powerful prognostic implications.⁸ Thus, minimizing acute rejection will facilitate further improvements in long-term outcomes in patients with kidney transplants.

Despite greater numbers of kidney transplants under the Share 35 policy, greater immunologic mismatch and use of deceased donors was observed,² which in turn may lead to more acute rejection episodes that could impede improvements in long-term allograft survival. Rates of graft loss are particularly high among late adolescents and young adults,⁹ perhaps related to high rates of medication nonadherence.¹⁰ Potential solutions were included in the Patient Protection and Affordable Care Act, which now allows young adults to stay on their parents' insurance plans until 26 years of age and facilitates greater access to individual insurance. This law offers young adults health

insurance that should be more affordable because of cost-assistance programs administered through the various state health insurance marketplaces.¹¹

Novel approaches on the horizon that may simultaneously address both the issue of minimizing immunologic risk and improving medication adherence include acquiring immune tolerance¹² or regeneration of tissues and organs.¹³ Reducing injury and poor allograft function related to nonimmunologic mechanisms is also critical to achieving longer term gains. Further decreases in delayed graft function may prevent subsequent increases in glomerular hyperfiltration within the remaining nephrons that then leads to progressive dysfunction from interstitial fibrosis and tubular atrophy.

Hypertension is common among pediatric kidney transplant patients, and inadequate blood pressure control is associated with reduced allograft function. Medications that inhibit the renin-

angiotensin-aldosterone system may be particularly beneficial in kidney transplant recipients to prolong allograft survival by reducing the activity of pro-fibrotic molecules such as transforming growth factor- β and inflammatory mediators.¹⁴ In the context of prolonged renal survival in a trial of nontransplant pediatric patients with a variety of kidney diseases,¹⁵ evaluation of the short-term safety and efficacy of such agents in pediatric kidney transplant recipients is warranted and necessary to facilitate longer term studies.¹⁶

The advances in patient and allograft survival after kidney transplantation described by Van Arendonk et al² are certainly remarkable. Despite this success, however, there remains considerable room for improvement. A number of promising paths toward additional gains will require dedicated and focused effort despite the challenging nature of studies in this complex population.

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