We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Urinary Tract Infection in Renal Allograft Recipients

Lovelesh Kumar Nigam, Aruna V. Vanikar,
Rashmi D. Patel, Kamal V. Kanodia and
Kamlesh S. Suthar

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.77171>

Abstract

Renal replacement therapy in the form of renal transplantation (RT) is the treatment of choice in these patients. Various factors influence the graft survival, infections being most common. Infections account for 16% of patient deaths and 7.7% of death censored graft failure in renal transplant patients. Urinary tract infection (UTI) is the most common infectious complication accounting for 45–72% of all infections. According to few studies UTI may have a negative impact over the long term survival of renal allograft. There are multiple factors that predispose these patients to UTI. Elderly age group, female gender, increased duration of catheterization and anatomical abnormalities of the urinary tract are most common predisposing factors. *E. coli* is the most frequently isolated organisms from the urine of these patients. We would proceed further with two cases which presented as UTI in post-transplant period. The first patient transplanted (living donor related) for diabetes induced end stage renal disease had developed UTI 4 years post-transplant. The other patient underwent deceased donor renal transplant for adult polycystic disease related chronic kidney disease, presented 2 years post-transplant with UTI.

Keywords: renal transplantation, urinary tract infection, renal allograft, graft function, immunosuppression

1. Introduction

Clinical information (Case 1): A 53-year-old male patient, with a history of arterial hypertension, type 2 diabetes mellitus, and renal failure, caused by diabetic nephropathy diagnosed 5 years back and was on maintenance hemodialysis. The patient underwent live donor renal transplantation in June 2013. The intraoperative and post-operative period was unremarkable

and he was put on Tacrolimus based immunosuppression thereafter consisting of Prednisone (20 mg/day), Mycophenolate sodium (360 mg/day), and Tacrolimus (1.5 mg/day level:4.6 ng/ml). He was on regular follow-up for routine urine examination, serum creatinine and serum electrolytes and hemogram. Nearly 4 years post-transplant he was admitted with complaints of low grade intermittent febrile episodes and painful micturition. There was slight rise in the serum creatinine levels to 2.4 mg/dL (baseline: 1.8 mg/dL). The urine output was however normal. Complete blood count performed revealed neutrophilic leukocytosis with total count of $14.2 \times 10^6/\mu\text{L}$, with predominance of neutrophils on differential, the absolute neutrophil count of $14 \times 10^6/\mu\text{L}$. Urine examination revealed urine albumin of +1 by dipstick method, pH of 5.0 and specific gravity of 1.020. **Clinical information (Case 2):** A 38-year-old female patient, underwent deceased donor renal transplantation for adult polycystic kidney disease induced chronic kidney disease. The intraoperative and post-operative period was unremarkable and she was on conventional Tacrolimus based immunosuppression thereafter consisting of Prednisone (20 mg/day), Mycophenolate sodium (360 mg/day), and Tacrolimus (1.5 mg/day; level:6.8 ng/dL). She was on regular monitoring for routine urine examination, renal function tests and complete blood counts. Nearly 2 years post-transplant she was admitted with complaints of intermittent high grade febrile episodes, pain in abdomen and nausea. The serum creatinine level at the time of presentation was found to be raised to 3.6 mg/dL (baseline: 1.2 mg/dL). The patient had normal urine output. Complete blood count performed revealed neutrophilic leukocytosis with total count of $18.6 \times 10^6/\mu\text{L}$, with predominance of neutrophils on differential, the absolute neutrophil count of $12 \times 10^6/\mu\text{L}$. Urine examination revealed urine albumin of +2 by dipstick method, pH of 4.6 and specific gravity of 1.040. **Summary:** So here we have two patients who underwent renal transplant for end stage renal disease and presented with signs and symptoms of urinary tract infection. Both the patients presented with rise in serum creatinine as well as pyuria on urine examination(not written in the text above)clinical suspicion of urinary tract infection. We would in further sections study how we proceeded with both the cases, investigations performed and management of both. In this brief review we would discuss the incidence of urinary tract infection in post-transplant patients, risk factors and how to manage a case with UTI.

1.1. Incidence of posttransplant urinary tract infections

Transplantation has become the gold standard treatment of end-stage disease in the present era. Of all the organs that are transplanted, kidneys remain the most frequently transplanted organ [1–5]. RT is regarded as an effective treatment for patients with advanced chronic renal disease [1, 2]. Over the years various studies have been carried out globally to understand the factors that influence the graft function [1]. Multiple factors including technical expertise, donor-recipients related demographics, immunosuppressive regimens, infections, comorbid conditions have been implicated to influence the graft survival [1–3]. Infections are a common cause of morbidity and mortality after transplantation and it is widely known that RT patients have poor resistance to infection [4, 5]. Infections have been ranked second, as a cause of death in RT patients. According to the U.S. Renal Data System, the rate of first infection in the initial 3 years after kidney transplantation is reported to be 45.0 per 100 patient-years of follow-up. It has been postulated that in immunocompromised RT recipients, UTI is the most common infection that affects the graft function and is held responsible for longer hospital stay and increased health care cost [3, 6, 7]. Becerra et al. stated that the length of stay in patients who develop UTI is 74 and 76% higher in men and women renal transplant recipients respectively, when compared to those without UTI [8].

