0041-1337/03/7611-1578/0
TRANSPLANTATION
Copyright © 2003 by Lippincott Williams & Wilkins, Inc.

Vol. 76, 1578–1582, No. 11, December 15, 2003
Printed in U.S.A.

LONG-TERM RESULTS OF PEDIATRIC RENAL TRANSPLANTATION INTO A DYSFUNCTIONAL LOWER URINARY TRACT

PATRICK P. W. LUKE,[1,2,3,5] DANIEL B. HERZ,[1] MARK F. BELLINGER,[1] PRADIP CHAKRABARTI,[2] CARLOS A. VIVAS,[1] VELMA P. SCANTLEBURY,[2] THOMAS R. HAKALA,[1] ANTHONY M. JEVNIKAR,[4] ASHOK JAIN,[2] RON SHAPIRO,[2] AND MARK L. JORDAN[1]

Background. **The authors reviewed their long-term experience with pediatric renal transplantation into a dysfunctional lower urinary tract to evaluate the results of contemporary lower urinary tract evaluation and management on graft survival and function.**

Methods. **Between 1990 and 1996, 21 renal transplants were performed in 20 children with dysfunctional lower urinary tracts and 61 transplants were performed in 61 patients with normal lower urinary tracts. The minimum follow-up was 36 months (mean, 62.0±19.6 months). The cause of lower urinary tract dysfunction included posterior urethral valves (n=13), prune belly syndrome (n=4), meningomyelocele (n=2), and urogenital sinus abnormality (n=1). Urodynamics were performed on all children with dysfunctional lower urinary tracts. Using these perioperative assessments, lower tract management strategies were devised, including timed voiding alone (n=6), clean intermittent catheterization (n=8), bladder augmentation (n=4), and supravesical urinary diversion (n=2).**

Results. **Overall 5-year actuarial patient and graft survival rates were 100% versus 95% (*P*=not significant [NS]) and 83% versus 69% in the dysfunctional and normal urinary tract groups (*P*=NS), respectively. Mean serum creatinine levels in dysfunctional and normal urinary tract patients with functioning grafts at 3 years were 1.3±0.5 and 1.3±0.7 mg/dL, respectively (*P*=NS). However, 35% of patients with a dysfunctional lower urinary tract experienced urologic complications.**

Conclusions. **Pediatric renal transplantation into a dysfunctional lower urinary tract yields outcomes comparable to transplantation into the normal lower urinary tract. Because of the high urologic complication rates, careful surveillance of lower urinary tract function by urodynamic evaluation is essential to optimize these outcomes.**

Renal transplantation in pediatric patients is highly successful (*1*). However, transplantation into the dysfunctional lower urinary tract (DLUT) has been associated with relatively high complication rates (*2*, *3*) and inferior graft survival according to historic case series (*4–6*). With the evolution of lower urinary tract evaluation (*7*, *8*) and management using anticholinergic medications, clean intermittent catheterization (CIC) (*9–11*), and bladder augmentation procedures (*12*, *13*) in the past 20 years, improvements in renal function and lower urinary tract preservation have been accomplished in the majority of pediatric patients with congenital lower urinary tract anomalies.

Contemporary studies have indicated that renal transplantation outcomes in adult patients with DLUT are comparable to those observed in patients with normal lower urinary tracts (NLUT) (*14–16*). However, there are limited data regarding the results of transplantation in the pediatric population (*17*). A distinction between pediatric and adult patients needs to be emphasized, because adherence to strict timed voiding schedules and CIC regimens is far more challenging in the pediatric and adolescent population, placing these patients at greater risk for upper tract deterioration. We hypothesize that with rigorous lower tract follow-up and compliance with contemporary techniques in the management of lower tract dysfunction, pediatric renal transplant patients can maintain excellent long-term graft survival and function in accordance with the excellent results seen in the adult population. In this report, we compared the long-term outcomes of pediatric renal transplantation in children with DLUT with outcomes in children with NLUT during the 1990s at the University of Pittsburgh Medical Center.

