



## Surgical Treatment of Vesicoureteral Reflux in Kidney Transplant Patients with Symptomatic Urinary Tract Infection: A Single Institution Review of 123 Patients

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### Abstract

**Introduction:** Renal transplant patients are at a higher risk for urinary tract infections and vesicoureteral reflux is a well-known risk factor for recurrent urinary tract infections. The exact incidence of vesicoureteral reflux is difficult to determine in renal transplant patients because routine VCUG (voiding cystourethrogram) is not performed. Majority of patients with VUR (Vesicoureteral reflux) are asymptomatic, however those patients with recurrent symptomatic UTI tend to have higher grade of VUR. We have experienced a 3% symptomatic reflux rate in our transplant patients and have performed reconstructive surgery on a majority of them. Because there is a paucity of published data regarding success rate of such reconstructive surgery, we have reviewed our data.

This study represents the largest dataset looking into outcomes following corrective surgery for VUR in renal transplant patients with recurrent symptomatic UTI.

**Patient and Methods:** Demographic and Clinical data on all the renal transplant patients with recurrent symptomatic UTI who had undergone corrective surgery for VUR was abstracted (July 1993 to December 2014). The benefit of the surgical correction of VUR was assessed by follow-up urine culture and sensitivity. Standard statistical methods were used for data analysis.

**Results:** A total of 123 patients who had under gone corrective surgery for VUR associated symptomatic UTI formed the study group. The mean age of the patients was 44.6±14.4 years with Male: Female ratio of 1: 2.5. Majority of the patients (71.5%) underwent a uretero-ureterostomy using the ipsilateral native ureter with an end to end anastomosis, 15.4% of patients underwent a uretero-ureterostomy using the ipsilateral native ureter with an end to side anastomosis, 8.9% of patients underwent a uretero-neocystostomy using the Politano-Leadbetter technique due to an absence of a suitable ipsilateral native ureter, 3.3% of patients underwent a uretero-neocystostomy using the Lich-Gregoir technique and 0.8% of patients underwent a uretero-pyelostomy using the ipsilateral native ureter. Overall cure from symptomatic UTI was observed in 95.1% of patients. There were no procedure related complications, however there was graft loss noted in 4.9% (N=6) of patients due to allograft rejection. There was one mortality due to an unrelated cause.

**Conclusion:** Corrective surgery for VUR associated with recurrent symptomatic UTI in renal transplant patients is a highly effective option. The surgeon should investigate the availability of the ipsilateral ureter as it is critical for success of the operation.

**Keywords:** VUR; Recurrent UTI; Renal transplant recipients

### Introduction

Renal transplant patients are at a higher risk for urinary tract infections and vesicoureteral reflux is a well-known risk factor, especially for recurrent urinary tract infections [1]. Vesicoureteral reflux occurs in 2-86% of renal transplant patients [2-6]. The exact incidence of vesicoureteral reflux is difficult to determine as most patients are not routinely subjected to a voiding cystourethrogram (VCUG). In fact, a VCUG is usually ordered when a patient has recurrent urinary tract infections (UTI) [6,7]. Vesicoureteral reflux is graded based on International Reflux Study Committee Scale [8]. Many believe that low grade reflux has no effect on the long term outcome of renal allograft; however, those patients with high grade reflux especially with recurrent symptomatic UTI come

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under scrutiny [7]. It is an ongoing debate as to whether reflux in these patients is clinically significant. Some surgeons feel that the anti-reflux reimplantation techniques are unnecessary and may lead to increased risk of ureteral obstruction [9,10].

We have previously published our experience with urologic complications in over 2500 kidney transplants [6]. We have observed a 3% incidence of clinically significant vesicoureteral reflux in these patients. These patients have been treated in a variety of ways including antibiotic suppression, Deflux injection and reconstructive surgery. Deflux has not been successful and most of our patients undergo reconstructive surgery. Our goal was to review our actual success rate defined as resolution of symptomatic UTI's after a reconstructive operation.

