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# Pediatric renal transplantation and the dysfunctional bladder

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**Abstract** We retrospectively reviewed our long-term experience with pediatric renal transplantation into a dysfunctional lower urinary tract to evaluate graft survival, function, and special urological complications. Between 1967 and March 2000, a total of 349 renal transplantations were performed in children younger than 18 years. Malformations of the lower urinary tract were the reasons for end-stage renal failure in 66 children (18.6%). The cause of urinary tract disorders included: meningomyelocele connected with neuropathic bladder ($n=4$ transplantations); prune belly syndrome ($n=5$ transplantations); VATER association ($n=2$ transplantations); posterior urethral valves ($n=27$ transplantations); and vesico-uretero-renal reflux ($n=28$ transplantations). The majority of the patients underwent surgical interventions to preserve renal function or to prepare renal transplantation. The 1- and 5-year graft survival rate was evaluated with special reference to the underlying disease. The 1-year graft survival rate in all children with lower urinary tract malformations was 83.3%, compared with 88% for all children. In those children with vesico-ureteral reflux, it was 92.8% and in the children with Vater association and prune belly syndrome, it was 85.7%. One graft was lost in the children who had neurogenic bladder, so the 1-year graft survival rate was 75%. The worst 1-year graft survival rate was obtained for boys who had posterior urethral valves (1-year graft survival rate: 74%; 5-year graft survival rate: 62.9%). Concerning the 5-year graft survival rate, it was 70% for all children with malformations of the urinary tract. The best rate was obtained for children with reflux in the native kidneys (78.5%), followed by those with VATER association and prune belly syndrome. As an additional child with neurogenic bladder lost his graft, the 5-year graft survival rate was 50%. Pediatric renal transplantation into a dysfunctional bladder can be connected with high urological complication rates which may contribute to worse graft survival. The 1- and 5-year graft survival rate in children with malformations of the lower urinary tract is worse than in children without bladder dysfunction. We regarded a striking difference between graft survival and the urological disorders which led to renal insufficiency. We obtained the worst graft survival rates in children with posterior urethral valves which are usually connected with bladder emptying problems and dysfunctional voiding. Potential pediatric transplant recipients must be classified according to pathophysiological as well as anatomical abnormalities of the urinary tract and all urological problems have to be

solved prior to transplantation. At our center, living donors are favored to plan transplantation of these children properly.

**Keywords** Renal transplantation · Children · Urological disorders

## Introduction

The prognosis of end-stage renal disease in children changed completely within the past 30 years. Renal transplantation remains to be the therapy of choice in children with renal insufficiency [1]. About 15–25% of children with end-stage renal failure have associated structural urological disorders (including posterior urethral valves, prune belly syndrome, myelodysplasia, or urogenital sinus abnormalities such as VATER association) connected with lower urinary tract dysfunction [2, 3, 4].

It has been shown that patients with poorly functioning bladders have inferior graft survival and an increased risk of complications such as urinary tract infections [5, 6].

A normal bladder is a low-pressure urinary reservoir, is large, adequate compliant, continent, and empties completely. When this function is not achieved in a natural bladder, complications, such as deterioration in renal function leading to end-stage renal disease, may occur [7]. Bladder dysfunction, presenting as dysfunctional voiding disorders (including, for example, incontinence, frequency, urgency, or obstructive urinary symptoms), can also affect graft function if untreated; thus, in patients with a low compliant, small volume bladder, reconstructive bladder surgery (such as bladder augmentation or urinary diversion) aims at creating a low-pressure reservoir that is continent and easily emptied and protects the upper urinary tract or the renal allograft [8].

Increased risk for urological complications, such as urinary tract infections and dysfunctional voiding, as well as high-pressure reflux into the graft, are sometimes observed in children with dysfunctional bladders. As severe, recurrent infections might threaten graft function, there should be an increased awareness on optimal management of the bladder function before and following renal transplantation.

In this retrospective study, we report the outcome and urological complications in 66 renal allografts transplanted in pediatric patients with a urological disorder.

