Comparison of Renal Transplantation Outcomes in Children With and Without Bladder Dysfunction. A Customized Approach Equals the Difference

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Purpose: We examined the development of urological abnormalities in a group of pediatric renal transplant recipients.
Materials and Methods: We reviewed 211 patients younger than 19 years who underwent 226 renal transplants. Three groups of patients were studied—136 children with end stage renal disease due to a nonurological cause (group 1), 56 children with a urological disorder but with an adequate bladder (group 2a) and 19 children with lower urinary tract dysfunction and/or inadequate bladder drainage (group 2b). A total of 15 children in group 2b underwent bladder augmentation (ureterocystoplasty in 6, enterocystoplasty in 9), 2 underwent continent urinary diversion, 1 underwent autoaugmentation and 1 underwent a Mitrofanoff procedure at the bladder for easier drainage. Kidney transplantation was performed in the classic manner by extraperitoneal access, and whenever possible the ureter was reimplanted using an antireflux procedure.
Results: At a mean followup of 75 months 13 children had died, 59 grafts were lost and 15 children had received a second transplant. Two patients in group 2a required a complementary urological procedure to preserve renal function (1 enterocystoplasty, 1 vesicostomy). A total of 12 major surgical complications occurred in 226 kidney transplants (5.3%), with a similar incidence in all groups. The overall graft survival at 5 years was 75%, 74% and 84%, respectively, in groups 1, 2a and 2b.
Conclusions: With individualized treatment children with severely inferior lower urinary tract function may undergo renal transplantation with a safe and adequate outcome.

Key Words: kidney transplantation; pediatrics; urinary bladder, neurogenic; urologic diseases

The outcome of ESRD in children has completely changed within the last 20 years. Renal transplantation is the therapy of choice in children with renal insufficiency, as well as in infants. About 15% to 25% of children with ESRD present with a dysfunctional lower urinary tract and associated structural abnormalities that should be treated before renal transplantation.[1,2]

It has already been established that patients with a dysfunctional bladder have inferior graft survival and an increased risk of complications.[3] A low pressure reservoir with adequate capacity and compliance, as well as efficient urinary drainage, represents an important prerequisite for a successful renal transplant in this specific population.[4–8]

We hypothesize that individualized management of severe lower urinary tract disorders in pediatric candidates for renal transplantation is associated with excellent long-term graft function and survival. We report a retrospective comparison of kidney transplantation in children with tailored correction of urinary tract abnormalities to the same procedure in children without these conditions.

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MATERIALS AND METHODS

We retrospectively analyzed 226 pediatric renal transplantations conducted between January 1989 and December 2005. During this period 211 patients younger than 19 years (119 males and 92 females) received 226 renal allografts. Of these allografts 180 were from living related donors and 46 were from cadaveric donors. A total of 15 subjects received 2 renal allografts.

The immunosuppressive regimen was based on cyclosporine, corticosteroids and azathioprine until 1995. After that mycophenolate mofetil replaced the azathioprine. In 2000 tacrolimus replaced cyclosporine, and, therefore, the children were treated with tacrolimus, mycophenolate and corticosteroids.

All candidates for kidney transplantation were submitted to abdominal ultrasound. Voiding cystourethrography was also indicated for children with a history of urinary tract infection, incontinence and/or previous urological manipulation. Urodynamic study was performed in cases of neurogenic dysraphism, posterior urethral valves and obstruction, as indicated by cystogram.

The subjects were divided into 2 major groups. Group 1 was composed of 136 children with ESRD due to a nonurological kidney disease, and group 2 was composed of 75 children with ESRD caused by a urological abnormality. Group 2 was further categorized into 2 subgroups—2a, which contained 56 patients with urological abnormalities and adequate lower urinary tract function, and group 2b,

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TABLE 1. *Patient demographic data and ESRD diagnosis*

	Group 1	Group 2a	Group 2b	p Value
No. pts	136	56	19	
No. transplants:				
Primary	136	56	19	0.449
Redo	8	6	1	
Gender:				
M	66	41	12	0.006
F	70	15	7	
Median yrs age (range)	13 (3 to 18)	12 (1 to 18)	13 (4 to 16)	0.396*
Median mos followup (range)	79 (1 to 201)	72 (1 to 193)	61 (9 to 122)	0.510*
Donor:				
Living	109	53	18	0.153
Deceased	35	9	2	
Cause of ESRD:				
Nonurological	136			
Renal dysplasia†		23		
Vesicoureteral reflux		12	3	
Posterior urethral valve		11	5	
Neuropathic bladder			8	
Prune belly syndrome		2	1	
Other		8	2	