PATIENTS AND METHODS

Patient Demographics

Between 1990 and 1996, 21 renal allografts were transplanted into 20 patients with DLUT (18 male patients and 2 female patients). Over the same period of time, 61 renal allografts were transplanted into 61 patients with NLUT (26 male patients and 25 female patients). Patients were followed for a minimum of 36 months (mean, 62.0±19.6 months; range, 36–98 months) from the time of transplantation. Patient demographics are shown in Table 1. Patients were comparable in all demographic categories except for the cold ischemia time, which was higher in the DLUT group than in the NLUT group (*P*=0.008).

DLUT Patients

The cause of lower urinary tract dysfunction included 13 patients with posterior urethral valves (PUV), four with prune belly syndrome (PBS), two with meningomyelocele, and one with urethral atresia-imperforate anus syndrome. Preoperatively, patients with lower urinary tract dysfunction were evaluated using voiding cys-

[1] Department of Urology, University of Pittsburgh Medical Center, Childrens Hospital of Pittsburgh, Pittsburgh, PA.

[2] Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Childrens Hospital of Pittsburgh, Pittsburgh, PA.

[3] Division of Urology, London Health Sciences Centre, London, Ontario, Canada.

[4] Division of Nephrology, London Health Sciences Centre, London, Ontario, Canada.

[5] Address correspondence to: Patrick P. W. Luke, M.D., F.R.C.S., Division of Urology, 339 Windermere Road, London, Ontario N6A 5A5, Canada. E-mail: patrick.luke@lhsc.on.ca.

Received 14 April 2003. Revision requested 15 May 2003. Accepted 27 June 2003.

DOI: 10.1097/01.TP.0000090866.00241.0C

TABLE 1. Patient demographics

	NLUT (%)	DLUT (%)	*P* value
Mean age (yr)	11.2±5.4	9.3±5.6	NS
No. of transplants	61	21	
Living-related transplant	25 (41)	9 (43)	NS
Second transplant	7 (12)	4 (19)	NS
Third transplant	5 (8)	1 (5)	NS
HLA matches	2.8±1.3	3.0±1.2	NS
% PRA	7.8±19.6	4.1±10.4	NS
Donor age (yr)	27.8±15.8	28.7±11.8	NS
Cold ischemic time (hr)	8.1±8.2	14.7±13.1	0.008

NS, Not significant; PRA, panel reactive antibody; HLA, human leukocyte antigen.

tourethrography (VCUG), renal ultrasonography, and urodynamics (cystometrography, postvoid residual urinary volume).

Preoperative Lower Urinary Tract Evaluation and Management

Using these urodynamic studies, patients were managed according to their degree of bladder dysfunction. We categorized patients into separate groups according to lower tract management (Table 2). In group 1, six patients with low postvoid residuals and low terminal bladder pressures were considered to have safe bladder storage parameters and were managed with timed voiding. These patients were otherwise allowed to void spontaneously. In group 2, eight patients had adequate bladder capacities, but because of poor bladder wall compliance parameters or elevated postvoid residual volumes, clean intermittent catheterization with or without anticholinergic medications were necessary to reduce terminal bladder pressures and postvoid residuals. In group 3a, the two patients with preexisting bladder augmentations (enterocystoplasty) displayed excellent storage capacity and bladder compliance. The two patients in group 3b had small, fibrotic, noncompliant bladders and therefore required bladder augmentation (ureterocystoplasty) at the time of transplantation. All patients in groups 3a and 3b were required to perform CIC to reduce postvoid residual volumes postoperatively. Patients in group 4 had preexisting urinary diversions. The first child, who was diagnosed with urethral atresia-imperforate anus syndrome and a dysplastic right kidney, had a left cutaneous pyelostomy created shortly after birth. The second child had a right cutaneous pyelostomy after having undergone bilateral nephrectomy for complications from PBS. They were not candidates for undiversion, because of inability or reluctance to perform CIC. Therefore, they received transplants into their supravesical diversions.