## Patients and methods

### Patient demographics

We started the performance of pediatric renal transplantations in 1967. In order to report a sufficient, at least 3-year follow-up period, we stop our retrospective analysis in March 2000. Between 1967 and March 2000, a total number of 1641 renal transplantations had been performed at the Department of Urology, University Hospital Heidelberg. A number of 349 pediatric renal transplantations had been performed (all recipients were younger than 18 years). The median age of all children at time of transplantation was 11 years (and varied from 1 to 18 years). A total number of 55 children had living related donors.

The distribution of primary diagnosis leading to end-stage renal failure is presented in Table 1. Sixty-six children had a urological disorder leading to renal insufficiency (including 28 children who had vesico-uretero-renal reflux). Patient characteristics are described in Table 2.

### Immunosuppression

The immunosuppressive treatment varied depending on the date of renal transplantation. Since 1996 the immunosuppressive therapy is a triple combination of cyclosporin A, prednisolone, and mycophenolate mofetil. The initial dose of cyclosporin A is 500 mg/m$^2$ per day per os, starting 6 h postoperatively. Afterwards, the cyclosporin dose is adjusted according to whole blood levels, aiming at levels of 200 ng/ml during the first 2 months and 150 ng/ml thereafter. Prednisolone (300 mg/m$^2$) is given intraoperatively, then the dose is tapered off weekly to an ultimate dose of 4 mg/m$^2$ 7 weeks following renal transplantation. Treatment with mycophenolate mofetil (1200 mg/m$^2$) is started 1 day following transplantation. Before 1996, Azathioprine was administered instead of mycophenolate mofetil.

**Table 1** Underlying diseases

| Disease | No. of children | Percentage |
|---|---|---|
| Renal dysplasia (including polycystic kidney diseases) | 101 | 28.8 |
| Nephrotic syndrome | 70 | 20 |
| Glomerulonephritis | 59 | 17 |
| Malformation of the urinary tract (including vesico-ureteral reflux) | 66 | 18.9 |
| HUS | 14 | 4 |
| Oxalosis/zystinosis | 10 | 3 |
| Others | 29 | 8.3 |

**Table 2** Children with malformations of the lower urinary tract: patient demographics

| Kind of malformation | No. of transplantations | Median age (years) | Donor age (years) | Living-related transplants | Time of dialysis (months) | Cold ischemic time (h) | Immunosuppressive treatment |
|---|---|---|---|---|---|---|---|
| Posterior urethral valves | 27 | 9 (2–17) | 20 (1–59) | 2 of 27 | 12 (1–59) | 23.5 (1–59) | regimen 1: $n=11$; regimen 2: $n=8$; regimen 3: $n=2$; regimen 7: $n=1$ |
| Prune belly syndrome/ VATER Association | 7 | 4 (3–14) | 29 (8–42) | 1 of 7 | 13 (0–60) | 19 (2.5–23.5) | regimen 1: $n=5$; regimen 2: $n=1$; regimen 3: $n=1$ |
| "Neurogenic bladder" | 4 | 7 (2–13) | 11.5 (0.5–53) | 0 of 4 | 19 (1–43) | 24.5 (20–27) | regimen 1: $n=3$; regimen 3: $n=1$ |
| Vesico-ureteral reflux | 28 | 11 (2–15) | 32 (1–62) | 5 of 28 | 9 (0–62) | 19 (0.5–32) | regimen 1: $n=8$; regimen 2: $n=5$; regimen 3: $n=5$; regimen 4: $n=4$; regimen 5: $n=3$; regimen 6: $n=1$; regimen 7: $n=1$ |
| $p$ value | | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

Regimen 1: CSA, prednisolone, mycophenolate mofetil.
Regimen 2: CSA, prednisolone, azathioprine.
Regimen 3: CSA, prednisolone.
Regimen 4: FK 506, prednisolone.
Regimen 5: FK 506, prednisolone, azathioprine.
Regimen 6: prednisolone, azathioprine.
Regimen 7: ATG, predinsolone.

Episodes of acute rejection are treated with steroids. In case of steroid resistant rejection, a switch to FK 605 and cyclosporin withdrawal is performed.

The graft was considered to have failed when a patient received another renal transplant or resumed dialysis.

## Preoperative lower urinary tract evaluation and management

The complete evaluation of the urinary tract included ultrasonography of the native kidneys, voiding cystourethrography, and urodynamic studies (especially measurement of the uroflow and the postvoiding residual urinary volume).