* Kruskal-Wallis test.
† Including cystic kidney diseases.

which contained 19 patients with lower urinary tract dysfunction in terms of compliance, capacity or inadequate bladder drainage. The demographics of each group are listed in table 1. The groups were not homogeneous in terms of sex distribution ($p = 0.006$).

Patients with a small defunctionalized bladder secondary to long-term anuria were submitted to bladder cycling either by a percutaneous cystostomy or continuous bladder irrigation through a 3-way Foley catheter to restore bladder capacity. A cystometric study was repeated 3 to 4 weeks later to assess whether bladder capacity gain was achieved. Children with long-term anuria and small bladder due to nephropathic etiology underwent transplantation without preoperative urodynamic investigation. The bladder capacity was recovered as soon as the bladder was refunctionalized by the allograft.

All children in group 1 and subgroup 2a presented with a lower urinary tract considered adequate for receiving a kidney allograft. On the other hand, all subgroup 2b patients had undergone different surgical procedures to create a reservoir with good capacity, adequate compliance and efficient bladder drainage (table 2). This group was composed of 8 patients with known neuropathic bladder (myelomeningocele, sacral agenesis) and 11 patients with either inadequate compliance (terminal bladder pressure greater than 30 to 40 cm water) or difficulties with bladder drainage. Among the 19 patients in this group 15 underwent bladder augmentation, 2 underwent urinary diversion, 1 was treated with bladder autoaugmentation and 1 underwent a Mitrofanoff procedure. In 8 patients the bladder augmentation was performed with dilated ureters, with both ureters being used in 2 patients and a single ureteral unit being used in 6. Urodynamic studies confirmed the improvement in bladder condition. Two patients who had undergone bladder augmentation with ureter did not demonstrate adequate improvement in bladder capacity or compliance, and were further submitted to classic enterocystoplasty. Seven other patients also had the bladder augmented primarily with a bowel segment, for a total of 9 patients undergoing enterocystoplasty, with ileum used in 6, sigmoid in 2 and an ileocecal segment in 1.

Two subjects with complex congenital anomalies were treated with continent urinary diversion with ileal segment and Monti procedure. One boy with the prune belly syndrome and megalourethra underwent a Mitrofanoff procedure with the appendix implanted at the bladder for easier catheterization. All children with an augmented bladder or neurogenic bladder with difficulties in spontaneous drainage were trained in CIC before transplantation.

TABLE 2. *Procedures performed in 19 patients (group 2b) with lower urinary tract dysfunction to obtain adequate urinary reservoir and bladder drainage*

Method	No. Procedures
Ureterocystoplasty:	8*
One ureter	4 Successful
Both ureters	2 Successful
Enterocystoplasty:	9*
Ileum	6
Sigmoid	2
Ileocecal	1
Continent diversion	2
Bladder autoaugmentation	1
Mitrofanoff procedure	1

* Two of 8 children initially undergoing ureterocystoplasty had treatment failure and subsequently underwent classic enterocystoplasty.

RESULTS

The transplantation was performed in the classic manner using extraperitoneal access in all subjects, even those weighing less than 20 kg.[9] Whenever possible the ureter was reimplanted into the bladder by extravesical access using an antireflux procedure. The ureter was implanted into the bowel portion of the reservoir in 5 patients (3 undergoing augmentation and 2 undergoing continent diversion). In 3 of these patients a Double-J® stent was left in situ. In 1 additional case a ureteroureteral anastomosis was performed using the native ureter due to difficulties in dissecting the bladder wall, and a Double-J stent was also left indwelling. A transurethral Foley catheter was left indwelling for 10 days in patients with bladder enlargement and in 5 days in the remainder of the children. The Double-J catheter was

TABLE 3. *Occurrence of vascular and urological complications by group*

	Group 1	Group 2a	Group 2b
Total kidney transplants (%)	144 (4.9)	62 (4.8)	20 (10)
No. vascular complications:*			
Venous thrombosis	3		
Arterial thrombosis		1	
No. urological complications (%):†			
Fistula	3 (2.1)	1 (1.6)	1 (5)
Stenosis	1 (0.7)	1 (1.6)	1 (5)

* Combined complication rate 1.77%, p = 0.250.
† Combined complication rate 3.5%, p >0.999.

removed within 3 weeks in 3 children and after 2 months in 1 boy.