## Patients and Methods

A retrospective review was performed on all patients with recurrent urinary tract infection (UTI) following renal transplant between July 1, 1993 and December 31, 2014 at the Saint Barnabas Health Care System. According to our institutional policy all renal transplant patients routinely received urine analysis at every office visit. Patients with positive urine culture (with colony count of  $>10^5$  CFU/ml) and fever ( $>38^\circ\text{C}$ ) or positive blood culture (with colony count of  $>10^5$  CFU/ml) formed the symptomatic UTI group. Asymptomatic group was formed by patients with positive urine culture in the absence of fever and positive blood cultures. These patients were further evaluated with voiding cystourethrogram (VCUG) followed by cystoscopy and retrograde pyelogram. International Reflux Study Committee Scale was used to grade vesicoureteral reflux (VUR) [8]. All patients with recurrent symptomatic UTI with VUR (at least three episodes of in a year) were given the options of antibiotic suppression, Deflux injection or reconstructive surgery. For those who chose surgery, the vesicoureteral reflux was corrected by any of the following three methods including uretero-ureterostomy (UU), ureteroneocystostomy (UNC) or ureteropyelostomy (UPL) depending on the availability or lack of a suitable ipsilateral native ureter. The UU was created end to end or end to side fashion using the ipsilateral native ureter. However, the UNC was created using the Politano-Leadbetter or Lich-Gregoir fashion if there was no suitable ipsilateral native ureter and UPL was created using the ipsilateral native ureter if transplant ureter was too short to reach the bladder or the native ureter. Demographic and clinical data was abstracted including age, gender, type of renal transplant (Living donor, Deceased donor), type of surgical correction for VUR, post intervention follow-up data including urine c/s results. Persistent UTI after corrective surgery was defined as positive urine culture ( $>100,000$  CFU) on at least three consecutive urine cultures with or without associated with fever ( $>38^\circ\text{C}$ ) and positive blood cultures ( $>10^5$  CFU/ml).

Saint Barnabas Health Care System is one of the busy renal transplant centers, third largest in the US for living donor renal transplant. All the renal transplants are performed by two fellowship trained transplant surgeons and majority of ureteral reimplantations are performed by one transplant urologist. The transplant urologist kept a detailed record of all urologic complications on these patients as he treated them. Between July 1993 and June 1994, the ureteroneocystostomy (UNC) was performed using the Politano-Leadbetter technique without routine use of a ureteral stent. Since July 1994, the Lich-Gregoir technique was adopted with a routine use of an indwelling ureteral stent.

**Table 1:** Demographic and clinical characteristics of 123 patients with vesicoureteral associated recurrent UTI undergoing corrective surgery.

N	123
Age, Mean $\pm$ SD	44.6 $\pm$ 14.4
Gender, M: F	35: 88
Type of Renal Transplant, N (%)	
DDRT	67 (54.5)
LDRT	56 (48.5)
Type of Intervention, N (%)	
UU EE	88 (71.5)
UU ES	19 (15.4)
UNC - Politano	11 (8.9)
UNC - Lich	4 (3.3)
Ureteropyelostomy	1 (0.8)
Post-intervention UTI, N (%)	
Yes	51 (41.5)
No	72 (58.5)
Symptomatic UTI	13 (10.5)
Post-intervention persistent UTI	10 (8.1)

**Abbreviations:** N: Number of Patients; SD: Standard Deviation; DDRT: Deceased Donor Renal Transplant; LDRT: Living Donor Renal Transplant; UU: Uretero-Ureterostomy; EE: End to End; ES: End to Side; UNC: Uretero-Neocystostomy; UTI: Urinary Tract Infection