The majority of our patients underwent various surgical interventions (long time) before transplantation in order to preserve renal function.

### *Posterior urethral valves*

Valve ablation had been performed in all boys who had posterior urethral valves. A number of 7 children underwent temporary high diversion (cutaneous ureterostomy) in order to prevent the progression of renal failure. In 2 children, unilateral ureteroneocystostomy had been performed to treat ureterovesical junction obstruction of a native kidney. One boy with poor bladder capacity had bladder augmentation (enterocystoplasty) about 3 years before transplantation. Ureteronephrectomy of the native kidneys had been performed in 10 boys before renal transplantation.

### *VATER association and prune belly syndrome*

Two children with imperforate anus had an anus praeter created shortly after birth. Two patients had unilateral cutaneous pyelostomy after having undergone contralateral ureteronephrectomy. One child with a noncompliant bladder had urinary diversion (ileal conduit) prior to transplantation.

### *"Neurogenic bladder"*

In order to assure sufficient storage capacity and adequate bladder compliance, two children got bladder augmentation (enterocystoplasty). Two children had urinary diversion (ileal conduit) as their parents were unwilling to perform clean intermittent catheterization.

### *Vesicoureteral reflux*

Surgical correction of reflux had been performed in all children with VUR. Ureteroneocystostomy using an

intravesical approach (including a psoas hitch) was the most commonly used technique. Bilateral nephroureterectomy had been performed in 4 children and unilateral nephroureterectomy was done in 5 cases, due to persistent vesicoureteral reflux and recurrent urinary infections.

### Surgical procedure

Renal transplantation was performed in a standardized technique: the renal artery was anastomosed end to side to the aorta (between the bifurcation and the branching of the inferior mesenteric artery). The vein was anastomosed end to side to the distal caval vein. The ureter was anastomosed into the urinary bladder using and extravesical ureteroneocystostomy after positioning a double J catheter (as described by Röhl and Ziegler) [9].

In order to guarantee a complete drainage of the bladder, the suprapubic or transurethral catheter was removed about 7 days following transplantation. Usually, the double J Stent was left in situ for about 6 weeks.

### Postoperative lower urinary tract management

Urodynamic assessment, including voiding cystourethrography, was performed in patients who were at risk for bladder dysfunction and who developed complications (e.g., urinary tract infections).

### Statistical analysis

Data are given as median values. The statistical significance was evaluated by analysis of variance (ANOVA), Bonferroni's multiple comparison test. Graft survival was assessed using Kaplan-Meier cumulative survival plots. Groups were compared using the log-rank and chi-square test. Other data were assessed using the Fisher's exact test.

A $p$ value of $< 0.05$ was considered to show a statistical significant difference between two groups.

## Results

### Allograft function

The 1- and 5-year patient survival was 100%. Table 3 shows the 1- and 5-year graft survival rates in the children with special reference to their underlying diseases. The 1-year graft survival rate was 74% in children with posterior urethral valves and 92.8% in children with vesico-ureteral reflux, respectively ($p$: n.s). The 5-year graft survival was 62.9% (in children with PUV) and 78.5% (in children with VUR; $p$: n.s.)

**Table 3** Graft survival rates

| Underlying disease | 1-year graft survival rate (%) | 5-year graft survival rate (%) |
|---|---|---|
| Posterior urethral valves | 74 (20 of 27) | 62.9 (17 of 27) |
| Prune belly syndrome/ VATER association | 85.7 (6 of 7) | 71.4 (5 of 7) |
| "Neurogenic bladder" | 75 (3 of 4) | 50 (2 of 4) |
| Vesico-ureteral reflux | 92.8 (26 of 28) | 78.5 (22 of 28) |
| $p$ value | n.s. | n.s. |

No difference of statistical significance could be obtained in graft survival (Fisher's exact test)

Figure 1 shows graft survival data. The mean follow-up duration time in our study was $86.7 \pm 13.8$ months. The reasons for graft loss were acute rejection or chronic graft dysfunction in all cases.

Three boys (who had posterior urethral valves) had severe vascular complications (venous thromboses of the graft).

