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# Limited surgical interventions in children with posterior urethral valves can lead to better outcomes following renal transplantation

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Abstract: There is currently no consensus as to the most appropriate means by which children with posterior urethral valves (PUV) are to be managed prior to transplantation. We compared (i) renal allograft survival and function in patients with PUV vs. those with non-obstructive causes of ESRD and (ii) graft outcomes in children who had limited interventions (Group 1) vs. those with more extensive urologic surgeries to decompress the urinary tract (Group 2). Twenty-six pediatric renal transplant recipients had ESRD due to PUV (Group 1, n = 16; Group 2, n = 10). The study group was compared to 23 matched controls with ESRD due to non-obstructive causes. Five yr patient and graft survival was similar in all patients with PUV (Groups 1 and 2) when compared to all other kidney recipients in the transplant program, 96.2% vs. 98.0% and 87.5% vs. 87.0%, respectively. Although calculated creatinine clearance (Ccr), was similar between the PUV group and controls for the first 4 yr, the 5 yr graft function was significantly lower in the PUV group. (53.7±15.7 vs. 70.2±21.0 mL/min/1.73 $m^2$; p = 0.03). When the two PUV groups were compared, graft survival was equivalent, but graft function was significantly better at 5 yr in Group 1(60.4±10.8 vs. 33.8±9.3 mL/min/1.73 $m^2$; p = 0.02). Thus, patients with PUV managed by a limited intervention approach of vesicostomy with delayed valve ablation or primary valve ablation, had better outcomes. When ESRD is virtually certain, additional pre-transplant surgeries affecting the urinary tract should be avoided.

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Key words: graft survival – creatinine clearance – children – end stage renal disease – bladder – urologic surgical procedures – kidney transplantation

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Posterior urethral valves (PUV) are the most common cause of lower urinary tract obstruction in the male pediatric population, with an incidence ranging from 1/4,000 to 1/7,500 births (1). Posterior urethral valves often cause bilateral antenatal hydronephroses and, in approximately 30–50% of patients, obstruction leads to chronic renal insufficiency or end-stage renal disease (ESRD) (1–3). The bladder and upper urinary tract are exposed to many structural and functional changes that can accelerate renal deterioration if they are not managed properly.

Analysis of long-term renal transplant outcomes in children with PUV has produced conflicting data. Many studies have described higher rates of graft loss and higher serum creatinine levels in PUV patients than matched controls (4–8). Investigators hypothesized that these poorer outcomes were due to persistent bladder dysfunction resulting from the initial

Abbreviations: PUV, posterior urethral valves; ESRD, - end stage renal disease; Ccr, creatinine clearance; LD, living donor.

obstruction (9). Other studies have shown that PUV patients have transplant outcomes similar to controls (10–12).

The choice of the initial management strategy for newborn infants with PUV and renal insufficiency is critical, and may help to avoid complications that jeopardize graft outcomes. However, guidelines for the initial management of PUV have been controversial. Urologists and nephrologists choose from four recognized treatment strategies to manage the unique problems of a given child with PUV and renal insufficiency. Current practices include: (a) primary valve ablation soon after birth; (b) vesicostomy drainage of the bladder soon after birth followed by a staged primary resection of the valves and closure of vesicostomy at approximately 1 yr of age or 10 kg in weight; (c) bilateral nephrostomy drainage or other urinary diversion procedure, and (d) primary valve resection followed by bladder augmentation. We have attempted to discern if different management practices influence patient morbidity, growth, and subsequent renal transplant outcomes. To our knowledge, this type of analysis has not been previously done and may explain the conflicting transplant outcomes in previous publications.

## Methods

### Patient and control group selection

Retrospective chart reviews were conducted for the 179 consecutive pediatric kidney recipients in the Pediatric Renal Transplant Program registry at the Lucile Packard Children's Hospital (LPCH), who received renal transplants between 1991 and 2000. Patients were selected for inclusion in the study population if they had been diagnosed with posterior urethral valves by voiding cystourethrography.

Transplant recipients were compared to 23 matched transplant recipients with ESRD due to non-obstructive causes, who served as controls. Patients were matched according to age, sex, ethnicity, graft type (living related or cadaveric), type of induction therapy, and type of immunosuppression (Table 1).

### Posterior urethral valve subgroup assignment based on the amount of surgical intervention

Of the 26 PUV patients, 16 were defined as having had limited interventions in the form of either early vesicostomy followed by delayed valve ablation (62.5% 10/16) or primary valve ablation (37.5% 6/16). These patients were assigned to Group 1, the limited intervention group. Ten of the 26 PUV patients had one or more additional urologic surgeries to decompress their urinary tract (6 nephrostomies and/or pyelostomies, 2 bladder augmentations, 1 bilateral reimplantation of ureters, 1 ureterostomy and multiple urethral dilatations after failed resection). These 10 patients were assigned to Group 2. Baseline comparisons between both groups of patients are shown in Table 1. There was a bias toward more living donors (LD) in Group 1, but the mean HLA mismatch was similar between the two groups.