1.2. Burden of the disease

UTI is the most common type of hospital-acquired infection, accounting for nearly 40–50% of all infectious complications among RT patients followed by viral infections, pneumonia and surgical site infections [8, 9]. As per the data from Spanish Network for the Study of Infections in Transplantation (RESITRA) the incidence of cystitis per 100 recipient-years was 13.84 for renal, 3.09 for liver, 2.41 for heart and 1.36 for lung transplant recipients [10]. The incidence of pyelonephritis per 100 recipient-years was 3.66 for renal, 0.8 for liver, 0.3 for heart and 0.6 for lung transplant recipients. UTI-associated bacteremia was seen in 39% of renal, 3% of liver, 3% of heart and none of the lung transplant recipients [11, 12]. The prevalence of UTI in RT patients ranges from 13 to 80% according to various studies [1, 2, 6, 13–16]. Few authors have also reported an incidence as low as 4% to as high as 75% [17–20]. The vast difference could however be attributed largely due to lack of uniform diagnostic criteria to define UTI, implementation of prophylactic regimen and ill-defined period of follow-up. The incidence of UTI in the early post-transplant period (first 6 months) is higher as compared to late periods. However it is this early occurrence of UTI that has a profound effect over the allograft survival. Nearly 84% of symptomatic UTI cases are recorded in the first 6 months after transplant [21].

Recurrent UTI is also one of the major cause that poses threat to renal allograft and the prevalence ranges from 2.9 to 27% in renal transplant recipients. Mohammad et al. reported an incidence of recurrent UTI in nearly 51.7% patients who underwent renal transplantation [22].

1.3. Definition and diagnostic criteria for UTI

A urinary tract infection is an infection causing signs and symptoms of cystitis or pyelonephritis (including the presence of signs of systemic inflammation), which is documented to be caused by an infectious agent. The diagnostic criteria for UTI are similar to those that are used for general population, however all symptomatic UTI are considered as complicated UTI in RT patients [23–25].

Pain and tenderness over the renal allograft or costovertebral region indicates symptomatic infection of the upper urinary tract.

Asymptomatic bacteriuria in women is defined as two consecutive clean-catch voided urine specimens >24 hours apart with isolation of the same organism in quantitative counts of $\geq 10^5$ CFU/mL. However in males a single clean catch urine specimen with isolation of single organism in quantitative counts of $\geq 10^5$ CFU/mL is regarded as asymptomatic bacteriuria. In case of urethral catheterization bacteriuria is defined as isolation of a single organism in quantitative counts of $\geq 10^2$ CFU/mL in a single specimen.

2. Risk factors associated with development of UTI in renal transplant recipients

Post-transplant UTI in renal allograft recipients is of multifactorial origin and is determined by interaction between host factors, abnormalities associated with the anatomy of the urinary tract and the virulence of the pathogenic organisms. A few common extensively studied

factors are listed below. Few studies have found strong correlation of increased predilection to development of UTI, whereas other researchers have not been able to prove the association.

2.1. Gender

Most of the studies show that incidence of UTI is more common in females as compared to male patients who undergo renal transplantation [12]. The mean distance from the urethra to anus is less in females as compared to males, which leads to increased susceptibility for vaginal colonization with uropathogens [14, 26]. Meneguetti et al. reported female sex as the only risk factor for post-transplant UTI [27]. Camargo et al. also reported a higher incidence of UTI in female patients [44.4%], despite higher prevalence of male patients in the study. However few studies do report a higher incidence of UTI in males. This could be due to the larger number of male patients receiving transplant in majority of the cohorts [8]. It is well documented that women with recurrent UTI have increased susceptibility to vaginal colonization with uropathogens. Sexual intercourse, using spermicidal products, maternal history of UTI and UTI at an early age predispose these patients to recurrent infections of the urogenital tract [1].

2.2. Catheterization and presence of ureteral stent

It has been observed that increased hospital stay and late removal of the catheter is an independent risk factor for developing UTI [1]. Ostaszewaska et al. reported a strong correlation between occurrence of UTI and length of hospital stay [28]. Stamm et al. reported that the risk of UTI in renal allograft recipients is more by approximately 5% with each day of bladder catheterization [29]. Dantass et al. also had similar observations [30]. Fayek et al. report a higher rate of UTI of 14.2% in transplant recipients with stents as compared to 7.9% without stent [31].

2.3. Anatomical abnormalities

Structural abnormalities of native or transplanted kidney predisposes to increased risk of developing UTI [1, 2]. The anatomical abnormalities could be vesicoureteral reflux, neurogenic bladder or presence of benign prostatic hyperplasia, are usually associated to increased risk for developing UTI [14, 28, 29].

2.4. Immunosuppressants

A wide variety of immunosuppressants are used in transplant medicine either as induction agents or for maintenance therapy. Recipients subjected to antimetabolite (azathioprine or mycophenolate mofetil) and induction therapy with cell depleting antibodies (antithymocyte globulin) are reported to have higher incidence of UTI [1, 32–34]. Prednisone dose of >20 mg/day and multiple rejection therapies are associated with increased risk [35].

2.5. Deceased versus living donor transplants

It has been documented by various studies that the incidence of UTI is more in patients who receive kidney from deceased donor as compared to living donor. Taminato et al., reported that there is a greater risk for the patients who receive organ from deceased donor as against recipients of living donor with an odds ratio of 2.65 [36]. Similar observations were reported

by Ostaszewaska et al., R.Parasuraman et al., Camargo et al., Orhan Deniz Kara et al. and Abdulmalik MA et al. [2, 26, 28, 37, 38].

