

Original Articles

Urinary Tract Infections During Early Posttransplant Period in Adult kidney Allograft Recipients

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Abstract:

Background: Urinary tract infections (UTIs) represent the most common cause of bacterial infection in renal allograft recipients. The purpose of this study was to evaluate UTI in renal transplant recipients at earlier post transplant period (first 3 months) and isolation of causative organism.

Materials & methods: We studied 31 patients (18 males and 13 females), aged 27 ± 8.8 years. UTIs occurring during the first three months were analyzed. During this period, all episodes of infection, transplant function, graft survival and patient survival were monitored.

Results: Twenty two patients had suffered from different types of infection within first 3 months of transplantation, most of the infectious episodes occurred during hospital stay. Most of the infection occurred in urinary tract and most of the episodes of UTI were asymptomatic, presented with bacteriuria. Most of the isolated organisms were Gram negative E.Coli. Out of 51 episodes of bacterial infection, UTIs account for 49 episodes (96%) Patients' age, sex and acute rejection episodes did not correlate with UTI. Patient who had prolonged urethral catheterization had suffered from significantly more number of UTI in comparison to short period of urethral catheterization ($p=0.02$). Similar incidence of UTI were observed in ureteric stented and non stented patients but non stented patients had suffered from significant number of urological complication ($p<0.02$). Antibiotic sensitivity pattern revealed that, all isolates were sensitive to ciprofloxacin, ceftriaxone and ceftazidime, ranged between, 67 to 100% and highly resistant to ampicillin, cotrimoxazole and cephradine.

Conclusion : Short term renal graft function was not found to be affected by UTI occurrence. UTIs are common infectious complications in renal transplant recipients and often relapse and require hospitalization.

Keyword: urinary tract infections (UTIs), renal transplantation, acute rejection episodes.

Introduction:

Since 1950s when first successful renal transplantation was done, every effort was directed towards improvement of graft survival.¹ Yet urinary tract infections (UTIs) continue to be a source of morbidity and graft failure. UTI may initiate allograft rejection and have been associated with reactivation of later CMV infection.² UTI is the most common infection following renal transplantation [approximately 44–47%].^{3,4} Due to variation in study design and working definition, the reported incidence of post-transplantation UTI varies considerably from 10% to 98%.⁵ Patients are at risk of UTI in the first month after transplantation.⁶ The bacteremia-

associated mortality of kidney allograft recipients is around 11% during this period.⁷ Owing to use of prophylactic antibiotics for the first 6 months after transplantation, change in antimicrobial protocol and immunosuppressive protocol, reported incidence (7-40%) in first 6 months in 1992 has fallen to 13.3% in 1st month, 14.7% in the period of the second month to the sixth month and 72% after 6 months in 2007.^{8,9} It was argued that patients who develop post transplant- infections (all infections, not only UTI) at whatever period of post transplantation are more likely to die from causes including cardiovascular disease.^{10, 11} Hence forth, it is desirable to reduce the incidence even

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further. Urinary tract infection following transplantation is associated with tissue invasion by pathogens. Female sex and Diabetes mellitus are important preoperative factors for UTI.¹ Use of ureteric stents and prolonged urinary catheterization are intraoperative risk factors.^{12,13} However, the optimum duration for urethral catheterization is unknown.¹ Excessive immunosuppression, Graft dysfunction and rejection, infection of native urinary tract and Instrumentation of urinary tract constitute post-operative factors.¹

Organisms that cause UTI after renal transplantation can be bacterial, fungal, viral, parasitic or mycoplasmal.¹ The spectrum of bacterial UTI pathogens in transplant recipients is similar to that in the non-transplantation population, with Gram-negative bacterial infections accounting for more than 70% of UTIs.⁴ It is likely that the organism and the strain that cause most post-transplantation UTIs vary between centers, depending on local immunosuppressive and antimicrobial protocols.¹

Symptomatic post-transplantation UTI can present as acute cystitis (frequency, urgency, dysuria, haematuria and suprapubic pain) or transplant pyelonephritis, and/or native pyelonephritis (rigors, loin pain in native kidney or pain over graft and pyrexia). Uncomplicated acute bacterial cystitis accounted for 77% of UTIs and acute pyelonephritis accounted for 19% of UTIs.^{14, 15} Immunosuppressive therapy can mask the clinical manifestations and signs of infection. Pain over the graft is often absent or difficult to localize because the transplanted kidney is denervated. Diagnosis of post-transplantation UTI is, therefore, difficult, unless routine analysis is performed.^{16, 17} For all these reasons, prevention of UTI in early period after renal transplantation is important. Early removal of urethral catheter and use of perioperative antibiotic have been advocated to reduce infectious complications.¹⁸ The complication with UTI is usually related to how quickly an etiologic diagnosis is made and therapy instituted. Great skill and attention is required for the transplant clinician to recognize early, often occult signs of infection.