### Statistical analysis

The primary variables of interest were 5 yr patient and graft survival rates and calculated creatinine clearance (Ccr). Secondary variables analyzed included age at transplantation, ethnicity, donor type, HLA mismatches, height standard deviation score, early post-transplant incontinence, unresolved post-transplant hydronephrosis, rejection episodes, tacrolimus vs. cyclosporin A- based immunosuppression, dual vs. triple immunosuppression therapy, and pre- and post-transplant urinary tract infections. Creatinine clearance was calculated using the Schwartz equation (13). Patients were characterized as having frequent urinary tract infection if they had more than three infections/year. The conclusion section of the *Pediatric Radiology* renal ultrasound report was used to identify patients with persistent (>6 months post-transplant) hydronephrosis. Continuous variables were compared between groups using the student's *t*-test or ANOVA. The relationships between nominal variables were compared using the Fisher's analysis. Statistical significance was defined as a p-value $< 0.05$.

## Results

### PUV vs. non-obstructive causes of renal failure

Baseline patient characteristics are shown in Table 1. Patients with PUV were diagnosed at a mean age of $6.4 \pm 17.1$ months. There were no differences between the combined PUV group and the control group with respect to age at transplant, ethnicity, donor type, induction therapy or immunosuppression. Patients receiving a LD transplant had a lower mean number of HLA mismatches when compared with CAD transplant recipients, $2.6 \pm 0.9$ vs. $3.4 \pm 1.2$ ($p = 0.06$).

Table 1 Baseline patient characteristics

| | Posterior urethral values (n=26) | | | Control | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | p value | Combined | (n=3) | p value |
| Age at transplant | 5.6±5.5 | 8.8±4.5 | 0.12 | 7.6±5.7 | 10.3±4.8 | 0.09 |
| Gender (male/female) | 16/0 | 10/0 | 1.00 | 26/0 | 23/0 | 1.00 |
| Ethnicity | | | | | | |
| African American | 1 | 1 | 0.12 | 2 | 0 | 0.15 |
| Asian | 0 | 0 | 1.00 | 0 | 0 | 1.00 |
| Caucasian | 8 | 6 | 0.11 | 14 | 11 | 0.42 |
| Hispanic | 7 | 1 | 0.02 | 8 | 9 | 0.31 |
| Pacific Islander | 0 | 2 | – | 2 | 1 | 0.41 |
| Other | 0 | 0 | 1.00 | 0 | 2 | – |
| LD/CAD | 13/3 | 6/4 | 0.04 | 19/7 | 19/4 | 0.26 |
| Mean HLA mismatch | 3.0±0.7 | 3.0±1.3 | 1.0 | 3.0±1.0 | 2.6±1.0 | 0.17 |
| Induction therapy | | | | | | |
| OKT3 | 2 | 1 | 0.13 | 3 | 0 | 0.08 |
| ALG/ATG | 3 | 3 | 0.10 | 6 | 7 | 0.33 |
| Daclizumab | 5 | 1 | 0.07 | 6 | 4 | 0.40 |
| None | 6 | 5 | 0.10 | 11 | 12 | 0.28 |
| Immunosuppression | | | | | | |
| CsA+Pred+AZA | 10 | 5 | 0.10 | 15 | 15 | 0.37 |
| CsA+Pred+MMF | 4 | 4 | 0.08 | 8 | 8 | 0.50 |
| Tacro+Pred | 1 | 1 | 0.12 | 2 | 0 | 0.15 |
| Tacro+AZA | 1 | 0 | 0.10 | 1 | 1 | 0.55 |

When PUV patients were compared to the matched controls with non-obstructive causes of ESRD, there were no significant differences for any of the data points, except the 5 yr creatinine clearance. At 5 yr post-transplant, the PUV group showed a significantly poorer Ccr (Table 2). Kaplan-Meier comparison showed no significant difference, at any tme, between the rates of rejection in patients with PUV compared with controls (Fig. 1). Five yr non-censored graft survival was 88.5% for the PUV group vs. 100% for control group. There was one patient death in the PUV group (40 months post-transplant) due to post transplant lymphoproliferative disorder. There were two grafts lost, 41 and 49 months post-transplant in the PUV group, one from Group 1 and one from Group 2. Both allografts were lost due to acute rejection attributed to non-compliance. When compared to the entire