2.6. Human leucocyte antigen (HLA) match and rejection episodes

HLA compatibility and association with UTI was studied by Ostaszewaska et al. They observed that individuals with more than four HLA mismatches are more likely to develop UTI [28]. Patients who develop rejection episodes show increased incidence of UTI. These individuals are subjected to increased dosages of immunosuppression which may likely predispose these individuals to increased risk of developing UTI [9]. Moradi et al. evaluated the relationship between UTI and biopsy proven chronic rejection in a cohort of 100 patients over a period of 5 years. They concluded that patients with chronic rejection had more episodes of UTI as compared to those without rejection [39].

2.7. Other proposed factors

Apart from the important factors listed above, various other factors have been implicated in developing UTI. Older age has been related to an increased risk for UTI. The same study reported that an increase of 5 years in age at transplant increased the risk for UTI. Benign prostatic hyperplasia and menopause, was an additional risk factor for developing UTI [26, 37, 38]. Delayed graft function (DGF), usually associated with deceased donor organ transplant has been documented as a risk factor for development of UTI [9]. Study reported that occurrence of DGF strongly correlates with the incidence of UTI, with 61.8% patients with UTI developing delayed graft function [28]. Other factors that have been implicated are presence of comorbid conditions like hypertension and diabetes, prolonged cold ischemia time, serum creatinine levels of >2 mg/dL and chronic viral infections [6, 14, 26–28, 35, 37, 39].

3. Etiology of UTI in renal transplant patients

3.1. Etiological agents

The most common type of UTI is bacterial followed by fungi and rarely viruses are implicated in pathogenesis of UTI. Gram negative bacteria are the most common pathogens cultured from the urine of renal transplant patients with UTI, followed by candida and viruses.

3.2. Bacteria

E. coli is the most common, accounting for more than 70% of the cases. Enterobacteriaceae, Enterococci, *Pseudomonas* and coagulase-negative staphylococci are other common agents. Mycobacterium tuberculosis, Salmonella and Mycoplasma are encountered rarely [2, 6, 38, 41, 42]. A retrospective study by Espinar MJ et al., showed that renal allograft recipients are particularly susceptible to infection by Enterobacteriaceae-producing extended-spectrum β -lactamases (ESBLs). Diabetes mellitus, previous antibiotic prophylaxis or therapy, previous UTI, relapsing infection and patients with delayed graft function after transplant represented risk factors for infection by ESBL positive Enterobacteriaceae. It was also observed that these patients present

early with UTI and exhibit higher resistance to fluoroquinolones, trimethoprim-sulfamethoxazole and gentamicin. Pourmand MR et al. and Tawab et al. studied renal transplant recipients who developed recurrent UTI. *E. coli* was the most common cultured organism from the urine of patients with recurrent UTI. Coagulase negative staphylococci and *Bacillus* were rare [2, 9, 22].

3.3. Fungus

Candida is the most common cause for UTI in renal transplant recipients and is usually asymptomatic. Serious complications can occur following ascending infections. Fungal balls can be formed that may cause obstruction at the ureterovesical junction [2, 3, 43].

3.4. Viruses

The most common viruses that cause viral UTI in a renal transplant patient are cytomegalovirus and type 1 human polyomavirus (BKV). Clinically they present with fever, acute graft rejection, tubulointerstitial nephropathy and renal vascular disease. BKV-associated nephropathy may be a frequent cause of recurrent post-transplant infections and these patients usually present as sterile pyuria, eosinophiluria and hematuria. Ureteral cell hyperplasia leading to ureteral obstruction has also been reported [2, 3, 40–43].

3.5. *Schistosoma haematobium*

Trematode involves the urinary tract and kidney, and the diagnosis is based on the visualization of parasite ova in urine specimens. The urine should be collected close to noon, when egg excretion is maximal. Reactivation of a prior infection due to immunosuppression has been described in solid organ transplant recipients. Any solid organ transplant recipient from an endemic at risk-area developing hematuria (with or without eosinophilia) should have urine examined to rule out the infection. *S. haematobium* should be treated with praziquantel both in the pre and post-transplant period, as chronic infection can lead to squamous cell carcinoma of the bladder [44].

3.5.1. Causative organisms and identification of the organisms in our cases

Case 1: The microscopic examination of the urine sediment revealed plenty of pus cells with occasional red blood cells and bacilli. (**Figure 1**). Urine culture study was performed. On nutrient agar large, circular, low convex, grayish, white, moist, smooth and opaque colonies were observed. On MacConkey Agar media the colonies were circular, moist, smooth, and pink and found to be lactose fermenting. (**Figure 1a**) On Gram's stain, pink gram negative rods were identified. (**Figure 1b**) The sample was further subjected to VITEK 2 system for identification and culture sensitivity. *Escherichia coli* was identified as the causative organism with sensitivity to Piperacillin/ Tazobactam, Sulbactam, Imipenem, Meropenem, Amikacin, Colistin, Levofloxacin and Minocycline. However resistance to Trimethoprim/ Sulfamethoxazole, Gentamycin and Cefepime was observed.