In our country, data regarding UTI of renal allograft recipient at earlier post transplant period are scarce. The present study was carried out to find out the prevalence of UTI of Renal Allograft Recipient within first three months of transplantation, determine the cause of UTI, isolation of causative organisms and their susceptibility pattern to common antimicrobial agents as well as type and consequence of UTI of renal allograft recipient.

Materials and methods:

This is a prospective observational study carried out in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, over a period of two years from January 2002 to December, 2003. Before starting of the study, protocol was approved by the concerned authorities and at enrollment, informed written consent was obtained from each patient. Total number of patients was 31. Eighteen males and 13 females with mean age 27 ± 8.8 yrs (range 15 to 50 yrs) were included in this study. All patients received live related renal transplantation at transplantation unit of Nephrology Department, BSMMU, Dhaka. They were studied prospectively for 3 months after transplantation. During this period all episodes of UTI (both nosocomial and community acquired), transplant function, three months graft survival and patient survival were monitored. Subjects who had primary graft failure after transplantation were excluded. All patients received same type of immunosuppression protocol, started day before Transplantation with Cyclosporine (8mg/kg/day initially, then reduced by 1mg/kg every month up to 3mg/kg/day as maintenance dose); prednisolone (0.5 mg/kg/day initially then tapered to 10mg/day at 6 month); Azathioprine (initially 50 mg/day, then was increased to 2.5mg/kg/day after 3 months). Acute Rejection was treated by 500mg Methyl prednisolone for successive 3 days. Urethral catheter was inserted intraoperatively. All patients received 1gm intravenous ceftriaxone in perioperative period. Urinary catheter was removed around 7 days after operation. Patients were observed in transplantation unit for an average $1\frac{1}{2}$ months. Patients were investigated weekly during hospitalization. After discharge from hospital, they were investigated monthly until 3 months of transplantation and whenever UTI was suspected. After discharge from hospital, patients were regularly seen at the out patient department and when indicated, culture and other diagnostic measures were performed. Although the presence of bacteriuria with a concentration of at least 10^5 organism per ml. in the midstream clean catch or catheterized sample of urine fulfilled the criteria for UTI in renal transplant recipients, other criteria such as pyuria (>10 pus cell/HPF) fever and dysuria were frequently used for diagnosing UTI. UTI was considered to be catheter related if infection occurred during urethral catheterization or within 24 hours after catheter removal with growth of organisms from catheter tip culture. Before enrollment in this study, base line investigations like urine routine and microscopic examination, culture and sensitivity from morning midstream clean catch sample were done within seven days prior to transplantation. Serum urea, creatinine, electrolyte were done day before transplantation. After transplantation, all the patients had undergone the

following investigations- urine routine and microscopic examination, culture and sensitivity, complete blood count, serum urea, creatinine and electrolyte at 3rd, 7th, 14th, 21st, 28th day, end of 2nd and 3rd month and whenever infection was suspected. Urinary catheter tip and drain tube tip, culture and sensitivity were done in all cases.

Statistical Analysis

Results were expressed as mean \pm standard deviation (mean \pm SD). Fisher exact test or chi-square tests were performed for data analysis. All analysis were done using SPSS windows package and p value <0.05 were considered significant.

