Special Considerations in Pediatric Kidney Transplantation

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Universally accepted as the treatment of choice for children needing renal replacement therapy, kidney transplantation affords children the opportunity for an improved quality of life over dialysis therapy. Immunologic and surgical advances over the last 15 years have improved the pediatric patient and kidney graft survival. Unique to pediatrics, congenital genitourinary anomalies are the most common primary diseases leading to kidney failure, many with urological issues. Early urological evaluation for post-transplant bladder dysfunction and emphasis on immunization adherence are the mainstays of pediatric pretransplant and post-transplant evaluations. A child's height can be challenging, sometimes requiring an intra-abdominally placed graft, particularly if the patient is <20 kg. Maintenance immunosuppression regimens are similar to adult kidney graft recipients, although distinctive pharmacokinetics may change dosing intervals in children from twice a day to thrice a day. Viral infections and secondary malignancies are problematic for children relative to adults. Current trends to reduce/remove corticosteroid therapy from post-transplant protocols have produced improved linear growth with less steroid toxicity; although these studies are still ongoing, graft function and survival are considered acceptable. Finally, all children with a kidney transplant need a smooth transition to adult clinics. Future research in pertinent psychosocial aspects and continued technological advances will only serve to optimize the transition process. Although some aspects of kidney transplantation are similar in children and adults, for instance immunosuppression and immunosuppressive regimens, and rejection mechanisms and their diagnosis using the Banff criteria, there are important differences this review will focus on and which continue to drive innovation.

Key Words: Kidney transplant, Pediatric, Graft survival, Surgical outcomes, Steroid withdrawal

Kidney transplantation is the optimal treatment for children with CKD; historically, this has not always been the case. After the first kidney transplant on the Herrick brothers, identical twins, in 1954, kidney transplant quickly became an accepted and preferred mode of therapy in adults.[1] Fraught with high rates of graft loss, children were often allowed to die of kidney failure, as there was no available replacement therapy. In 1982, kidney transplant in children became acceptable when 12 children with weight <9 kg were transplanted with adult kidneys, their graft loss paralleling adult outcomes (83% from 18 months to 9 years).[2] The passage of 30 years has seen improvements in pediatric surgical techniques, refined pretransplant preparations, improved donor selection, and introduced more potent immunosuppression (IS). Subsequently, these advances have yielded enhanced outcomes in successive cohorts; between 1987 and 2012, the 10-year patient and graft survival rates improved from 77.6% and 46.8% (after 1987) to 90.5% and 60.2% (after 2001), respectively.[3]

BEFORE TRANSPLANTATION

Indications for Kidney Transplant

When the need for renal replacement therapy approaches, kidney transplantation can be considered. In children, however, dialysis may be necessary before transplantation so that nutritional and metabolic conditions are optimized, and to stabilize a child while awaiting a suitable donor. The Pediatric Committee of the American Society of Transplant Physicians lists the indications for kidney transplantation in children: (1) symptoms of uremia not responsive to standard therapy; (2) failure to thrive because of limitations in total caloric intake; (3) delayed psychomotor development; (4) hypervolemia; (5) hyperkalemia; and (6) metabolic bone disease because of renal osteodystrophy.[4] Many pediatric centers prefer a recipient weight of >10 kg, to minimize the risk of vascular thrombosis and to accommodate the larger adult-sized kidney.[5]

Children have a high potential for disease recurrence (focal segmental glomerulosclerosis, immunoglobulin A, and hyperoxalosis), therefore it is important to establish the cause of the end-stage renal disease etiology. Congenital anomalies of the kidney and urinary tract account for the preponderance of pediatric end-stage renal disease cases. Subcategories of congenital anomalies of the kidney and urinary tract, such as aplastic/hypoplastic/dysplastic

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kidneys (15.8%), remain the most common primary diagnosis, followed by obstructive uropathy (15.3%). Focal segmental glomerulosclerosis is the most common acquired renal disease, which remains the third most common overall (11.7%). In contrast, in adults, diabetes mellitus or hypertension (HTN) is the most common whereas rare in children.[6]