Mean followup was 79, 72 and 61 months for groups 1, 2a and 2b, respectively (table 1). Two patients in group 2a required an additional procedure to preserve renal function due to hydronephrosis. One subject was treated with ileocystoplasty because his neurogenic bladder status was not recognized before transplantation, and ureteral stenosis developed. Another child who presented with a psychiatric disorder leading to problems in performing CIC was treated with vesicostomy, since he had adequate bladder capacity and compliance.

A total of 12 major surgical complications (5.3%) occurred in 226 renal transplantations, with 7 (4.9%) in group 1, 3 (4.8%) in group 2a and 2 (10%) in group 2b (table 3). All patients with vascular thrombosis had lost the graft. All urological complications were surgically treated, and no graft was lost due to this reason.

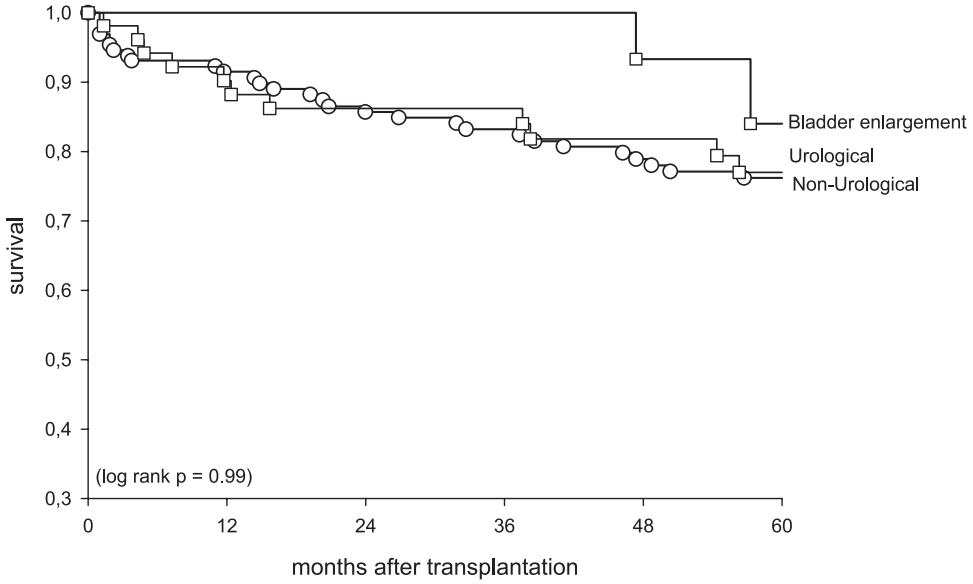
Urinary leakage occurred in 5 patients, and was diagnosed within the first 3 postoperative days in 3 patients. In the 2 remaining patients the leakage was detected at 3 weeks after transplantation. In 1 patient with a continent urinary diversion the urinary fistula resolved with clinical maneuvers such as continuous catheterization through the stoma. In 1 patient the leakage occurred at the bladder and was surgically treated. Three patients presented with necrosis of the distal portion of the ureter and were successfully treated with ureteroureterostomy using the native ureter.

Ureteral stenosis was observed in 3 patients, 1 in each group, before postoperative month 4. In all cases the stenotic segment was short and was localized at the level of the ureterovesical junction. The ureter was implanted into a bowel portion of the reservoir in 1 patient and at the bladder wall in 2 patients. A Double-J catheter was left indwelling in 2 cases. Stenosis occurred in 20% of the patients undergoing ureteral implantation into an intestinal portion of the urinary reservoir (3 patients undergoing augmentation and 2 undergoing urinary diversion), compared to 2 of 220 patients (144 in group 1, 62 in group 2a and 14 in group 2b) undergoing reimplantation into the bladder (p = 0.065). A total of 10 children were maintained on CIC, of whom 3 had undergone bladder augmentation with ureter (all with neurogenic bladder) and 7 had undergone augmentation with a bowel segment (neurogenic bladder in 4, posterior urethral valve in 2 and exstrophy in 1).