Postoperative Lower Urinary Tract Evaluation and Management

Postoperative upper tract sonography was performed in all patients. Urodynamic assessment was performed in selected patients who were at risk for upper tract deterioration from lower tract dysfunction (Table 3). In addition, all patients were placed on prophylactic antibiotics three times weekly.

Immunosuppression

All patients received tacrolimus-prednisone immunosuppression, without antibody induction. Target tacrolimus and corticosteroid dosing was performed according to guidelines previously published by our group (*1*). In addition, corticosteroids were completely withdrawn 6 months posttransplantation in 85% of DLUT (17 of 20) and 90% of NLUT (55 of 61) patients. These patients have remained steroid-free at last follow-up. Rejection episodes were treated with a bolus and recycle of corticosteroids as previously described by our group (*1*). Corticosteroid-resistant rejections were treated with antilymphocyte antibody therapy.

TABLE 2. Pretransplant urodynamics in DLUT patients[a]

Group	No.	Bladder capacity (mean±SD) (mL)	Terminal bladder pressure (mean±SD) (cm H_2O)
1—Timed voiding	6	187±254	18±8
2—CIC	8	198±92	26±5
3a—Bladder augmentation (pretransplant)	2	450±141	6±1
3b—Bladder augmentation (at time of transplant)	2	46±6	82±10
4—Preexisting diversion	2	47±33	66±20

[a] Lower tract management of patients was determined according to pretransplant urodynamic evaluation. Patients were classified into groups according to lower urinary tract management. The urodynamic characteristics of patients in these groups are represented in this table.

CIC, Clean intermittent catheterization.

TABLE 3. Pre- and Posttransplantation urodynamics in DLUT patients[a]

Patient	Pretransplant		Posttransplant	
	Bladder capacity (mL)	Terminal bladder pressure (cm H_2O)	Bladder capacity (mL)	Terminal bladder pressure (cm H_2O)
Timed Voiding				
1	350	7	625	5
CIC				
2	150	26	250	22
3	180	24	225	25
Augmentation (pretransplant)				
4	600	5	350	31
Augmentation (with transplant)				
5	42	89	150	19
6	50	75	225	12

[a] The pre- and posttransplantation urodynamic characteristics in selected patients are represented in this table. Posttransplantation urodynamics were performed in patients who had complications or bladder augmentation at the time of transplantation.

CIC, Clean intermittent catheterization.

Statistical Analysis

Patient and graft survival rates were calculated using Kaplan-Meier cumulative survival plots and groups were compared using the log-rank (Mantel-Cox) chi-square test. Other data were assessed using the Student *t* test and analysis of variance. Data are expressed as mean±SD. A value of $P<0.05$ was used to indicate statistical significance.

RESULTS

Patient and Allograft Survival

Figure 1 shows the patient and graft survival data. The mean follow-up duration in this study was 62.0±19.6 months (range, 36–92 months). The 5-year actuarial patient survival rates were 100% and 95% in the DLUT and NLUT groups, respectively (*P*=not significant [NS]). Overall, there were three deaths, all in the NLUT group and all related to sepsis. The 1- and 5-year actuarial graft survival rates were 100% and 83% in DLUT patients, and 97% and 69% in NLUT patients, respectively (*P*=NS). The two graft losses in the DLUT group were attributed to biopsy-proven chronic rejection and were not related to lower tract dysfunction. In both cases of graft loss in this group, the causes of DLUT were PUV and PBS, and these patients had been managed with timed voiding alone. Table 4 lists the cause for graft loss in both DLUT and NLUT groups.

Allograft Function

The mean serum creatinine in the DLUT and NLUT patients with functioning grafts was 1.3±0.5 and 1.3±0.7 mg/dL at 3 years, respectively (*P*=NS). Renal function in the DLUT patients was similar regardless of DLUT management: mean serum creatinine was 1.2±0.4 mg/dL in patients who were managed by timed voiding, 1.5±0.7 mg/dL in patients who required CIC, 1.3±0.3 mg/dL in patients with bladder augmentation, and 1.2±0.3 mg/dL in patients who underwent transplantation into their urinary diversions (all *P*=NS).