Results:

Characteristics of Recipients

A total of 31 patients were enrolled over a period of 2 years from January, 2002 to December, 2003 in the department of nephrology, Bangabandu Sheikh Mujib Medical University (BSMMU), Dhaka. Among the enrolled patients, 18 were males and 13 were female, mean age was 27 ± 8.8 yrs (range 15-50 years). (Table I) Each patient was studied for first three months of post transplant. The underlying cause of end stage renal disease (ESRD) was Chronic Glomerulonephritis (CGN) 28 (91%), Hypertensive nephrosclerosis 1 (3%), Diabetic nephropathy (DN) 1 (3%) and Hereditary renal disease 1 (3%) (Table I). 30 (Thirty) patients received first transplant and a single patient received 2nd transplant or retransplantation. Infectious complications occurred in 22 (71%). Among them 42 (79%) episodes of UTI, 3 (6%) episodes of RTI, 2 (4%) episodes of wound infection and 4 (7%) septicaemia. Bacteria were responsible for 51 (96%) episodes and 2 (4%) were due to viral infection.

Table-I

Characteristics of the study population (Recipient n=31)

Characteristics (n=31)	Values
Age (mean \pm SD)	27.8 \pm 8.8
Male/female	18/13
ESRD aetiology:	
CGN	28 (91%)
DN	1 (3%)
Hereditary nephrosclerosis	1 (3%)
Hereditary renal diseases	1 (3%)
Early Complications:	
Infection	22 (71%)
Acute rejection	08 (26%)
Surgical complications	06 (19%)

UTI:

13 (72%) males and 9 (69%) females had suffered from UTI with 1.1 episodes per male patient and 1.6 episodes per female patient. That was not statistically significant (p=NS) (Table II).

Table II

Sex distribution of Urinary Tract Infection

	Male (n=18)	Female (n=13)	p
UTI + ve n (%)	13 (72)	9 (69)	ns
UTI -ve n (%)	5 (28)	4 (31)	

ns : not significant

All UTI were bacterial infection. 11 (50%) patients suffered from one episode of UTI and another 11 (50%) suffered from repeated UTI (more than 2.8 episode per infected patient). The presentations were associated with pyuria and bacteriuria 24 (57%), bacteriuria 9 (21%), bacteriuria, pyuria and fever 5 (12%), pyuria and fever 4 (10%) (Figure 1).

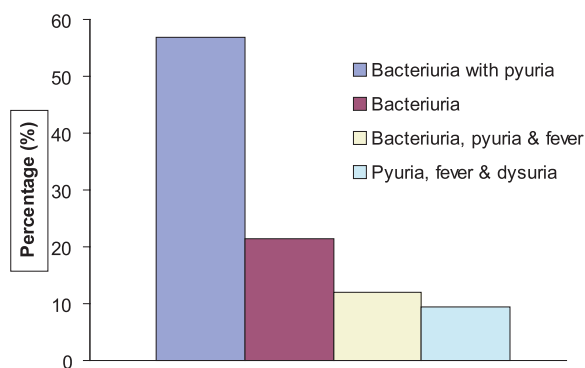


Fig.-1: Presentation of UTI

Catheter and stent related UTI:

The mean duration of urethral catheterization was 11.8 ± 6.5 days (range 7 to 36 days). Thirteen of 24 patients who had urethral catheterization for more than 7 days had suffered from catheter related UTI but none of seven patients who had catheterization for less than 7 days had suffered from UTI. And this was statistically significant (p=0.02). (Table III). In total 15 (48%) recipients underwent ureteric stenting and the other 16 (52%) recipients did not. 11 (73%) of stented patients had suffered from UTI (1.3 episode per patient) and 11 (68.7%) of non-stented patients had suffered from UTI (1.3 episode per patient). There was no difference in infection in these two groups. (Table III). UTI in non-stented patients who had urological complications, developed 2.5 episodes per patient and in non-complicated patients 0.7 episode per patient. So incidence of UTI was higher in complicated patient (Table IV).

Table-III
Catheter and stent related UTI

	UTI +ve	UTI -Ve	P value
Catheter related			
<7days (n=7)	0	100(100%)	0.02
>7days(n=24)	14(54%)	11(46%)	
Stent related			
With stent (n=15)	11	4	ns*
Without stent(n=16)	11	5	

* ns: not significant

Table-IV
Complication Related to Stenting

	Stented Patient (n=15)	Non Stented Patient (n=16)	P value
Surgical Complication	0	6	0.02
No Complication	15	10	

Organism causing UTI:

The bacterial cause of UTI was 38 (90%). Among them *E. coli* -34 (88%) *Klebsiella* 2 (6%), *Pseudomonas* – 1 (3%) and *Enterococcus* – 1 (3%). Only 2 episodes of UTI were associated with septicaemia (Figure 2).