The patient was treated with intravenous administration of Cefoparazone-salbactam and Levofloxacin for 7 days. Urine routine and culture sensitivity studies were performed on sixth day. There was reduction in the total leucocyte count to $8.4 \times 10^6/\mu\text{L}$, with normal differential count. The serum creatinine level dropped from 2.4 to 1.8 mg/dL on seventh day. Urine routine microscopic examination revealed

a

b

c

Figure 1. Urine microscopy stained with hematoxylin and eosin stain shows plenty of leucocytes and few bacilli. (Hematoxylin and eosin, $\times 400$). (a) MacConkey agar media with circular, moist, smooth, and lactose fermenting pink colonies. The left upper quadrant is the patient sample and right upper quadrant depicts the positive control. (b) Gram's stain, these bacilli appeared to be as pink gram negative rods (Gram's stain, $\times 400$).

scattered 15–20 WBC/ hpf. The patient was shifted to oral antibiotics for next 3 days. The immunosuppression regimen constituted of Tacrolimus, Prednisone and Mycophenolate sodium. No tapering of the drugs was done. Urine examination and culture studies were negative thereafter. The patient responded well to the treatment and is on regular follow-up. His present serum creatinine is 1.8 mg/dL, 4 months

after the episode of urinary tract infection. **Case 2:** The microscopic examination of the urine sediment revealed clusters of pus cells, scattered epithelial cells and fungal buds and pseudohyphae. (**Figure 2**) Urine culture study was performed on Sabouraud's dextrose agar. 65 g of the media was suspended in distilled water, mixed to form a uniform suspension, heated, boiled and then sterilized at 118–121°C for 15 min. The urine sample was streaked using inoculating loop and incubated in 37°C for 48 hours. The growth appeared in 48 hours as cream/white colored, smooth and pasty colonies. (**Figure 2a**). A drop of inoculated broth media was placed onto the slide and a drop of lactophenol cotton blue stain was added and examined under the microscope which revealed the presence of chlamydospores. (**Figure 2b**).

The patient was treated with oral antifungal agent, fluconazole, 100 mg/day for 21 days along with conventional Tacrolimus-based immunosuppressive regimen. Urine routine and culture sensitivity studies were performed on tenth day. There was reduction in the total leucocyte count to $6.35 \times 10^6/\mu\text{l}$, with normal differential count. The serum creatinine level dropped to 1.6 mg/dL. Urine examination and culture studies were negative thereafter. The patient responded well to the treatment and is on regular follow-up. Her present serum creatinine is 1.76 mg/dL, 4 months after the episode of urinary tract infection.

Figure 2. Hematoxylin and eosin stained urine deposit reveals budding fungi along with pseudohyphae. (a) Creamy and smooth colonies of candida on Sabouraud's dextrose agar (red arrow). (b) Lactophenol cotton blue (wet preparation) reveals budding fungi (LCB, X 400) with chlamydospores (LCB, X 1000).

4. UTI and effect on renal allograft function

4.1. Negative impact of urinary tract infections in renal transplant recipients

It has been well documented that development of UTI in renal transplant recipients is associated with increased rates of health resource utilization, which includes length of stay as well as more economic burden. Longer hospital stay exposes these individuals to increased risk of development of nosocomial infection [2, 8].

4.2. Effect on graft function

Mohan et al., in their prospective study of 31 patients who underwent renal transplantation, found that infections in the immediate post-transplant period adversely affected the graft survival. Mortality rate in patients with UTI was reported as 12.9% [9].

Abbott and colleagues undertook a retrospective cohort study of 28,942 Medicare primary renal transplant recipients in the U.S. Renal Data System database from 1996 through 2000, assessing Medicare claims for UTI occurring later than 6 months after transplantation based on ICD-9 codes, and found that the cumulative incidence of UTI during the first 6 months after renal transplantation was 17% (equivalent for both men and women) and at 3 years was 60% for women and 47% for men ($P < 0.001$ in Cox regression analysis). Late UTI was significantly associated with an increased risk of subsequent death and graft loss [45].

In a study by Dhamidharka et al., who analyzed US Renal Data System database over the period of 1996 to 2000 (up to 36 months post-transplant). 265 (30.5%) pediatric patients had either inpatient or outpatient claims for UTI out of total 870 pediatric patients who qualified for the study. The authors found that early UTI (less than 6 months after transplant) was significantly [$P = 0.007$ upon multivariable Cox regression] associated with higher adjusted hazard ratio of graft loss, and late UTI was not associated with such an outcome. Risk for post-transplantation death was not increased significantly after either early UTI (AHR 1.23; 95% CI 0.37 to 4.08) or late UTI (relative risk 2.22; 95% CI 0.90 to 5.44) [46].

Pelle, et al. as well as Giral et al. reported that acute pyelonephritis of the graft is accompanied by renal failure and is an independent risk factor for impaired renal function as well as graft loss [47, 48]. Bodro et al. reported 1-year mortality rate of 3% in patients who developed worsening of graft function secondary to graft acute pyelonephritis. They further discovered that in patients with UTI due to a resistant strain of bacteria, the impairment of graft function is more frequent than in patients who develop UTI due to non-resistant strain bacteria [13]. Several hypotheses have been put forward to explain the negative impact of UTI on graft function. It has been postulated that bacterial infection activated the immune system, which can trigger the rejection cascades leading to acute or chronic rejections, causing deterioration of the graft function. Some authors propose that inflammation secondary to infection can cause scarring of the renal tissue, leading to loss of the functioning nephron mass causing impairment of renal function [49–51]. Reduction in the immunosuppressive agents following an episode of infection may accentuate the rejection process [13].