## Results

We have performed 3,452 renal transplants during the study period, of which 123(3.6%) patients formed the study group. The mean age of the study group was 44.6 $\pm$ 14.4 years with Male to Female ratio of 1:2.5. There were 56(48.5%) deceased donor renal transplant patients and 67(54.5%) living donor renal transplant patients. 88(71.5%) of patients underwent ureteroureterostomy with an end to end anastomosis, 19(15.4%) patients underwent ureteroureterostomy with an end to side anastomosis, 11(8.9%) patients underwent ureteroneocystostomy using Politano- Leadbetter technique, 4(3.3%) patients underwent ureteroneocystostomy using Lich- Gregoir technique and one patient (0.8%) underwent a ureteropyelostomy. Follow-up of these patients revealed 51(41.5%) patients had at least one episode of UTI after corrective surgery, of which 13(10.3%) patients had symptomatic UTI and 10(8.1%) of patients had persistent UTI (Table 1). All patients with persistent UTI were treated with antibiotics based on sensitivity results. The ten patients with persistent UTI after corrective surgery underwent re-evaluation with cystoscopy, retrograde pyelogram as well as VCUG, and none of the patients had persistent VUR. Among the 10 patients with persistent UTI, four (3.2%) patients achieved negative urine culture, two (1.6%) patients remained asymptomatic with positive urine cultures, for three (2.4%) patients follow-up data was not available and one patient died of unrelated cause. Overall graft loss was observed in 6(4.9%) of patients due to allograft rejection, however none of these were observed in patients with persistent UTI.

## Discussion

Renal transplant patients are at a higher risk for urinary tract infections. The clinical spectrum ranges from asymptomatic bacteriuria to pyelonephritis. Nearly 25% of renal transplant patients develop UTI in the first year of renal transplant of which asymptomatic bacteriuria (urine c/s  $>10^5$  CFU/ml) accounts for 44%, uncomplicated

(without systemic signs) UTI for 32%, and complicated (with systemic signs) UTI for 24% [11-13]. Recurrent UTI is traditionally described as three or more symptomatic UTI in a year [11]. Urinary tract infection is the most common infectious complication seen in renal transplant recipients and is associated with acute rejection, impaired graft function, allograft loss and death [12-14]. Urinary tract infection in the renal transplant recipients is associated with several risk factors, including female gender, advanced age, recurrent UTI prior to transplant, Vesicoureteral reflux (VUR), prolonged urethral catheterization, ureteral stent placement, deceased donor renal transplant, history of polycystic kidney disease and delayed graft function [11,13,15]. Detailed discussion of all the risk factors and stepwise management of UTI in renal transplant recipients is beyond the scope of this report, our focus was to review and report outcomes of corrective surgery in VUR associated recurrent UTI.

Vesicoureteral reflux (VUR) is defined as abnormal flow of urine from the urinary bladder to the ureter and the kidney. The true incidence of vesicoureteral reflux in renal transplant patients is unknown, in the absence of standard protocol for diagnostic studies. In the literature, VUR is reported to occur in 2-86% of recipients [2-5]. The incidence of VUR rises in the immediate post-transplantation period and reaches a plateau after 9 months [5]. The clinical consequences of VUR, both early and late, are largely debated. The complication rates secondary to VUR, urinary tract infection, pyelonephritis, and reflux nephropathy and graft failure vary in different reports, but no statistically significant differences were observed when compared to those without VUR [16]. However, some believe that recurrent urinary tract infections trigger immunological insult similar to that seen in chronic rejection [17] while others such as Coosemans et al. and Mastrosimone et al. [2,5] observed no impact of VUR on graft survival and graft function. In other studies, higher rates of graft failure were found in patients with VUR compared to patients without reflux (48 vs. 16%) [18]. Nevertheless, UTIs are frequent after renal transplantations and may adversely impact renal allograft function, even in the absence of VUR [19].

