Efficacy of antibacterial prophylaxis for preventing urinary tract infections in renal transplant recipients

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Efficacy of Antibacterial Prophylaxis for Preventing Urinary Tract Infections in Renal Transplant Recipients

Abstract

Background: The increased incidence of urinary tract infections (UTIs) following organ transplantation necessitates the use of antibacterial prophylaxis. The goal of this review is to describe observational studies concerning the use of antibacterial prophylaxis to prevent UTIs in renal transplant recipient (RTRs).

Methods and Findings: Materials were gathered through a structured search of the databases available at the King Saud bin Abdulaziz University for Health Sciences on-line library for articles published between 2007 and 2013. However, due to the scarcity of prospective trials in this topic during this period, this review will be comprehensive rather than systematic. The increased recurrent UTIs in RTRs were associated with immunosuppressive therapy, which necessitates the use of antibacterial prophylaxis to reduce during the first year post-transplantation. However, the efficacy and optimal duration of antibacterial prophylaxis for UTIs remains debatable.

Conclusions: Although many studies have agreed on the importance of routine antibacterial therapy, UTI prevalence in RTRs is high. Reducing infection complications may be accomplished by properly choosing of immunosuppressants and antibacterials to achieve a correct balance. However, there was no sufficient evidence to confirm the potential efficacy of antibacterial prophylaxis, hence; more research is needed to further delineate the consequences of using antibacterials in RTRs.

Keywords: Nosocomial Infections; Urinary Tract Infections; Renal Transplant Recipients; Antibacterial Prophylaxis.
Introduction

Kidney transplantation is still the treatment of choice and a life-saving measure for patients with end-stage kidney disease where dialysis is not feasible. The risk of death for renal transplant recipients (RTRs) is less than half of that for dialysis patients [1]. The main challenge after successful organ transplantation is to avoid the immune reaction of recipient against the donor organ, which could lead to rejection and loss of the transplant. Immunosuppressive drugs are usually used to prevent rejection and to maintain organ function [2]. However, the immunosuppressive agents currently used to suppress immunological functions expose patients to a higher rate of infectious complications which occur as a result of patient exposure to nosocomial pathogens [3].

Nosocomial infections are considered common causes of morbidity and mortality among hospitalized patients [4]. Nosocomial infections are often infections of the urinary tract, the lower respiratory tract, and surgical wounds. According to the World Health Organization, a nosocomial infection or hospital-acquired Infections is defined as “an infection acquired in a hospital or other health care facility by a patient 48 hours after admission who was admitted for a reason other than that infection.” [5]. Recently the term “healthcare-associated infection” has been suggested to incorporate ‘nosocomia’ or ‘hospital-acquire’ infection [6]. These infections are usually occurred as a consequence of the surgical procedures or intervention used in diagnose or treatment of the patient’s complaints. However, they also include infections acquired in the hospital but appear after discharge, in addition to occupational infections among health care providers [7]. Nosocomial infections occur both in the developed and developing countries [8]. Nosocomial infections do not only affect the general health of patients, but also impose a significant burden to patients and public health. Nosocomial infections lead to increased length of stay and require additional medical interventions that results in additional costs [9]. Although many of those nosocomial infections are preventable, the incidence of nosocomial infections has remained almost stable during the last two decades in spite of the improved health system [10].

Urinary tract infections (UTIs) are the most common nosocomial infections, which account for more than 40% of all nosocomial infectious cases [11]. Moreover, recurrent UTIs are very common complication post renal transplantation [12]. Therefore, surveillance for UTIs in RTRs is regarded as an important factor for an effective infection control program. The aim of this review is to provide a broad contextual understanding of the association between antibacterial use and prevention of UTIs in RTRs. This review will also discuss the epidemiology, prophylaxis and the treatment strategies for UTIs in RTRs and to critically examine literature about the effectiveness of antibacterial prophylaxis for preventing UTIs in RTRs; in addition to providing relevant recommendations. This review is comprehensive rather than systematic, and is limited to literature available in databases at the on-line library of King Saud bin Abdulaziz University for Health Sciences (KSAU-HS).