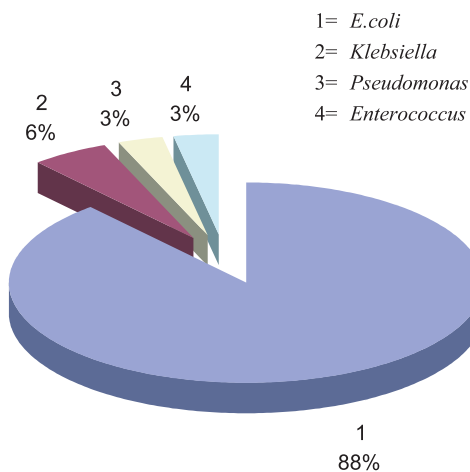


Fig-2: Organism Causing UTI

Sensitivity pattern of bacterial isolates to different antimicrobial agents:

Antibiogram of different bacteria isolated from various specimen showed - *E. coli*

were 78% sensitive to ceftriaxone, 74% to ciprofloxacin and ceftazidime, cotrimoxazole 18% and Ampicillin only 6%. *Pseudomonas* was sensitive to ceftazidime 50% followed by 33% to ceftriaxone and ciprofloxacin but 100% resistant to cotrimoxazole and Ampicillin. *Klebsiella* was 100% sensitive to ceftriaxone, ciprofloxacin and ceftazidime but 100% resistant to Ampicillin. *Enterococcus* was 100% sensitive to ceftriaxone, ceftazidime and Gentamycin but resistant to Ampicillin, cotrimoxazole and ciprofloxacin. The organisms which were resistant to all above mentioned drugs, antibiogram were done with Amikacin, Imepenam and Netilmycin showing 100% sensitivity to these three drugs.

Outcome of study population:

Acute rejection:

Acute rejections occurred in 8 (26%) cases that were diagnosed clinically, based on rising serum creatinine, fever, and graft tenderness, decrease in urine output within first 3 months. None had died due to acute rejection. Five (62.5%) of the acute rejection cases had infection (including Respiratory tract infection, wound infection and UTI) while 17 (73.9%) cases had infection in the non-rejection group. This was not statistically significant (P= 0.65). (Table V)

Table V
Relation of Acute rejection with Infection:

	Acute Rejection (n=08)	No Rejection (n=23)	P
Infection	5	17	0.65
No Infection	3	6	

Patients survival

Out of 31 patients 7 patients expired within first 3 months due to CMV infections, *Mycobacterium tuberculosis*, and cardiovascular disease and none due to UTI.

Discussion:

The precise incidence of post transplant UTI is unknown because of variations of definitions of UTI in different series. It varies from clinically significant UTI to asymptomatic culture positive UTI. In early era of renal transplantation infection was associated with graft loss but later on improved organ procurement method, newer immunosuppressive protocol and quick, early intervention of infection has markedly reduced lethal burden of infection over patient and graft survival.^{8,9}

During first month, wound and urinary tract are commonest sites of infection, during second to six month, risk of tuberculosis, nontyphoidal salmonella, pneumocystis

pneumonia and CMV infection are more common. After 6 months intensity of immunosuppression is reduced, so community acquired infections occur.¹⁹

In the present study, 71% patients had suffered from infection within first 3 months of post transplant period. Among them 42 (79%) episodes are of UTI. All UTI were of bacterial origin, male and female had suffered from similar incidence of UTI (72% vs 69%), that was statistically insignificant ($p=NS$). Most of the episodes of UTI (90%) were associated with bacteriuria caused by *E.coli*. The occurrence of UTI was associated with the duration of urethral catheterization. Mean duration of urethral catheterization was 11.8 ± 6.5 days. Incidence of UTI increased significantly when the duration of urethral catheterization was more than 7 days. Similar incidence of UTI was found in ureteric stented and non stented patients (73% vs 69%) that were statistically insignificant. Patients who were not stented, had more urological complications and more incidence of UTI.