Biopsy-proven rejection occurred in 62% (13 of 21) of DLUT patients and in 48% (30 of 61) of patients with NLUT (*P*=NS). All rejection episodes in DLUT patients were reversed with a steroid recycle, whereas 4 of 30 (13%) NLUT patients with rejection required OKT3 therapy for steroid-resistant rejection.

Lower Tract Function

Patients with DLUT were managed according to preoperative bladder function as determined by urodynamic evaluation. Postoperative reevaluation with urodynamics was performed if complications arose or if bladder augmentation was performed at the time of transplantation. Terminal bladder pressures greater than 40 cm H_2O were considered detrimental to upper tract function, and pressures less than 20 cm H_2O were considered to be consistent with safe storage (*7, 18*). The consequence of bladder pressures between 20 and 40 cm H_2O was less clear. In general, these patients were managed with CIC if there were any other abnormalities in urodynamic parameters.

Six patients were managed with timed voiding alone (group 1). These patients had an adequate mean bladder capacity (187±254 mL), low mean terminal pressure of 18±8 cm H_2O, and low mean postvoid residual urinary volumes (19±15 mL). Although two grafts were lost to chronic rejection in this group, the remaining patients continued to void spontaneously without the need for anticholinergic medications or CIC. Postoperatively, one patient developed a urinary tract infection. Subsequently, he was reevaluated with urodynamics and VCUG. All urodynamic parameters remained within acceptable limits (Table 3).

The eight patients managed with CIC with or without anticholinergic medication demonstrated adequate preoperative bladder capacities (mean, 198±92 mL). However, ter-