Pediatric Allocation System

Historically, the kidney allocation system favored transplantation of children by providing "extra" points, which enabled faster allocation. In December 2014, to enhance system equity and efficiency for adults and children, the kidney allocation was modified. Relevant to children, new listings had wait time accrued with dialysis start time, a new index, the Kidney Donor Profile Index, scored donor kidneys and children were given priority for "better" kidneys, those with low Kidney Donor Profile Index of <35%.[7] In line with the old allocation system, preemptive listing is still considered best practice (estimated glomerular filtration rate <20 mL/min/1.73 m^2).[8]

Urological Issues

A pediatric urologist is recommended to follow patients at high risk for post-transplant bladder dysfunction. Patients with lower urinary tract obstruction, particularly those with posterior urethral valves and urethral atresia, and neurogenic bladder (eg, spina bifida, tethered cord, and anorectal malformation) are at highest risk for post-transplant bladder dysfunction. These patients should have pretransplant urodynamic evaluations. A recent series demonstrated that more than half of ureteral obstructions occurred in the first 100 days post-transplant, and ureteral obstruction was significantly higher in patients with a history of posterior urethral valves.[9] Clean intermittent catheterization and anticholinergic medication are the mainstays of therapy for children with significant bladder dysfunction and have resulted in declining rates of enterocystoplasty. For children who require catheterization and who cannot tolerate catheterization per urethra, appendicovesicostomy would be a consideration.

Vaccinations

The importance of complete vaccination before IS with transplantation cannot be overemphasized, particularly live vaccines, which are contraindicated after transplant. A recent survey showed age-appropriate immunization compliance mandatory for transplant evaluation nationwide. When given a live vaccine, transplant should be delayed by minimum of 4 weeks. Inactivated vaccines are encouraged after transplantation after 3 to 6 months post-transplant.[10] Influenza and pneumococcal vaccinations are annually updated or per standard pediatric care.

Given the disproportionate burden of human papillomavirus (HPV)-related disease in CKD and transplant patients, the potential for HPV vaccination to prevent genital tract disease and subsequent secondary malignancies is substantial. Epidemiologic studies of adults have shown a 6-fold increase in cervical cancers and 5-fold increase in vulvovaginal cancers by the second year post-transplant compared with women in the general population.[11] Nelson and colleagues compared HPV vaccine antibody responses among 3 cohorts (age 9-21 years) CKD, dialysis, and post-transplant. Antibody response to quadrivalent-recombinant HPV was sustained (100% antibody response to all 4 serotypes: 6, 11, 16, and 18) in young women with CKD and on dialysis up to 35 months after completing 3 dose series. After transplant, the antibody response declined significantly to all 4 serotypes: 62.5% for 6, 50% for 11, 75% for 16, and 50% for 18.[12]

Although working toward a consensus statement, evidence to date provides enough support to recommend early vaccination before transplant. Gardasil 9, providing coverage against 5 additional HPV serotypes, is the newest HPV vaccine for patients aged 9 to 26 years.[13] Studies on this vaccine efficacy in transplant patients are ongoing.

CLINICAL SUMMARY

- Children with congenital anomalies of the kidney and urinary tract represent the most prevalent etiology for chronic kidney disease and are high risk for post-transplant bladder dysfunction.
- Growth after transplant is dependent upon age at transplant, allograft function, and corticosteroid use; currently, in spite of encouraging studies, reluctance persists for widespread adoption of steroid avoidance due to uncertainty with long-term outcome.
- With improving surgical outcomes and immunosuppressant management leading to longer graft survival, the pediatric nephrologist's role should extend to preventative care, including monitoring for secondary malignancies.
- Mitigating sensitization to optimize re-transplantation after graft loss and emphasis on improving transition to adult care continues the unique challenges of pediatric transplantation.

SURGICAL COMPLICATIONS

Pediatric kidney transplant presents a host of challenges not commonly encountered in the adult population. In recent years, a better understanding of urological abnormalities, perioperative volume management, and donor selection have resulted in significant improvements in surgical outcomes. Although size-matched organs were once thought to be optimal, outcomes (especially related to graft thrombosis) improved greatly with preferential allocation of adult-sized kidneys to children.[14]

Transplants are performed intra-abdominally, uniquely for children under 20 kg in weight; selection of vessels for implantation is done to provide optimal blood flow to the allograft. The aorta and vena cava are predominantly used for small recipients and the common iliac vessels for older children.[15] Maintenance of aortic blood flow and optimal volume status is critical, as the recipient's cardiac output must increase dramatically to maintain allograft perfusion.[16] With this in mind, aggressive intraoperative