Studies from Netherlands and Israel showed that the commonest infection in 1st month after transplantation was UTI and commonest organism causing UTI were gram negative organism.^{20,21} But study in Netherlands showed male preponderance (70% vs 42%).²⁰ In India the commonest infection during 3 months after kidney transplantation is UTI, the commonest organism is *E. coli*, male and female are equally affected and higher incidence was with prolonged catheterization.²² Like our study Similar incidence of UTI in male and female, with higher incidence in prolonged catheterization was also found by Miroz E. et al.²³ In study by Renoult E. et al most common organism were *E.coli* followed by *Staph. aureus*, and *Klebsiella*, more in female and stented patients.¹²

Alexopoulos E et al. had shown that, 50% infection rate within two months of transplantation. The most commonly isolated organisms were *E.coli* followed by *Pseudomonas aeruginosa* and *Proteus mirabilis*. Recurrence or re-infection were 73%, and, 55% had episodes of asymptomatic bacteriuria.²⁴ In the present study, similar information mentioned in above studies were found. UTIs were 79%, male and female had similar incidence of UTI, 50% had suffered from single episode and other 50% had recurrent episodes of UTI. Significantly higher incidence of UTI was present after catheterization more than 7 days and 90% UTI was associated with bacteriuria.

A shorter duration of catheterization could be an important measure to reduce UTI. A urethral catheter is needed after transplantation, for maintaining urine drainage, to prevent early obstruction, urinary leaks and vesical fistula. It has been demonstrated that duration of urethral catheterization is the most important risk factor for UTI and advantages of

early removal of the catheter have been emphasized.^{12,13,18} Catheter removal after 8.2 ± 3.8 days were associated with 74% incidence of UTI whereas catheter removal within 36 hours was associated with an incidence of 8% UTI.¹² Ramsay et.al. have shown, catheter removal within 48 hours after transplantation reduced the rate of UTI from 17% to 5.6%.²⁵ The duration of urethral catheterization varies considerably in renal transplantation centers in Europe but the duration was less than 1 week in 84% of these centers.²⁶ In the present study, mean duration of urinary catheterization was 11.8 ± 6.5 days and UTIs were significantly higher with prolonged catheterization.

In Bangladesh, Ahmed S. et.al., reported that, isolated organisms from urinary tract infection were *E. coli* (59%), *Klebsiella* (12.5%) and *Pseudomonas* (5.6%). Antibiotic susceptibility pattern of organisms showed, all isolates were sensitive to ciprofloxacin, ceftriaxone and gentamycin at very high percentage ranging from 75 to 100% except *Pseudomonas* to ciprofloxacin (55%) and also showed higher resistance to cotrimoxazole, amoxycillin and cephradine.²⁷ In the present study, *E. coli* was the commonest isolated pathogen constituting 77% and sensitivity pattern revealed that, all isolates were sensitive to ceftriaxone, ciprofloxacin and ceftazidime, in between 67 to 100% except *Pseudomonas*, which was 33% sensitive to ceftriaxone and ciprofloxacin and 50% to ceftazidime. Pathogens showed higher resistance to ampicillin, cotrimoxazole and cephradine like above mentioned study. Similar information of sensitivity pattern of *Pseudomonas* were found in both studies. Sensitivity of *E. coli* to ciprofloxacin, ceftriaxone and gentamycin declined, probably because the immunosuppressed status of these patients which may cause emergence of resistant pathogens. The organisms (*E. coli*, *Pseudomonas*, *Klebsiella*) which were resistant to above mentioned drugs, were 100% sensitive to Amikacin, Netilmycin and Imepenam.

In a 2005 Cochrane review, it revealed that routine intraoperative ureteric stenting is associated with an increased risk of UTI (RR of 1.45, 95% CI 1.04-2.15).²⁸ Our study differs from that probably due to small population size. There is conflicting data regarding association of UTI with patient and graft survival.¹ In our study graft survival or patient 's survival is not affected by UTI. However long term effect of UTI on graft survival is to be evaluated by further study.²⁹

Considering all parameters, it can be concluded that, UTI is the commonest infection in transplant patient within 1st three months of transplantation. UTI has no impact over graft survival or patient survival in the short term. Early removal of urethral catheter to reduce the risk of urinary tract infection

is recommended. A further prospective study with a large number of patients and a long term follow up should be carried out to confirm the above findings.

Conflict of Interest : None

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