### Bladder/reservoir function

Patients with urinary diversions did well. In 2 children with meningomyelocele, the performance of clean intermittent catherization, which is mandatory in order to preserve renal function, was not possible; therefore, the graft was transplanted into their supravesical diversions which was the best solution in order to protect the graft function.

The children with augmented bladders had sufficient capacity and maintained adequate bladder emptying without catheterization but with frequent and double micturition. In 1 case clean intermittent self-catheterization via the native urethra was performed with good success.

### Urological complications

No severe technical complications were observed, although the transplant operation was technically difficult in all cases. Urinary tract infections were the most frequently regarded complications.

A lot of urological problems occurred in boys with posterior urethral valves: In 10 cases we observed recurrent urinary tract infections with two episodes of urosepsis in two boys. Complete urodynamic assessment, including voiding cystourethrography, was performed and revealed a low-grade reflux into the graft in 1 case; therefore, tunneled ureteral reimplantation of the graft ureter had been performed. Nevertheless, afterwards the child had seven more urinary tract infections despite complete bladder emptying and the correction of the reflux.

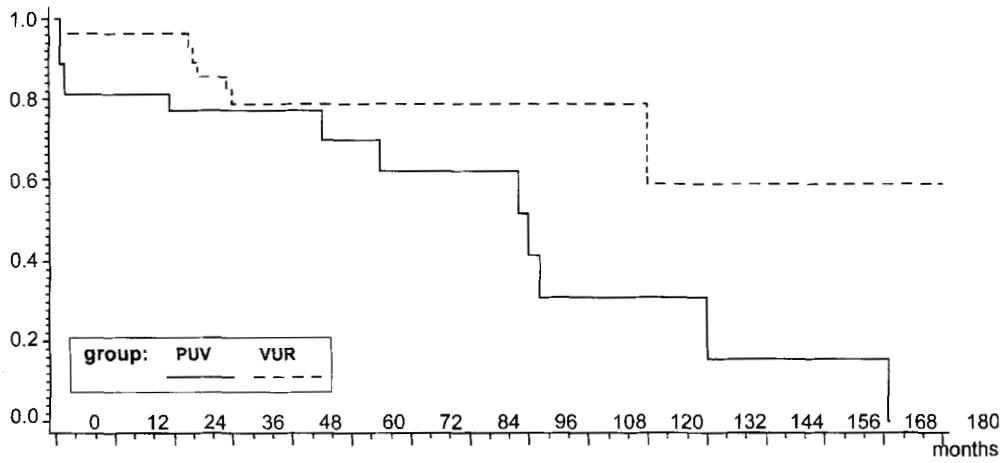


**Fig. 1** Graft survival in patients with posterior urethral valves (*PUV*) and vesico-ureteral reflux (*VUR*)

As vesico-ureteral reflux into the native kidney was documented in another boy; unilateral ureteronephrectomy of the native kidney was performed in this child. High bladder pressure could be excluded in this case.

As complete urodynamic investigations were performed in children with urinary tract infections, high voiding pressures and a relatively small bladder capacity (< 250 ml) could be regarded in three boys. Urethrocystoscopy showed no evidence of anatomical obstruction of the bladder neck or urethra. Subsequently, medical treatment with anticholinergics and $\alpha$ antagonists achieved satisfactory bladder capacity and voiding pressure. Children were advised to do frequent and timed voiding, so postvoiding residual urine volume was not observed.

In one boy, who had recurrent, symptomatic urinary tract infections, a urodynamic investigation documented a poor flow rate and elevated residual volumes as well as a non-compliant, low-capacity bladder. In addition, a urethral stricture was observed. As the child was not in current treatment at our department and the parents refused to allow clean, intermittent catheterization, the child was treated with a cutaneous vesicostomy.

Three boys who had posterior urethral valves suffered from irritating voiding symptoms of urgency and enuresis nocturna. As the posttransplant urodynamic re-evaluation showed moderate bladder capacity and excluded high voiding pressure, postvoiding residual urine volume, or a reflux into the graft, anticholinergics were successfully administered.

In one child who had urinary tract infections, nephrolithiasis developed 6 months following renal transplantation. It could be treated successfully with shock-wave lithotripsy and residual stone fragments could be removed ureterorenoscopically.