The major causes of VUR are related to the surgical technique and the quality of urinary bladder wall [20]. Generally, a longer submucosal tunnel, a tension-free anastomosis, and firm muscular support for the ureter are fundamental to ureteroneocystostomy to prevent VUR, which could make it difficult to achieve in a patient with a very thin bladder [21]. There is a higher incidence of VUR in females than males likely because females tend to have thinner bladder than males. On uni-variate analysis, creatinine clearance <60 ml/hr, short ureteric submucosal anti-reflux tunnel (<3cm), dialysis duration > 60 months, pre-transplant bladder capacity <130 ml and experience of surgeon significantly increased risk of VUR, whereas on multivariate analysis only creatinine clearance <60ml/hr was found to be significant [22].

There should be a high index of suspicion for VUR in renal transplant recipients with recurrent urinary tract infections, even though the association between VUR and UTI has been seriously doubted by some. (74, 77, 80) In a prospective study by Favi et al. [16], 41% of patients with recurrent UTI had mild to moderate VUR. The higher incidence of pyelonephritis associated with VUR demonstrated previously has been disproved in recent studies [23]. Although VUR has been considered to be of secondary importance to the success of transplantation, periodic evaluation of renal recipients suffering from VUR is advisable. Vesicoureteral reflux is diagnosed

by voiding cystourethrogram, which is routinely performed in some renal transplant units as a part of protocol. Most programs perform voiding cystourethrogram only in the presence of recurrent UTI or pyelonephritis [24]. Radionuclide voiding cystography using <sup>99m</sup>Tc-labelled collidate offers safe alternative with less radiation exposure and high sensitivity and specificity compared to standard voiding cystourethrogram. Other alternatives for diagnosing VUR include ultrasound voiding cystography and duplex ultrasonography to study resistive index. Kmetec et al. [24,25] observed significantly low resistive indices during voiding in patients with VUR compared to patients without VUR.

Asymptomatic patients should be observed. They should not be treated with antibiotics as it would cause selection of resistant bacteria over time. For the symptomatic patients there are three options: antibiotic suppression, Deflux injection and reconstructive surgery. For older patients who are not eager to undergo a major operation, antibiotic suppression can be quite successful without deterioration of renal function or recurrence of symptomatic UTIs. Unfortunately, Deflux injections have given only good short term results and in our experience as no patient had a long term success beyond one year. For younger patients or others who do not wish to continue daily antibiotics, reconstructive surgery is recommended. The type of reconstructive surgery chosen depends on the availability of ipsilateral native ureter and the viability and length of transplant ureter after it is freed for reconstruction.

Few researchers have reported outcomes of corrective surgery for VUR. Dincan A et al., reported on outcomes following corrective surgery in 60 renal transplant recipients with VUR associated symptomatic UTI. In their study population 50% (N=30) of patients underwent uretero-ureterostomy and the other 50% (N=30) of patients underwent repeat ureteral reimplantation. The authors noted resolution of recurrent symptomatic UTI in 93.4% (N=56) of patients. Unfortunately, 6.6% (N=4) of patient continued to have symptomatic UTI, but none of these patients were found to have persistent VUR on voiding cystourethrogram. In a similar study, Krishnan A et al. [28], reported outcomes of corrective surgery in 16 pediatric patients with VUR associated symptomatic UTI. In the same study all the 16 patients underwent a repeat ureteral reimplantation. The authors noted resolution of symptomatic UTI in 75% (N=12) of patients, whereas 25% (N=4) of patients had persistent symptomatic UTI. Of the four patients with persistent recurrent UTI, one patient (25%) was found to have persistent VUR. The current study represents the largest series reporting outcomes of corrective surgery for VUR associated symptomatic UTI in renal transplant patients. In this study we noted overall resolution of symptomatic UTI in 95.1% (N=117) of patients. At the end of the study only 1.6% (N=2) of patients had asymptomatic UTI (Urine C/s >10<sup>5</sup> CFU/ml), follow up data was not available in 2.4% (N=3) of patients and the sole patient had died due to unrelated cause. There were no procedure related complications, however there was graft loss noted in 4.9% (N=6) of patients due to allograft rejection.

In conclusion, corrective surgery for VUR associated with recurrent symptomatic UTI in renal transplant patients is a viable and highly effective option.

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