Various studies like the one by Ostaszewska et al., have found out no significant difference related to UTI and graft survival [28]. Fiorante et al. also in their study of 189 renal allograft recipients, over a follow-up of 36 months, did not find an association between asymptomatic and symptomatic bacteriuria with graft dysfunction. They also did not report statistically significant association between graft dysfunction and acute pyelonephritis of the graft [42]. Similarly, Ariza et al. and Lee et al. did not report any significant graft survival and UTI [52].

5. Management of UTI

Definitive diagnostic and treatment protocols for renal transplant patients are not well-defined. The current treatment protocols depend mainly on the severity of the infection, the local epidemiological data and the results of the culture reports. Complete urinalysis with microscopy along with culture studies is recommended. It has been proposed that bactericidal antibiotics should be preferred to bacteriostatic ones, which might be insufficient to cure the infection since the immune system cannot eradicate the dormant bacteria. Managing the predisposing factors is equally essential. The need for adequate immunosuppression and dose adjustment is also important. Various pharmacological interactions exist between antibiotics used to treat post-transplant UTI and immunosuppressant drugs. Ciprofloxacin and erythromycin are implicated in raising Calcineurin inhibitor (CNI) levels. Levofloxacin and ofloxacin usually do not interfere with CNI levels. Antifungal agents inhibit cytochrome P450 and increase CNI levels. Rifampin, imipenem and cephalosporin can reduce CNI levels. Nephrotoxic antibiotics (e.g., aminoglycosides, amphotericin) may have synergistic effects with CNIs, increasing renal damage.

UTI can co-exist with CMV, BKV and other viral and fungal diseases.

5.1. Management of asymptomatic bacteriuria

No definitive consensus or management is available for treatment of asymptomatic bacteriuria. However many of the researchers agree that there is no need to subject patients with asymptomatic bacteriuria to antibiotics as there are not enough studies that prove that asymptomatic bacteriuria heralds a negative outcome. Also studies have shown that treatment of this entity does not prevent occurrence of significant bacteriuria in the later post-transplant period [39]. Few studies have demonstrated that use of antimicrobials in patients with asymptomatic bacteriuria is usually unsuccessful in removing the offending agent; also it does not prevent the occurrence of subsequent UTI [53]. Study by Goya et al. proposed that considering asymptomatic bacteriuria as a precursor for symptomatic bacteriuria and subsequent development of pyelonephritis and high risk of developing symptomatic UTI in early transplant period that may affect the graft function it is recommended to keep patients with asymptomatic bacteriuria under screening schedules. Treatment with narrow-spectrum antibiotics of short duration of 5–7 days following culture report is recommended [54].

5.2. Symptomatic UTI

Symptomatic bacteriuria is classified further as mild, moderate and severe. Any predisposing conditions have to be treated. For mild cases empirical therapy with oral antibiotics, preferably ciprofloxacin with or without amoxicillin for a period of 5–7 days is recommended. For moderate infections, treatment with ciprofloxacin or ceftriaxone or ampicillin-salbactam is advised for 14 days after the culture sensitivity reports are obtained. For severe symptomatic UTI empirical treatment with piperacillin-tazobactam or cefepime is recommended over a period of 14–21 days following culture sensitivity report. Multi-drug resistant organisms need to be kept in mind before starting the empirical therapy. Carbapenem is the drug of choice for such cases. For recurrent UTI the treatment is extended to 6 weeks.

5.3. Candiduria

In patients with asymptomatic candiduria, there is no recommended treatment. In cases of symptomatic candiduria fluconazole, 200–400 mg, orally per day for 14 days is the treatment of choice. Fluconazole may have drug interactions with Calcineurin inhibitor, hence dose adjustment is recommended. Disseminated cases would require treatment by intravenous amphotericin B, 0.3–1 mg/kg/day for 1–7 days. Flucytosine [25 mg/kg every 6 h for 7–10 days] can also be used, but with caution, especially in cases of renal dysfunction. Monitoring for cytopenias, rash, gastrointestinal symptoms and hepatotoxicity is recommended [55, 56].

6. Prevention

Although the data from various studies does not provide a concrete evidence for post-transplant UTI to have a profound effect on graft dysfunction, but overall it is necessary to control infection related mortality. It is quite obvious from certain studies that UTI or any infection leads to increase in duration of stay at hospital as well as it adds to economic burden as discussed in this review. Infection of any sort can have a psychological effect on the transplant recipient too. With advent of wide range of antimicrobials available as well as vast advancement in the field of transplantation medicine, losing graft function to infections should not be acceptable. Hence it is important to identify the various risk factors and employ strategies to prevent the development of infections in these subset of patients. Individuals with high risk factors like those having structural anomalies of the urinary tract, old age patients, females, presence of comorbid conditions like diabetes, hypertension should be kept under proper surveillance. In case of living donors a thorough screening for infections before transplantation though serological tests, urine analysis and hematology is advisable to rule out possibility of any infections.

Certain studies have emphasized the role of antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ) for prevention of UTI. TMP-SMZ is a broad spectrum

Figure 3. Scheme for evaluating a case of recurrent UTI.

antimicrobial agent, with relatively low cost and is mostly used for prevention of *Pneumocystis carinii* infection [2, 14, 51]. Ariza-Heredia et al. have reported the effect of TMP-SMZ prophylaxis offers great protection to prevent UTI in the first year. Four patients who were not offered this prophylaxis due to certain reasons developed UTI in first year of transplant as against those who received the prophylaxis [14].