All children who developed at least one urinary tract infection were treated with a chemoprophylaxis, so the incidence of symptomatic infections decreased.

## Discussion

Renal transplantation in children has to be successful in many ways: first of all, excellent patient survival, good graft survival and sufficient quality of life has to be achieved.

There is an increasing awareness that congenital urological disorders may adversely influence the outcome and success of renal transplantation [2]. Previously, patients with severe lower urinary tract malformations had been excluded from renal transplant programs, as it appeared reasonable that a bladder that contributed to the destruction of the native kidneys would threaten a renal allograft [8, 10, 11, 12].

Children with posterior urethral valves are at risk for developing renal insufficiency [13, 14]. They may develop vesical dysfunction (the so-called valve bladder) which requires careful urological observation and intervention, especially if renal transplantation has to be planned and performed [15].

Compared with other series, we also observed a striking rate of urinary tract infections following renal transplantation, especially in children who had posterior urethral valves [13, 16]. If urinary tract infections were observed, they usually occurred recurrently. As colonization is usually present in children with bladder augmentation or ileum conduit, only positive urine culture together with elevation of the C-reactive protein was taken to prove urinary tract infections. Urinary tract infections were graded as asymptomatic, symptomatic with urinary symptoms, and serious with systemic symptoms and affection of the graft function. We did not observe a direct contribution to graft loss, but there is no doubt that recurrent symptomatic infections of the urinary tract may trigger rejection episodes and contribute to the development of chronic allograft dysfunction. It is very likely that the poor 1- and 5-year

graft survival rate in the children with posterior urethral valves is due to this problem.

The application of prophylactic antibiotics on a long-term basis helped to reduce the infection rates in our patients. Our standard practice now is to give long-term antibiotics (single dose at night) in all patients with bladder dysfunction following transplantation for at least 6 months. The treatment is continued if urinary tract infections occur. In case of urinary tract infections, ultrasound of the transplant, the native kidneys, and the bladder is performed in order to exclude a possible obstruction at the ureterovesical junction or stones.

The development of bladder and upper tract stones occurs in 8–52% of patients with bladder augmentation [17]. It is remarkable that we observed the occurrence of a stone only in 1 case which might be due to the frequent follow-up investigations (including ultrasound of the graft and native kidneys) in our department.

It is not surprising that the children with reflux had the best 1- and 5-year graft survival rates, as no signs of dysfunctional voiding and no reflux into the graft (except for 1 patient) had been observed in these patients.

The number of children who had prune belly syndrome and VATER association as well as neurogenic bladder was very low, so it is difficult to make definitive statements. Nevertheless, our data are in accordance with Fontaine et al. who described that renal transplantation in children with prune belly syndrome is not associated with higher incidence of graft failure than in a matched control group [18].

Concerning the optimal treatment of children with neurogenic bladder and end-stage renal failure, there are controversial points of view [13, 19, 20]. Whenever possible, kidney transplant ureters should be drained into the native bladder; in case of low capacity, anticholingergic treatment or augmentation cystoplasty (with ileum, native ureter, or colon) should be performed [13, 21].

Our patients with urinary diversions did well. Especially in children, the performance of clean, intermittent catheterization via the native urethra or a stoma is extremely difficult, and non-compliance by patients and parents has to be considered.

In case of voiding disorders and residual volume after double micturition, the patient must be instructed to perform clean intermittent self-catheterization. This prevents a high-pressure reflux into the graft and/or residual urine after voiding, which might threaten graft function by triggering repeated infections. If regular catherization is not accepted by the child or the parents, even incontinent urinary drainage has to be discussed in order to protect the graft function.

## Conclusion

In conclusion, children with renal insufficiency due to a dysfunctional bladder can receive a renal allograft and achieve good long-term results. Correction of structural urogenital abnormalities and optimization of emptying and storage functions of the bladder has to be achieved before renal transplantation. Besides, we recommend careful urodynamic surveillance following transplantation especially after the occurrence of any urological complication.

Our observations confirm that no one technique for the urinary drainage of the transplanted kidney should be considered as a standard approach as stable lower urinary tract pressures can be achieved using intermittent catheterization, medical therapy, timed voiding, augmentation cystoplasty, and supravesical diversion. The approach has to be customized for each child and the parents or persons in charge.

