Urinary Tract Infections in Renal Transplant Recipients

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Infection of the urinary tract is the most common infectious complication of renal transplantation. The microbiology of post-transplant urinary tract infections is similar to what is seen in the general population, although transplant patients may develop infections due to unusual or opportunistic pathogens. The optimal management of urinary tract infections in renal transplant recipients is poorly studied, but recommendations for treatment are available. Antibiotic prophylaxis can reduce the risk of bacterial infection of the urinary tract post-transplant but is not used in all transplant centers. The influence of urinary tract infection on graft survival requires further study.

Introduction

Renal transplantation is now considered the preferred therapy for end-stage renal disease. From 1988 through 1994 more than 80,000 renal transplants were performed in 251 centers in the United States [1]. Bacterial infection of the urinary tract is the most common infection encountered among recipients of renal transplants, although the reported incidence varies quite remarkably from center to center. Simultaneous pancreas-kidney transplantation is becoming increasingly available for patients with end-stage renal disease due to insulin-requiring diabetes mellitus, and the data suggest that these patients are at an even higher risk of urinary tract infection (UTI) than renal transplant recipients. The bacteriology of UTI in the renal transplant patient is similar to that seen in the general population, although as a result of immunosuppression, renal transplant recipients are at risk for UTI with opportunistic pathogens as well. Recommendations for the management of UTI in the transplant population are mainly based on expert opinion; there are very little data available in the literature on which to make evidence-based decisions. Several studies have demonstrated that antibiotic prophylaxis can reduce the risk of UTI in the renal transplant recipient, but UTI prophylaxis is not routinely employed in all transplant centers. The influence of UTI on chronic rejection is unclear, with studies offering conflicting data regarding the impact of UTI on graft survival.

Incidence of Urinary Tract Infection in Transplant Recipients

The incidence of UTI among renal transplant recipients has been reported to be 35% to 79% [2•]. Reasons for the wide variation in the reported incidence of infection are unknown, but most likely include differences in the definition of UTI, frequency of sampling of urine for culture, and variations in the use of post-transplant antibiotic prophylaxis [3]. In a recent study from a university transplant center in Sweden, Takai *et al.* [4•] found that among 363 renal transplant recipients more than 16 years of age followed for a mean of 4 years, the incidence of UTI was 26%. In this center all patients received trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for at least 5 to 6 months post-transplant. Urine was cultured at least weekly while patients were hospitalized; in the outpatient clinic urine was obtained for culture in patients with pyuria, symptoms of UTI, or fever. UTI occurred most frequently during the first year following transplantation with most episodes occurring after the fifth month. UTI was more common in women than men (49% vs 14%, $P < 0.0001$). There was no significant difference in the incidence of UTI among recipients of cadaveric versus living donor grafts, and age had no influence on the risk of UTI.

In addition to female sex, other risk factors for UTI in the renal transplant recipient have been recognized and these are outlined in Table 1.

Abbott *et al.* [5] studied a national renal transplant database and found that UTI is the most common source of septicemia after renal transplant, accounting for almost one third of episodes. Women were found to have an increased risk for septicemia as compared with men, most likely due to their increased risk of UTI. Mean patient survival for transplant recipients hospitalized for an episode of septicemia was significantly reduced when compared with other transplant recipients. Pretransplantation dialysis was also found to be a risk factor for septicemia after transplant.

Smets *et al.* [6] reviewed their experience with infectious complications following simultaneous pancreas-kidney transplantation and found that UTI was the most common, accounting for almost 50% of all infections seen. In this

Table 1. Risk factors for urinary tract infection in renal transplant

Pretransplant urinary tract infection
Diabetes mellitus
Female sex
Prolonged dialysis prior to transplantation
Allograft trauma
Postoperative bladder catheterization
Technical complications with the ureteral anastomosis
Immunosuppression
Uremia/poor graft function
Bladder dysfunction
Increased urinary aluminum secretion

study, 57% of all bacteremias originated from a urinary tract source. Recipients of simultaneous pancreas-kidney transplantation have an increased incidence of rejection episodes and require higher levels of immunosuppression [7]. In addition, it is postulated that metabolic changes that occur in the bladder as a result of the drainage of pancreatic exocrine secretions such as increased urine pH and mucosal injury due to pancreatic enzymes may be responsible for the higher rate of infections seen in this population. Enteric-drained pancreas-kidney transplants are becoming more common in the United States and there are data that the risk of UTI is lower in these patients [8].