In cases with recurrent UTI anatomical and functional abnormalities like vesicoureteral reflux and neurogenic bladder need to be addressed and managed accordingly. The patients should be educated for basic preventive measures like hydration and frequent voiding. Radiological studies should be implicated to rule out the anatomical defects, obstruction, calculi and retained foreign bodies. Prostatitis should be considered as an important differential diagnosis in men who present with recurrent post-transplant UTI. Mitra et al. have proposed a scheme for evaluating a case of recurrent UTI (**Figure 3**) [57].

7. Recommendations

As the risk of UTI is very high in the first week of transplantation, we recommend that every renal transplant recipient should undergo urine routine examination with microscopy for first 10 days in the post-operative period irrespective of the fact that the patient has any

symptoms of UTI. This type of screening will be helpful in early diagnosis and treatment and preventing infection related mortality. Culture studies should be advised as and when required, and the treatment should be planned according to the organisms identified in the culture studies. Antibiotic prophylaxis should be given to patients who are at high risk for developing UTI. Urine examination should be advised during every follow-up. This practice will definitely help in early diagnosis of infection and help in preventing morbidity associated with UTI.

8. Conclusion

Urinary tract infections in the post-transplant period are quite common, more so during the early period of first 3 months. There are various risk factors attributed to development of UTI like female sex, delayed graft function, old age, anatomical anomalies and organs from the deceased donors being more common. Although few studies have identified UTI in post-transplant period as a negative predictor for graft function, further studies are still required to establish this relationship. The criteria to define asymptomatic bacteriuria and UTI are the same as that for general population. However in view of studies that show that post-transplant UTI has deleterious effect on graft function, it is necessary to design standard definitions, protocols for surveillance, prevention and management of UTI in renal transplant recipients.

However our protocol for renal transplant recipients involves regular follow-up by urine routine and microscopic examination and renal function tests, which helps in early detection of infections leading to prompt management. Thus, early intervention in both the patients led to restoration of the renal function with proper graft function.

Conflict of interest

None of the authors report any conflict of interest.

Abbreviations

RT	renal transplant
UTI	urinary tract infection.
CFU	colony forming units.
DGF	delayed graft function.
CNI	calcineurin inhibitors.
TMP-SMZ	trimethoprim-sulfamethoxazole

Author details

Lovelesh Kumar Nigam*, Aruna V. Vanikar, Rashmi D. Patel, Kamal V. Kanodia and Kamlesh S. Suthar

*Address all correspondence to: drloveleshnigam@gmail.com

Department of Pathology, Lab Medicine, Transfusion Services and Immunohematology, Institute of Kidney Disease and Research Sciences, BJ Medical College Campus, Ahmedabad, Gujarat, India

References

- [1] Tawab KA, Gheith O, Otaibi TA, Nampoory N, Mansour H, Halim AH, et al. Recurrent urinary tract infection among renal transplant recipients: Risk factors and long-term outcome. *Experimental and Clinical Transplantation*. 2017;**2**:157-163
- [2] Parasuraman R, Julian K. Urinary tract infections in solid organ transplantation. *American Journal of Transplantation*. 2013;**13**:327-336
- [3] Anastasopoulos NA, Duni A, Peschos D, Agnantis N, Dounousi E. The Spectrum of infectious diseases in kidney transplantation: A review of the classification, pathogens and clinical manifestations. *Infectious Diseases in Kidney Transplantation*. 2015;**29**:415-422
- [4] Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clinical Journal of the American Society of Nephrology*. 2012;**7**:2058-2070
- [5] Umesh L, Mahesh E, Kumar A, Punith K, Lalitha K, Suman G. Infections in renal transplant recipients. *Journal, Indian Academy of Clinical Medicine*. 2007;**8**(4):316-323
- [6] Gondos AS, Al-Moyed KA, Al-Robasi ABA, Al-Shamahy HA, Alyousefi NA. Urinary tract infection among renal transplant recipients in Yemen. *PLoS One*. December 2015. DOI: 10.1371/journal.pone.0144266
- [7] Espinar MJ, Miranda IM, Costa-de-Oliveira S, Rocha R, Rodrigues AG, Pina-Vaz C. Urinary tract infections in kidney transplant patients due to *Escherichia coli* and *Klebsiella pneumoniae*-producing extended-spectrum β -Lactamases: Risk factors and molecular epidemiology. *PLoS One*. 2015. DOI: 10.1371/journal.pone.0134737
- [8] Becerra BJ, Becerra MB, Safdar N. A Nationwide assessment of the burden of urinary tract infection among renal transplant recipients. *Journal of Transplantation*. 2015 Article ID 854640, 8 pages:<http://dx.doi.org/10.1155/2015/854640>
- [9] Mohan M, Neeraja M, Sudhaharan S, Raju SB, Gangadhar T, Lakshmi V. Risk factors for urinary tract infections in renal allograft recipients: Experience of a tertiary care center in Hyderabad, South India. *Indian Journal of Nephrology*. 2017;**27**:372-376. DOI: 10.4103/ijn.IJN_331_16