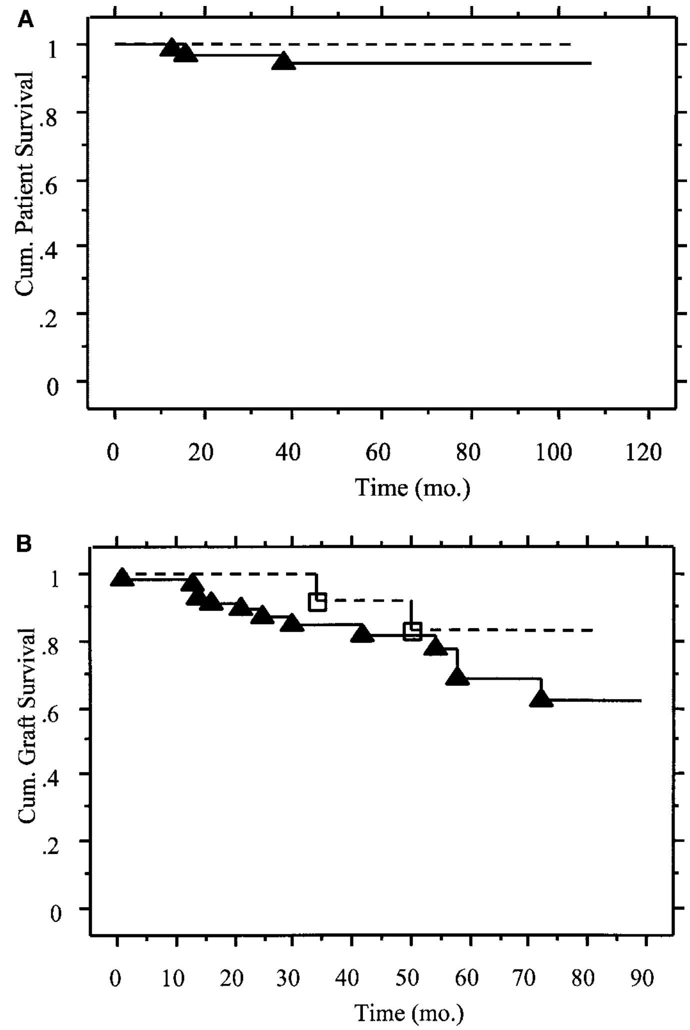

FIGURE 1. (A) Overall patient survival in DLUT and NLUT patients is similar. Patient survival was assessed using Kaplan-Meier cumulative survival plots. (*dashed line*) DLUT patient survival; (*solid line*) NLUT patient survival (*P*=NS). (B) Overall graft survival in DLUT and NLUT patients is similar. Graft survival was assessed using Kaplan-Meier cumulative survival plots. (*dashed line*) DLUT graft survival; (*solid line*) NLUT graft survival (*P*=NS).

TABLE 4. Cause of graft loss

NLUT (n=61)	DLUT (n=21)
Chronic rejection (2)	Chronic rejection (2)
Death with functioning graft (2)	
Recurrent disease (5)	

minal bladder pressures were moderately elevated (26±5 cm H_2O), necessitating CIC and a timed voiding regimen. Two patients were reevaluated with urodynamics after postoperative urologic complications (urinary infection and stricture). Again, postoperative functional bladder characteristics did not change appreciably (Table 3).

Two of four children in the bladder augmentation group underwent enterocystoplasty before renal transplantation. Preoperative bladder function was excellent in these patients (terminal bladder pressure, 6±1 cm H_2O; bladder capacity, 450±141 mL). Postoperatively, patients continued with CIC to optimize bladder drainage. One child developed a spontaneous bladder perforation 5 months posttransplantation, despite good preoperative function. The perforation sealed spontaneously, and after urodynamic reevaluation of the lower urinary tract, it was found that her bladder capacity had decreased from 600 mL to 350 mL, with a concomitant increase in terminal bladder pressure from 5 cm H_2O to 31 cm H_2O. Therefore, the frequency of CIC was increased from four to six times daily and anticholinergic medications were added to increase terminal bladder volumes to greater than 300 mL.

Two children had ureterocystoplasties performed at the time of transplantation, because of unacceptably high terminal bladder pressures (82±10 cm H_2O) and low bladder capacities (46.6±6 mL), respectively. Urodynamics performed postoperatively confirmed that these augmented bladders were capable of safe urinary storage (Table 3).

Poor bladder capacity (47±33 mL) and unacceptably high terminal bladder pressures (66±20 cm H_2O) rendered the final group of two patients candidates for bladder augmentation. However, refusal to self-catheterize in one and the inability to self-catheterize in another patient (cerebellar ataxia from Klippel-Feil syndrome) precluded the option of bladder augmentation in these two cases. Therefore, they received transplants into their preexisting supravesical urinary diversions.

Urologic Complications

Seven of 20 patients (35%) experienced 10 urologic complications. Four surgical procedures were required to manage these complications (Table 5). In the six patients managed with timed voiding alone (group 1), one developed an uncomplicated bacterial urinary tract infection, which responded to antibiotics. Two of eight patients managed with CIC alone (group 2) developed urologic complications. One patient had an uncomplicated urinary infection; the other patient (with a history of PUV) developed a filamentous urethral stricture that responded to simple urethral dilatation. Three of four transplants into augmented bladders (group 3) were followed by urologic complications. The first patient, who had a preexisting enterocystoplasty, developed a spontaneous bladder perforation several months posttransplantation. The perforation sealed spontaneously and the patient was treated by prolonged urethral catheterization alone. In addition, she later formed bladder stones, which were treated by cystolithopaxy. She subsequently developed two uncomplicated bacterial urinary tract infections over the next 2 years. VCUG did not demonstrate vesicoureteral reflux. Urodynamic assessment documented high terminal bladder pressures, and she was managed with increased CIC frequency and anticholinergic medication. During the subsequent 2 years, no further complications occurred. The two other patients in this group developed pyelonephritis associated with severe vesicoureteral reflux. These patients had nontunneled ureteral implantations at the time of the transplantation. Both patients were managed with successful tunneled ureteroneocystostomies, eliminating reflux and recurrent upper tract infection. One month posttransplantation, one patient also developed a urethral stricture, which was eventually managed by cutaneous vesicostomy, because CIC through the diseased urethra proved too arduous a task for this patient's family. No complications occurred in the two patients who received transplants into their preexisting urinary diversions (group 4).