Bladder augmentation or urinary diversion usually does not adversely affect the function and survival of grafts after renal transplantation in children, if excellent compliance by children and parents is guaranteed.

Tunneled ureteral reimplantation at the time of transplantation as well as antibiotic prophylaxis in patients with dysfunctional urinary tract minimize the risk for urinary tract infections which may trigger the development of acute rejection episodes and contribute to the manifestation of chronic allograft nephropathy.

## References


1. Broyer M, LeBihan C, Charbit M, Guest G, Tete MJ, Gagnadoux M, et al. Long-term social outcome of children after kidney transplantation. Transplantation 2004; 77:1033–1037
2. Koo HP, Bunchman TE, Flynn JT, et al. Renal transplantation in children with severe lower urinary tract dysfunction. J Urol 1999; 161:240–245
3. Churchill BM, Sheldon CA, McLorie GA, Arbus GS. Factors influencing patient and graft survival in 300 cadaveric pediatric renal transplants. J Urol 1988; 140:1129–1132
4. Zaragoza MR, Rittchey ML, Bloom DA, McGuire EJ. Enterocystoplasty in renal transplantation candidates: urodynamic evalutation and outcome. J Urol 1993; 150:1463–1466
5. DeFloor W, Tackett L, Minevich E, McEnery P, Kitchens D, Reeves D, et al. Successful renal transplantation in children with posterior urethral valves. J Urol 2003; 170:2402–2404
6. Reinberg, Y, Gonzalez R, Fryd D, Mauer SM, Najarian JS. The outcome of renal transplantation in children with posterior urethral valves. J Urol 1988; 140:1491

7. Crowe A, Cairns H, Wood S, Rudge C, Woodhouse C, Neild G. Renal transplantation following renal failure due to urological disorders. Nephrol Dial Transplant 1998; 13:2065–2069
8. Capizzi A, Zanon GF, Zacchello G, Rigamonti W. Kidney transplantation in children with reconstructed bladder. Transplantation 2004; 77:1113–1116
9. Adams J, Güdemann C, Tönshoff B, Mehls O, Wiesel M. Renal transplantation in small children: a comparison between surgical procedures. Eur Urol 2001; 40:552–556
10. Sheldon CA, Gonzalez R, Burn MW, et al. Renal transplantation into the dysfunctional bladder: the role of adjunctive bladder reconstruction. J Urol 1994; 152:972
11. Mochon M, Kaiser BA, Dunn S, et al. Urinary tract infections in children with posterior urethral valves after kidney transplantation. J Urol 1992; 148:1874–1880
12. Luke PW, Herz D, Bellinger M, Chakrabarti P, Vivas CA, Scantlebury VP, et al. Long-term results of pediatric renal transplantation into a dysfunctional lower urinary tract. Transplantation 2003; 76:1578–1582
13. Hatch DA, Koyle MA, Baskin LS, et al. Kidney transplantation in children with urinary diversion or bladder augmentation. J Urol 2001; 165:2265–2268
14. Salomon L, Fontaine E, Gagnadoux MF, et al. Posterior urethral valves: long term renal function consequences after transplantation. J Urol 1997; 157:992–995
15. Glassberg KI. The valve bladder syndrome: 20 years later. J Urol 2003; 166:1406–1414
16. Fontaine E, Gagnadoux MF, Niaudet P, et al. Renal transplantation in children with augmentation cystoplasty. J Urol 1998; 159:2110–2113
17. Palmer LS, Franco I, Kogan SJ, et al. Urolithiasis in children following augmentation cystoplasty. J Urol 1993; 150:726–730
18. Fontaine E, Salomon L, Gagnadoux MF, et al. Long term results in renal transplantation in children with prune belly syndrome. J Urol 1997; 158:892–894
19. Martin X, Aboutaieb R, Soliman S, et al. The use of long-term defunctionalized bladder in renal transplantation: Is it safe? Eur Urol 1999; 36:450–453
20. Jacoby K, Banowsky LH. Renal transplantation into ileal conduits: results and long term follow-up. Clin Transpl 1991; 5:365–367
21. Rink RC. Bladder augmentation: options, outcomes, future. Urol Clin North Am 1999; 26:111–113