Urinary tract infections that occur during the first 3 months following transplantation are often associated with transplant pyelonephritis and bacteremia, whereas infections that occur later tend to be less severe [2•]. Probably the most important risk factor for early UTI is the presence of a urethral catheter. In many transplant centers the urethral catheter may be left in place for as long as 5 to 7 days after transplant. Several studies have shown that early (within 48 hours) removal of the catheter can reduce the risk of UTI during the first month following renal transplant without increasing the risk of urologic complications [9,10]. The utility of ureteral stenting post-transplant is controversial and there are conflicting data regarding the use of ureteral stents and the risk of UTI. Renoult *et al.* [11] found that ureteral stents were associated with a higher risk of early UTI, whereas two other retrospective reviews failed to demonstrate any increased risk of infection [10,12]. Again, an important factor influencing the risk of infection associated with stenting may be early removal of the catheter.

Microbiology

In general, the microbiology of UTI in renal transplant recipients is quite similar to that seen in the general population. In the previously mentioned series of Takai *et al.* [4•], gram-negative organisms were responsible for the majority of UTIs with *Escherichia coli*, *Klebsiella*, *Proteus*, and *Enterobacter* species being the most common gram-negative isolates. Gram-positive organisms were responsible for approximately one fourth of UTIs; *Enterococcus* was the most common gram-positive isolate, followed by *Staphylococcus epidermidis*. *Candida albicans* was responsible for five (1.3%) infections. Although it is generally recommended that empiric therapy should include coverage for *Pseudomonas* species, this organism is uncommonly recovered from transplant patients with UTI.

Because of transplant-related immunosuppression, renal transplant recipients are also at risk for UTI due to pathogens not usually associated with infection of the urinary tract, as well as renal infection due to opportunistic pathogens. Infections due to *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Corynebacterium urealyticum*, *Salmonella* species, and Microsporidia have been reported in the renal transplant population [13–16]. Renal transplant recipients are at high risk for active disease due to *Mycobacterium tuberculosis*, and genitourinary tuberculosis has been described in transplant recipients [17]. Aspergillosis can occur as a complication of renal transplantation and generally presents as pulmonary disease or disseminated infection; however, isolated urinary tract aspergillosis has recently been reported in renal transplant recipients [18,19]. Cytomegalovirus is an important cause of infection after renal transplant, again generally presenting as a disseminated infection; however, cytomegalovirus ureteritis has been described in transplant patients presenting as post-transplant obstruction [20].

The BK polyomavirus has a tropism for renal epithelial tissues, and infections due to BK virus have been recognized as a complication of renal transplant for more than two decades. After renal transplantation, as many as 45% of patients will have viruria due to BK virus, and it is believed that reactivation of latent virus in the graft is the major source of the infection [21]. The majority of BK virus infections in renal transplant recipients are asymptomatic. Interstitial nephritis due to BK virus in renal transplants recipients is a more recently described entity and has been reviewed by Howell *et al.* [22].

Management

As previously discussed, early UTIs, defined as those occurring during the first 4 to 6 months following renal transplant, are generally felt to be potentially more severe and are associated with a greater risk of relapse as compared with those infections that occur later in the post-transplant course. For this reason prolonged antibiotic therapy has been advocated for early UTI . With advances in surgical techniques as well as the availability of more effective antimicrobial therapy, some experts believe that the morbidity associated with early infections may not be as great as previously thought and recommend standard (10- to 14-day) courses of therapy, reserving prolonged therapy for those patients with relapse of infection [23•].

Late UTIs are more likely to be benign and can be treated with 10 to 14 days of antimicrobial therapy guided by the results of culture and susceptibility testing [23•,24]. Some experts advise more prolonged courses of therapy for men

because of the possibility of infection involving the prostate [2•]. Short-course therapy has never been studied in this patient population and is not recommended. Because of their excellent penetration into the renal parenchyma, fluoroquinolones are considered the antimicrobial of choice for the treatment of infections due to susceptible isolates. Transplant recipients with relapsing UTI should be suspected of having an anatomic or functional abnormality of the urinary tract such as ureteral reflux, stricture of the ureterovesicle junction, or neurogenic bladder. Patients who present with late infections complicated by urosepsis have a high incidence of stones due either to hyperparathyroidism or formation of a concretion at the site of a suture in the ureteral anastomosis [2•].

The management of aymptomatic bacteriuria in transplant recipients has been controversial. In a recently published guideline on the management of infections in renal transplant recipients, the treatment of asymptomatic bacteriuria was not recommended [23•]. Some experts advocate treatment of asymptomatic bacteriuria during the early post-transplant period and observation for those who are more than 3 months post-transplant [25].