During followup 59 grafts were lost and 15 children received a second transplant. A total of 13 patients died with a functioning graft. At the last followup mean serum creatinine ± SD was 1.74 ± 1.44 mg/dl, 1.38 ± 0.70 mg/dl and 1.66 ± 0.63 mg/dl, respectively, in groups 1, 2a and 2b (p = 0.393). Overall 5-year graft survival, including death with a functioning graft, was 75%, 74% and 84%, respectively, in groups 1, 2a and 2b (p = 0.997, see figure).

DISCUSSION

Urological anomaly is a frequent cause of renal function impairment and ESRD in the pediatric population. Individualized management is the key for the success of a pediatric renal transplant program. Correction of structural urogenital abnormalities, and optimization of emptying and storage function of the bladder must be achieved before transplantation. The majority of children with urological abnormalities undergo at least 1 surgical or medical procedure during childhood to preserve renal function. Nevertheless, bladder function should be reevaluated before renal transplantation.



Overall graft survival (including death with functioning graft) in 3 groups evaluated at 12, 36 and 60 months

The primary issue in renal transplantation planning is to assess the bladder condition, even in those cases in which a previous supravesical diversion has been performed. A dysfunctional bladder that has contributed to the destruction of the native kidneys may also pose a risk to the allograft.

Bladder capacity, compliance, continence and emptying are important parameters to be considered before transplantation.[4,10] A detailed history of bladder function before the anuria period has been reached is extremely useful, especially for assessing continence status. In many cases continence may be difficult to achieve after transplantation.

Children with ESRD due to nephropathic disease only require an ultrasound to evaluate the upper urinary system, post-void residual and bladder morphology. On the other hand, patients with a history of urinary tract infection, incontinence, urological surgery or urinary diversion should be thoroughly evaluated before transplantation. Voiding cystourethrography is routinely performed to evaluate reflux, bladder characteristics and capacity, post-void residual and urethral condition. Cases suspicious for bladder dysfunction should be evaluated with urodynamic study. It is well-known that terminal bladder pressures greater than 30 to 40 cm H_2O are associated with upper tract deterioration.[11]

We prefer to optimize bladder storage and emptying without the interference of the immunosuppressive regimen on the healing process. An effective way of achieving bladder drainage should be established before transplantation. Patients with recurrent urinary tract infection, hydronephrosis and vesicoureteral reflux may require pre-transplantation nephroureterectomy. Bladder condition should be evaluated. The ureter when dilated provides an excellent source of augmentation material with urothelium and muscular backing, free from electrolyte and acid base disturbances, mucous production and risk of neoplasia.[12–14]

The necessity of the urological procedure should be particularized for each patient. With development of innovative reconstructive techniques and acceptance of CIC a permanent incontinent diversion is rarely required today. We prefer bladder augmentation over continent urinary diversion.

In relation to the etiology of lower urinary tract abnormalities all children in this series with neurospinal dysraphism (most frequently myelomeningocele) underwent bladder augmentation. Five of 16 patients with posterior urethral valves and 2 of 14 with vesicoureteral reflux who had undergone bladder augmentation had cystometric studies showing a final pressure of more than 35 cm H_2O. Continent urinary reservoir was performed in 2 patients, 1 with ambiguous genitalia and 1 with bilateral ectopic ureteroceles. Transplantation into a urinary diversion represents the exception, and should be reserved for incontinent patients.

Bladder cycling is an important step in the evaluation of the pediatric population presenting with bladder dysfunction and a small defunctionalized bladder. After 3 to 4 weeks bladder capacity is restored, allowing urodynamic studies to be done in adequate conditions. On the other hand, cycling the bladder may result in upper urinary tract dilatation. One child in this series with ESRD due to a posterior urethral valve and reflux, who underwent ureterostomy to preserve residual renal function, was treated with bladder cycling through the stoma. After 4 weeks both ureters were de novo dilated, making ureterocystoplasty a feasible procedure. Eight subjects with dilated ureters were treated with ureterocystoplasty, with both ureters being used in 2 instances.