DISCUSSION

McGuire et al. demonstrated that the presence of bladder leak point pressures (terminal bladder pressures) above 40 cm H_2O are associated with upper tract deterioration (*7*). In addition, others have suggested that normal bladder filling pressures are below 20 cm H_2O (*18*). Therefore, children were assigned to different management regimens (timed voiding and CIC) and procedures (bladder augmentation) according to preoperative assessment of bladder compliance and capacity to keep terminal bladder pressures well below 40 cm H_2O (Tables 2 and 3). Only two patients were unable or unwilling to perform CIC, and the allografts were therefore transplanted into their urinary diversions. Despite varying degrees of lower tract dysfunction, long-term graft outcome was

TABLE 5. Urologic complications in DLUT patients[a]

Group	No.	Complications	Surgery
1—Timed voiding	6	1 Uncomplicated UTI	None
2—CIC	8	1 Uncomplicated UTI	None
		1 Urethral stricture	Urethral dilatation (1)
3a—Bladder augmentation (pretransplantation)	2	1 Bladder perforation[b]	None
		1 Bladder stone[b]	Cystolithopaxy (1)
		2 Uncomplicated UTI[b]	None
3b—Bladder augmentation (at time of transplant)	2	2 Pyelonephritis/reflux	Ureteroneocystotomy (2)
		1 Urethral stricture	Cutaneous vesicostomy (1)
4—Diversion	2	None	None
Total	20	10	5

[a] Patients were classified according to lower tract management (groups 1–4).
[b] One patient had four separate complications.
CIC, Clean intermittent catheterization; UTI, urinary tract infection.

virtually identical among this group of patients. As a group, overall patient and graft survival and function were equivalent when NLUT and DLUT patients were compared. This suggests that good long-term renal function may be maintained if stable lower urinary tract pressures can be achieved using CIC, timed voiding, medical therapy, and augmentation cystoplasty. Although supravesical diversion has been historically associated with inferior graft survival and high complication rates (*3*, *4*), excellent long-term renal function and low complication rates were achieved in the two patients with low-pressure urinary diversions as well. Because the results of renal transplantation into the DLUT had been historically poor (*2*), our excellent results are a testament to the diligent preoperative workup and postoperative surveillance required to maintain upper tract integrity.

Five patients (25%) developed urologic complications requiring surgical intervention, and two others (10%) had uncomplicated urinary tract infections, consistent with the high complication rates found in other studies (*3*, *14*, *15*). The two cases of urethral strictures were likely related to complications from the original disease (PUV). One patient developed a spontaneous bladder perforation, recurrent urinary infections, and bladder stone formation, all of which are well-documented complications of enterocystoplasty (*19*, *20*). Despite acceptable pretransplant urodynamic parameters, these patients need to be followed closely, with emphasis on strict adherence to timed voiding and CIC schedules to minimize the frequency of these complications. In the same patient, urodynamic surveillance demonstrated that bladder functional characteristics had deteriorated, necessitating an increase in CIC frequency. We therefore recommend that VCUG, upper tract imaging, and urodynamic reassessment of the lower urinary tract be performed after the occurrence of any urologic complication. The two patients who had bladder augmentations performed at the time of transplantation developed pyelonephritis associated with high-grade vesicoureteral reflux. Both patients required tunneled reimplantation of the transplant ureters at a later date. Because of these complications, we now recommend that every attempt be made to perform tunneled ureteral reimplantation at the time of transplantation in patients with DLUT. This holds especially true in patients with bladder augmentations. Because these patients are at an increased risk for lower tract colonization with bacteria (*19*), a nonrefluxing ureteroneocystostomy would prevent the ascension of bacteria into the upper urinary tract. Although our urologic complication rate was high, no grafts were lost as a result of lower tract dysfunction. This highlights the importance of diligent lower urinary tract evaluation, surveillance, and management in this complex group of patients, both before and after transplantation.