Urinary tract infections due to *Candida* species may be associated with serious morbidity in renal transplant recipients including ascending infection and obstruction due to the formation of a fungus ball. Risk factors for candiduria in this population include urinary catheters, diabetes mellitus, high-dose corticosteroid therapy, and the use of broad-spectrum antibiotic therapy. Because of the potential morbidity of fungal UTI and the difficulties in differentiating potentially serious from nonserious fungal infection in the urinary tract, it is recommended that candiduria always be treated in renal transplant recipients [2•,23•,24]. Azole antifungals, such as fluconazole, are preferred for the treatment of candiduria.

Prevention

Two randomized, placebo-controlled trials have looked at the efficacy of TMP-SMX for the prophylaxis of infection in renal transplant recipients [26,27]. Fox *et al*. [26] found that TMP-SMX significantly reduced the risk of UTI as well as the risk of bloodstream infections. In addition, patients randomized to receive TMP-SMX prophylaxis had fewer hospital days with fever. Prophylaxis was not effective at preventing UTI in patients with urethral catheters, but the risk of infection in the treatment group after catheter removal was decreased threefold. In addition to reducing the risk of infection with enteric gram-negative organisms, prophylaxis reduced the risk of infections due to *Enterococcus* species and *Staphylococcus aureus*. Interestingly, patients who received prophylaxis were less likely than placebo recipients to become colonized with *Candida* species. The authors postulate that this finding may be due to less exposure to broad-spectrum antibiotics in the prophylaxis group because of a decreased incidence of infections. Maki *et al*. [27] also demonstrated a significant reduction in the incidence of bacterial infections in renal transplant recipients with the use of TMP-SMX prophylaxis. In this study hospital length of stay was longer in the placebo group and this group was also more likely to be readmitted to hospital after transplant. The cost of the transplant hospitalization was decreased by 7% in the prophylaxis group. TMP-SMX was found to have no demonstrable effect on cyclosporin pharmacokinetics. Both studies showed that TMP-SMX was well tolerated without hematologic, renal, or hepatic toxicity.

The occurrence of UTI due to a susceptible pathogen in a patient receiving prophylaxis suggests the possibility of an anatomic or functional abnormality of the urinary tract and should prompt further investigation.

Ciprofloxacin has also been shown to be effective for the prevention of UTI in renal transplant recipients in a randomized, placebo-controlled trial [28]. TMP-SMX has the advantage of providing prophylaxis not only for bacterial infections but also for the prevention of opportunistic pathogens, especially *Pneumocystis carinii*, as well as *Listeria* and *Nocardia* species.

Although prophylaxis has been shown to reduce the incidence of bacterial infections, no study has demonstrated an advantage in terms of graft or patient survival, and prophylaxis for the prevention of UTI is not used in many transplant centers. In our center daily TMP-SMX is given for 6 months following transplantation and 6 months after any rejection episode with the main goal to prevent *P. carinii* pneumonia.

Influence of Urinary Tract Infection on Graft Survival

At the present time the potential of bacterial infection of the urinary tract to precipitate graft rejection is unclear, and studies that suggest that UTI is a risk factor for transplant rejection as well as studies that fail to show any association between UTI and decreased graft survival have appeared in the literature. Cytokines that are activated in response to bacterial infection such as tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8 are also involved in the pathogenesis of graft rejection and there are data from a rat model that endotoxin from *E. coli* can accelerate chronic rejection [29]. In their recent study of UTI in renal transplant patients, Takai *et al*. [4•] found that UTI had no effect on the number of rejection episodes or graft survival. An earlier report from a transplant center with a relatively high incidence of UTI also failed to demonstrate an association between UTI and graft rejection [30].

Conclusions

Urinary tract infection is common after renal transplantation and the urinary tract is the most common source of bacterial sepsis in this patient population. A number of risk factors for UTI post-transplant have been defined. The most important risk for early UTI is the urethral catheter,

and early removal of the catheter is important in reducing the risk of infection. Infections that occur early after transplant have generally been felt to be more serious, although improvements in surgical technique and the availability of more effective antibiotic therapy may reduce the morbidity associated with early infections. Infections that occur later in the post-transplant course are usually benign. The microbiology of UTI in the renal transplant recipient in similar to what is seen in the general population, although these patients are clearly at risk for infection with opportunistic pathogens. Antimicrobial prophylaxis has been demonstrated to reduce the risk of UTI after renal transplant, but is not used in all transplant centers. The role of infection of the urinary tract in precipitating transplant rejection requires further study.

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