- [10] Silva M, Marra AR, Pereira CA, Medina-Pestana JO, Camargo LF. Bloodstream infection after kidney transplantation: Epidemiology, microbiology, associated risk factors, and outcome. *Transplantation* 2010;**90**:581-587
- [11] Vidal E, Torre-Cisneros J, Blanes M, et al. Bacterial urinary tract infection after solid organ transplantation in the RESITRA cohort. *Transplant Infectious Disease*. 2012;**14**:595-603
- [12] Fontserè S, Chacón N, Cordero E. Review of bacterial urinary tract infection in kidney transplant recipients: Incidence, risk factors and impact on the graft survival. *International Journal of Transplantation Research and Medicine* 2017;**3**:026. doi.org/10.23937/2572-4045.1510026
- [13] Bodro M, Sanclemente G, Lipperheide I, Allali M, Marco F, Bosch J, et al. Impact of urinary tract infections on short-term kidney graft outcome. *Clinical Microbiology and Infection* 2015;**21**:1104.e1-1101104.e8
- [14] Ariza-Heredia EJ, Beam EN, Lesnick TG, Kremers WK, Cosio FG, Razonable RR. Urinary tract infections in kidney transplant recipients: Role of gender, urologic abnormalities, and antimicrobial prophylaxis. *Annals of Transplantation*. 2013;**18**:195-204. DOI: 10.12659/AOT.883901
- [15] Brown PD. Urinary tract infections in renal transplant recipients. *Current Infectious Disease Reports*. 2002;**4**:525-528
- [16] Elkehili IM, Kekli AB, Zaak AS, Salem EL. Urinary tract infections in renal transplant recipients. *Arabian Journal of Nephrology and Transplantation*. 2010;**3**(2):53-55
- [17] Alangaden GJ, Thyagarajan R, Gruber SA, Morawski K, Gar nick J, et al. Infectious complications after kidney transplantation: Current epidemiology and associated risk factors. *Clinical Transplantation*. 2006;**20**:401-409
- [18] Khosravi AD, Montazeri EA, Ghorbani A, Parhizgari N. Bacterial urinary tract infection in renal transplant recipients and their antibiotic resistance pattern: A four-year study. *Iran Journal of Microbiology*. 2014;**6**:74-78
- [19] Origüen J, López-Medrano F, Fernández-Ruiz M, Polanco N, Gutiérrez E, et al. Should asymptomatic bacteriuria be systematically treated in kidney transplant recipients? Results from a randomized controlled trial. *American Journal of Transplantation*. 2016;**16**:2943-2953
- [20] Papasotiriou M, Savvidaki E, Kalliakmani P, Papachristou E, Marangos M, et al. Predisposing factors to the development of urinary tract infections in renal transplant recipients and the impact on the long-term graft function. *Renal Failure*. 2011;**33**:405-410
- [21] Albert X, Huertas I, Pereiro II, Sanfelix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in nonpregnant women. *Cochrane Database Systematic Review*. 2004 CD001209
- [22] Pourmand MR, Keshtvarz M, Talebi M, Mashhadi R. Incidence of recurrent urinary tract infection after renal transplantation. *Medical Bacteriology*. 2012;**1**(2 [2013]):27-34

- [23] Giessing M. Urinary tract infection in renal transplantation. *Arab Journal of Urology*. 2012;**10**:162-168
- [24] Smelov V, Naber K, Johansen TEB. Improved classification of urinary tract infection: Future considerations. *European Urology Supplements*. 2016;**15**:71-80 <http://dx.doi.org/10.1016/j.eursup.2016.04.002>
- [25] Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2010;**50**:625-663
- [26] Alkatheri AM. Urinary tract infections in Saudi renal transplant recipients. *Journal of Infectious Diseases and Immunity*. 2013;**5**(2):18-23. DOI: 10.5897/JIDI12.026
- [27] Meneguetti MG, Pereira MF, Bellissimo-Rodrigues F, Pisi Garcia TM, Saber LTS, Papini Nardim ME, et al. Study of the risk factors related to acquisition of urinary tract infections in patients submitted to renal transplant. *Revista da Sociedade Brasileira de Medicina Tropical*. 2015;**48**(3):285-290 <http://dx.doi.org/10.1590/0037-8682-0098-2015>
- [28] Ostaszewska A, Wszola M, Kuthan R, Domagała P, Góralski P, Diuwe P, et al. Urinary tract infection in patients after renal transplantation: Evaluation of risk factors. *MEDtube Science*. 2014;**2**:22-29
- [29] Dantas SR, Kuboyama RH, Mazzali M, Moretti ML. Nosocomial infections in renal transplant patients: Risk factors and treatment implications associated with urinary tract and surgical site infections. *The Journal of Hospital Infection*. 2006;**63**(2):117-123
- [30] Stamm WE. Catheter-associated urinary tract infections: Epidemiology, pathogenesis, and prevention. *The American Journal of Medicine*. 1991;**91**(3B):65S-71S
- [31] Fayek SA, Keenan J, Haririan A, et al. Ureteral stents are associated with reduced risk of ureteral complications after kidney transplantation: A large single center experience. *Transplantation*. 2012;**93**:304-308
- [32] Giral M, Pascuariello G, Karam G, et al. Acute graft pyelonephritis and long-term kidney allograft outcome. *Kidney International*. 2002;**61**:1880-1886
- [33] Almond PS, Matas A, Gillingham K, et al. Risk factors for chronic rejection in renal allograft recipients. *Transplantation*. 1993;**55**(4):752-756 discussion 756-757
- [34] Memikoglu KO, Keven K, Sengul S, Soypacaci Z, Erturk S, Erbay B. Urinary tract infections following renal transplantation: A single-center experience. *Transplantation Proceedings*. 2007;**39**:3131-3134
- [35] Munoz P. Management of urinary tract infections and lymphocele in renal transplant recipients. *Clinical Infectious Diseases*. 2001;**33**(Suppl 1):S53-S57
- [36] Taminato M, Fram D, Grothe C, Pereira RRF, Belasco A, Barbosa D. Prevalence of infection in kidney transplantation from living versus deceased donor: Systematic review and meta-analysis. *Revista Da Escola De Enfermagem Da U S P*. 2015;**49**(3):502-507