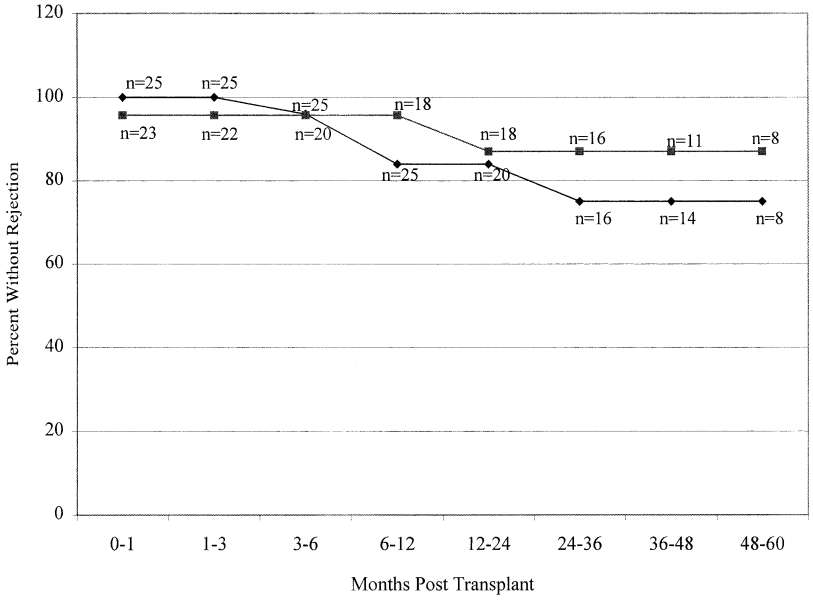


*Fig. 1.* Kaplan–Meier comparison of rejection. The percentage of patients that remain rejection free at each year post-transplant are shown. There is no significant difference, at any time, between the rate of rejection in patients with posterior urethral valves (◆) compared to controls (■).

Table 2 Comparison of renal allograft function: posterior urethral valve vs. control

| Months post-transplant | 6 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|
| Group 1 n = | 15 | 15 | 11 | 9 | 8 | 6 |
| Ccr (mL/min/1.73 $m^2$) | 92.4±36.2 | 82.1±16.9 | 63.3±12.3 | 63.1±17.6 | 70.7±14.7 | 60.4±10.8 |
| Group 2 n = | 10 | 10 | 9 | 7 | 6 | 2 |
| Ccr (mL/min/1.73 $m^2$) | 82.3±23.0 | 79.7±11.8 | 74.3±16.9 | 61.4±16.9 | 52.2±22.2 | 33.8±9.3 |
| p values | 0.44 | 0.71 | 0.13 | 0.85 | 0.08 | 0.02 |
| Combined PUV n = | 25 | 25 | 20 | 16 | 14 | 8 |
| Ccr (mLmin/1.73 $m^2$) | 89.0±18.6 | 79.8±15.9 | 68.3±15.2 | 62.4±16.7 | 62.2±20.3 | 53.7±15.7 |
| Control n = | 20 | 18 | 18 | 16 | 11 | 8 |
| Ccr (mL/min/1.73 $m^2$) | 88.8±27.7 | 83.4±31.3 | 78.2±26.6 | 67.8±20.1 | 73.2±17.0 | 70.2±21.0 |
| p values | 0.99 | 0.74 | 0.17 | 0.41 | 0.13 | 0.03 |

program (n=153), patients with PUV had similar allograft survival rates at 5 yr post-transplant, 88.5% vs. 87%. When PUV patients were compared to other pediatric kidney recipients in the program, 5 yr patient survival was similar (96.2% vs. 98.0%).

### Comparison of patients in Group 1 and Group 2

Comparing outcomes for the two PUV Groups, there were no significant differences in graft function between these groups at 6 months, 1, 2, and 3 yr. At 4 yr, there was a trend toward better graft function in Group 1, as these patients now had about 25% better function than patients in Group 2. By 5 yr, the difference in function became significant, with Group 2 patients having almost 50% poorer Ccr than the Group 1 patients. When 5 yr graft function was compared between Group 1 and the matched controls, there was no significant difference (60.4±10.8 vs. 70.2±21.0 mL/min/1.73 $m^2$; p=0.28). There was no significant difference in acute rejection episodes between the groups.

The morbidity of the two PUV groups was compared. There were no differences in age of onset of ESRD or unresolved post-transplant hydronephrosis (>6 months post-transplant), height < 5th percentile, frequent urinary tract infections (pre- or post-transplant), There was, however, a weak trend (p=0.1) towards increased incontinence in Group 2.