Functional augmentation is preferable to dry augmentation because it allows for the development of adequate bladder capacity and evaluation of bladder continence and function before transplant, mainly in patients undergoing ureterocystoplasty. For instance 2 patients with anuria who had undergone augmentation with ureter needed to be hospitalized postoperatively to gain bladder capacity of at least 120 ml. After 4 weeks of bladder cycling both patients were able to undergo a living donor transplantation.

A second urodynamic study should be performed after ureterocystoplasty to confirm improvement, mainly in compliance but also in bladder capacity, before considering a kidney transplant. Two patients who had previously been treated with ureteral reimplantation did not have an improved bladder condition, probably as a result of inadequate blood supply to the distal ureter. Both patients needed bladder enlargement with a bowel segment. Patients with a history of ureteral reimplantation are no longer candidates for ureterocystoplasty in our program.

Our first choice has always been to use the ureter to perform cystoplasty. When the ureter is unavailable or is dilated the only solution is to incorporate a bowel segment into the bladder. Detubularized ileum remains the most commonly used segment because of its abundance and reduced complication rates. The segment should be detubularized to interrupt peristaltic activity and reconfigured to create a spherical pouch, which increases capacity.

The enlargement should be performed over the dome and anterior surface of the bladder, leaving the lateral wall undisturbed for the future transplant ureteroneocystostomy. A U-shaped incision is performed longitudinally, creating a large surface for the bowel anastomosis and avoiding the formation of an hourglass-shaped augmented bladder.[4] This procedure was performed in a total of 10 cases, of which 7 were initially managed by enterocystoplasty, 2 initially were augmented ureter and 1 was enlarged after a kidney transplant (group 2a). No patient experienced a major metabolic complication, probably due to the use of intestinal segment, although the use of oral bicarbonate (1 to 4 gm daily) was required by 7 patients. Based on our experience, these patients do not need a controlled urodynamic study. Even patients waiting for a cadaveric kidney will recover bladder capacity with a successful transplant.[4]

The transplant was performed via extraperitoneal access and the ureter was implanted using the antireflux technique. The latter is especially important for patients on CIC to prevent contaminated urine from refluxing into the upper urinary tract. Whenever possible the bladder portion of the augmented reservoir should be used for the ureteral reimplantation. None of the 12 patients undergoing enterocystoplasty whose ureter was implanted into the bladder presented with ureteral stenosis, compared to 1 of 5 subjects who had the ureter implanted at the bowel portion of the augmented bladder ($p = 0.294$). When the reservoir cannot be adequately dissected a ureteroureteral anastomosis with the native ureter is a good option. This tactical approach was used in 1 case.

Children with urological anomalies receiving a transplant need close followup for urinary tract infections, and routine ultrasound should be done every 3 months during

the first year postoperatively. Therefore, we recommend that voiding cystourethrography and urodynamic reassessment be reserved for children with impairment of renal function or urological complications. Two patients in group 2a who had ESRD due to pyelonephritis and who were initially considered to have lower urinary tracts adequate for receiving a transplant presented with renal function deterioration and hydronephrosis, requiring an additional procedure to preserve graft function. We also observed a striking rate of urinary tract infection in the patients undergoing enterocystoplasty and/or CIC, with no influence on graft survival. Because of infection risk, every attempt should be made to perform tunneled ureteral reimplantation at the time of transplantation.[15,16] The incidence of urological complications was higher in the group undergoing major urological procedures (group 2b) but all of these complications were treated successfully without compromising graft or patient survival.

CONCLUSIONS

Based on our experience, a successful pediatric transplantation program requires an individualized approach for each patient. Our study reveals that anomalies of the lower urinary tract do not preclude kidney transplantation, refunctionalization of the urinary reservoir can be accomplished in patients with previously defunctionalized bladder before renal transplantation, and correction of structural anomalies and optimization of storage and emptying function of the bladder are recommended before transplant, development of reconstructive techniques and administration of CIC. Finally, permanent urinary diversion is rarely required today, with ureterocystoplasty preferable to enterocystoplasty.

Abbreviations and Acronyms

CIC = clean intermittent catheterization
ESRD = end stage renal disease

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