- [37] Camargo LF, Esteves ABA, Ulisses LRS, Rivelli GG, Mazzali M. Urinary tract infection in renal transplant recipients: Incidence, risk factors, and impact on graft function. *Transplantation Proceedings*. 2014;46:1757e1759 <http://dx.doi.org/10.1016/j.transproceed.2014.05.006>
- [38] Kara OD, Dincel N, Bulut IK, Ozdemir K, Yilmaz E, Gun ZH, et al. Infectious complications in pediatric renal transplant patients. *World Journal of Nephrology and Urology*. 2014;3(2):92-99
- [39] Moradi M, Abbasi M, Moradi A, Boskabadi A, Jalali A. Effect of antibiotic therapy on asymptomatic bacteriuria in kidney transplant recipients. *Urology Journal*. 2005;2(1):32-35
- [40] Satish R. Gokulnath. Intractable urinary tract infection in a renal transplant recipient. *Saudi Journal of Kidney Disease Transplantation*. 2009;20(3):458-461
- [41] Korth J, Kukalla J, Rath PM, Dolff S, Krull M, Guberina H, et al. Increased resistance of gram-negative urinary pathogens after kidney transplantation. *BMC Nephrology*. 2017;18:164
- [42] Fiorante S, Lopez-Medrano F, Lizasoain M, Lalueza A, Juan RS, et al. Systematic screening and treatment of asymptomatic bacteriuria in renal transplant recipients. *Kidney International*. 2010;78:774-781
- [43] Lopez-Medrano F, Aguado JM. Urinary Tract Infection in a Renal Transplant Recipients. *Monograph in Infectious Disease and Antimicrobial Agents*
- [44] Shams SF, Eidgahi ES, Lotfi Z, Khaledi A, Shakeri S, Sheikh M, et al. Urinary tract infection in a kidney transplant recipients 1st year after transplantation. *Journal of Research in Medical Sciences*;2016
- [45] Abbott KC, Swanson SJ, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. *American Journal of Kidney Diseases*. 2004;44(2):353-362
- [46] Dharnidharka VR, Agoda LY, Abbott KC. Effects of urinary tract infection on outcomes after transplantation in children. *Clinical Journal of the American Society of Nephrology*. 2007;2:100-106
- [47] Pellé G, Vimont S, Levy PP, Hertig A, Ouali N, et al. Acute pyelonephritis represents a risk factor impairing longterm kidney graft function. *American Journal of Transplantation*. 2007;7:899-907
- [48] Giral M, Pascuariello G, Karam G, Hourmant M, Cantarovich D, et al. Acute graft pyelonephritis and long-term kidney allograft outcome. *Kidney International*. 2000;61:1880-1886
- [49] Audard V, Amor M, Desvaux D, Pastural M, Baron C, Philippe R, et al. Acute graft pyelonephritis: A potential cause of acute rejection in renal transplant. *Transplantation*. 2005;80:1128-1130
- [50] Dupont PJ, Psimenou E, Lord R, Buscombe JR, Hilson AJ, Sweny P. Late recurrent urinary tract infections may produce renal allograft scarring even in the absence of symptoms or vesicoureteric reflux. *Transplantation*. 2007;84:351-355

- [51] Lorenz EC, Cosio FG. The impact of urinary tract infection in a renal transplant recipients. *Kidney International*. 2010;**78**:719-721. DOI: 10.1038/ki.2010.219
- [52] Chacon-Mora N, Diaz JP, Matia EC. Urinary tract infection in a renal transplant recipients. *Enfermedades Infecciosas y Microbiología Clínica*. 2017;**35**(4):255-259
- [53] Green H, Rahamimov R, Goldberg E, et al. Consequences of treated versus untreated asymptomatic bacteriuria in the first year following kidney transplantation: Retrospective observational study. *European Journal of Clinical Microbiology & Infectious Diseases*. 2012
- [54] Goya N, Takahashi K, Tanabe K, et al. Clinical studies of bacteriuria in renal transplantation recipients. Correlation with pyuria and symptomatic genitourinary tract infection. *Nihon Hinyokika Gakkai Zasshi*. 1991;**82**:947-954
- [55] Pappas PG, Silveira FP. *Candida* in solid organ transplant recipients. *American Journal of Transplantation*. 2009;**9**(4):173-179
- [56] Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clinical Infectious Diseases*. 2004;**38**:161-189
- [57] Mitra S, Alangaden GJ. Recurrent urinary tract infections in kidney transplant recipients. *Current Infectious Disease Reports*. 2011;**13**:579-587