CONCLUSION

We conclude that renal transplantation in children with a DLUT yields long-term outcomes comparable to those in children with NLUT. Because of the high urologic complication rates associated with these transplants, careful evaluation, surveillance, and management of the lower urinary tract are essential to optimize these outcomes.

REFERENCES

1. Shapiro R, Scantlebury VP, Jordan ML, et al. Pediatric renal transplantation under tacrolimus-based immunosuppression. Transplantation 1999; 67: 299.
2. Nguyen GH, Reinberg Y, Gonzalez R, et al. Outcome of renal transplantation after urinary diversion and enterocystoplasty: A retrospective controlled study. J Urol 1990; 144: 1349.
3. Hatch DA, Belitsky P, Barry JM, et al. Fate of renal allografts transplanted in patients with urinary diversion. Transplantation 1993; 56: 838.
4. Kelly WD, Merkel FK, Markland C. Ileal urinary diversion in conjunction with renal homotransplantation. Lancet 1966; 1: 222.
5. Reinberg Y, Gonzalez R, Fryd D, et al. The outcome of renal transplantation in children with posterior urethral valves. J Urol 1988; 140: 1491.
6. Bryant JE, Joseph DB, Kohaut EC, et al. Renal transplantation in children with posterior urethral valves. J Urol 1991; 146: 1585.
7. McGuire EJ, Woodside JR, Borden TA, et al. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981; 126: 205.
8. Kashi SH, Wynne KS, Sadek SA, et al. An evaluation of vesical urodynamics before renal transplantation and its effect on renal allograft function and survival. Transplantation 1994; 57: 1455.
9. Diokno AC, Sonda LP, Hollander JB, et al. Fate of patients started on clean intermittent self-catheterization therapy 10 years ago. J Urol 1983; 129: 1120.
10. Gill IS, Hayes JM, Hodge EE, et al. Clean intermittent catheterization and urinary diversion in the management of renal transplant recipients with lower urinary tract dysfunction. J Urol 1992; 148: 1397.
11. Flechner SM, Conley SB, Brewer ED, et al. Intermittent clean catheterization: An alternative to diversion in continent transplant recipients with lower urinary tract dysfunction. J Urol 1983; 130: 878.
12. Marshall FF, Smolev JK, Spees EK, et al. The urological evaluation and management of patients with congenital lower urinary tract anomalies prior to renal transplantation. J Urol 1982; 127: 1078.
13. Zaragoza MR, Ritchey ML, Bloom DA, et al. Enterocystoplasty in renal transplantation candidates: Urodynamic evaluation and outcome. J Urol 1993; 150: 1463.
14. Crowe A, Cairns HS, Wood S, et al. Renal transplantation following renal failure due to urological disorders. Nephrol Dial Transplant 1998; 13: 2065.
15. Hatch DA. Kidney transplantation in patients with an abnormal lower urinary tract. Urol Clin North Am 1994; 21: 311.
16. Griffin PJ, Stephenson TP, Brough S, et al. Transplanting patients with abnormal lower urinary tracts. Transpl Int 1994; 7: 288.
17. Indudharra R, Joseph DB, Perez LM, et al. Renal transplantation in children with posterior urethral valves revisited: A 10 year follow-up. J Urol 1998; 160: 1201.
18. Houle AM, Gilmour RF, Churchill BM, et al. What volume can a child normally store in the bladder at a safe pressure? J Urol 1993; 149: 561.
19. Mast P, Hoebeke P, Wyndaele JJ, et al. Experience with augmentation cystoplasty. Paraplegia 1995; 33: 560.
20. Couillard DR, Vapnek JM, Rentzepis MJ, et al. Fatal perforation of augmentation cystoplasty in an adult. Urology 1993; 42: 585.