## Discussion

Five-year patient and graft survival for PUV patients did not differ from all other pediatric transplant recipients at our center. However, when compared to matched controls, pediatric renal transplant recipients with PUV, in this study, experienced a more precipitous decline in renal excretory function. Whether PUV patients have long-term transplant outcomes comparable to matched controls remains controversial. Groenewegen et al. reported a non-significant, yet notable trend toward poorer 5-yr graft survival rates in PUV patients compared to matched controls receiving renal transplants for non-obstructive causes of ESRD (50% vs. 65%). They also reported that PUV patients have more post-operative urinary tract infections and higher 5 yr serum creatinine levels than controls (4). Other investigators have also described poorer 5-yr graft survival in PUV patients (5, 6). Although Bryant et al. found no significant difference in 5-yr graft survival, they noted significantly higher serum creatinine levels at 3 yr (7). Salomon et al. found no difference in graft survival at 5 or 10 yr, but found that there was a significant increase in serum creatinine levels at 10 yr in PUV patients. The difference in renal excretory function was attributed to the effects of the inherent abnormality of bladder function due to prolonged obstruction to bladder outflow *in utero* (8, 9). In contrast, other studies have found no significant differences in graft outcomes in PUV patients when compared with controls (10–12). Many of these studies have tried to interpret outcome parameters such as graft function based on bladder function. However, these assessments are difficult because the bladder abnormality varies between patients. Urodynamic studies are a way to assess bladder function, but in our hands these studies have not been reliable.

Pre-transplant management of the urinary tract in a patient destined to renal failure should be focused on avoiding unnecessary surgeries in a useless attempt to improve function of unsalvageable kidneys. This can also obviate a subsequent difficult transplant operation due to increased intra-abdominal scarring and adhesions, which can lead to subsequent complications post-transplantation, especially in infant and small child recipients of adult-size kidneys (14). For example, the UNOS

Registry reports that 34% of grafts lost in < 2-year-old recipients of living donor kidneys are lost for technical reasons, with vascular thrombosis leading the way at 24% (15). A scarred, small infant aorta or vena cava could result in a compromised anastomosis of the discrepantly large donor renal artery and vein with major impairment of blood flow to an adult-sized kidney with its large blood flow demand (16). A small, contracted urinary bladder as a result of prior supravesical diversion can also present a challenge for implantation of the transplant ureter, although we have recently shown that a novel re-implantation technique of the transplant ureter into the smallest of these abnormal bladders can be accomplished without post-transplant ureteral reflux or hydronephrosis (17).

When the PUV patients were separated into two groups, the mean 5-yr Ccr was significantly worse in patients who had multiple surgical interventions. However, when the mean 5-yr Ccr in Group 1 was compared to the matched controls, it is clear that the difference seen between the entire PUV group and controls was due to Group 2. These findings, together with the greater incidence of incontinence early post-transplant, seem to indicate that patients who underwent additional surgeries prior to transplant (Group 2) had overall poorer transplant outcomes than those who received only vesicostomy with delayed valve ablation or primary ablation to decompress the urinary tract (Group 1).

The additional urologic surgeries in Group 2 patients sought to preserve residual minimal renal function in these patients and avoid ESRD. However, patients who have a persistence of significant renal insufficiency after decompression are destined for eventual transplantation, so that all pre-transplant treatment and procedures should only be carried out to maximize the success of the transplant. Tietjen et al. conducted a study to determine whether supravesical urinary diversion was indicated in infants whose renal function remained impaired following vesicostomy or valve resection. Their findings suggested that the kidneys are already dysplastic and ESRD cannot be avoided with proximal supravesical diversion (18). This was no doubt the case in the patients in Group 2 who underwent supravesical diversion prior to transplant. Their surgeries did not avoid ESRD, but instead were correlated with inferior overall outcomes post-transplant.

Similarly, the other pre-transplant reconstructive surgeries in Group 2 patients did not successfully preserve renal function. It has been our preference to rehabilitate a thickened and defunctionalized small native bladder rather than perform a bladder augmentation with intestinal segments (19). Native small bladders can usually be rehabilitated without the need for self-catheterization after transplant and bladder capacity increases significantly (8–10-fold) within 4 months post-transplant, with many reaching full capacity (14, 15, 20). In patients with renal insufficiency, supravesical diversion, bladder augmentation, and ureteral re-implantations should probably be deferred so that definitive management of hydroureteronephrosis can be coordinated with the renal transplant surgery.

In conclusion, successful transplantation should be the ultimate objective for not only prolonging life, but also offering great potential to improve quality of life for children with ESRD secondary to PUV. With this as the goal, initial urologic management strategies for PUV patients with renal insufficiency should be carefully selected and carried out as a means to best prepare for subsequent transplant. We consider the following to be important factors in the management of children with PUV and established renal insufficiency: (i) complete relief of obstruction whether by staged vesicostomy and later ablation or primary ablation ; (ii) antibiotic prophylaxis pre- and post-transplant with a regular and frequent voiding pattern when the child is able to follow instructions; (iii) aggressive nutritional support to sustain positive growth patterns and maximize healing and recovery post-transplant; (iv) limit additional surgical procedures including stent/tube placements, supravesical urinary diversion, and repeated surgeries and (v) limit the residual urine capacity of these bladders at any given time, which can increase the risk of urinary tract infections.

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