Material and methods (literature search)

A structured search of these databases was utilized for search of relevant articles published between the years 2007 and Dec. 2013. Initially literature was located using combinations of subject headings including ‘nosocomial or hospital-acquired infections’, ‘urinary tract infections’, ‘antibiotic or antibacterial prophylaxis’, ‘Kidney or renal transplant’. Only articles published in English were included. In addition, a manual search of the reference lists of the identified articles and recent reviews was included to identify additional articles.
Unfortunately, no recent (2007-2013) prospective controlled randomized therapeutic studies were found in which antibacterial drugs were used for prophylaxis or treatment of UTIs in RTRs. A recent systematic review by Green et al. [12] about the use of antibacterial prophylaxis for UTIs in RTRs included all the randomized controlled studies of antibacterial prophylaxis given after renal transplantsations up to 2009. However, most included studies were outdated (1982-1997) and only one recent randomized controlled study by Khosroshahi et al. [13] was found and included in Green et al. review [12]. Therefore, due to the lack of prospective randomized controlled trials on the use of antibacterial prophylaxis for UTIs in RTRs after 2006, this review will include retrospective studies between 2007 and 2013 (see Table 1). One prospective randomized study has only been found [14], which investigated the efficacy of antibacterial prophylaxis to prevent UTIs at indwelling urinary catheter removal and was not specifically related to RTRs.

Additionally, data analysis was performed to estimate the variable determinant associated with increased risks of UTIs in RTRs. The impact of the female gender, immunosuppressive treatment and cytomegalovirus (CMV) infection as risk factors on UTIs was expressed as odd ratios of the pooled data from the corresponding studies with 95% confidence intervals computed with Fisher’s exact test using Graphpad Prism version 6 software packages. Odd ratio was interpreted as an approximation of the relative risk. All relevant determinants were grouped together by adding together the numbers of subjects. The use of pooled summary estimates has been declared to show more stability to risks of bias in random system generation, study features, and definitions of UTIs.

Table 1. Summary of retrospective studies addressing UTIs after renal transplantation included in this review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Median Age</th>
<th>Study period</th>
<th>Follow-up period</th>
<th>Post-operative prophylaxis</th>
<th>Incidence of UTIs</th>
<th>Frequency of recurrent UTIs</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>[15]</td>
<td>27 recipients (48% females)</td>
<td>41.3 ± 16.2 yr</td>
<td>NA</td>
<td>NA</td>
<td>Norfloxacin</td>
<td>55.5%</td>
<td>40.1%</td>
<td>Female gender, Advanced age</td>
</tr>
<tr>
<td>[16]</td>
<td>99 recipients (70% females)</td>
<td>53.3 ± 11.1 yr</td>
<td>2002 to 2012</td>
<td>53.5 months (average)</td>
<td>Cotrimoxazole</td>
<td>NA</td>
<td>36%</td>
<td>The immune-suppressant tacrolimus</td>
</tr>
<tr>
<td>[17]</td>
<td>154 recipients (53% females)</td>
<td>52 ± 15 yr</td>
<td>2010 to 2011</td>
<td>24 months</td>
<td>NA</td>
<td>48.2%</td>
<td></td>
<td>multidrug-resistant bacteria</td>
</tr>
<tr>
<td>[18]</td>
<td>77 recipients (41% females)</td>
<td>53.4 ± 11.2 yr</td>
<td>2008 to 2011</td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>Non-infected donor</td>
<td></td>
</tr>
<tr>
<td>[19]</td>
<td>344 recipients (72% females)</td>
<td>41.1 ± 1.2 yr</td>
<td>2000 to 2010</td>
<td>36 months</td>
<td>Cotrimoxazole, 3rd cephalosporin Ciprofloxacin</td>
<td>54.0%</td>
<td>46.0%</td>
<td>Renal calculi</td>
</tr>
<tr>
<td>[20]</td>
<td>393 recipients (31% females)</td>
<td>32.8 ± 9.5 yr</td>
<td>1986 to 2009</td>
<td>92 months</td>
<td>NA</td>
<td>53.69%</td>
<td>NA</td>
<td>Female gender</td>
</tr>
</tbody>
</table>
Descriptive Epidemiology of UTIs in RTRs

UTIs are the most frequent nosocomial infections in RTRs. It has been estimated that UTIs occur with frequencies ranging from slightly less than 10% to more than 90% among RTRs during the first year post-transplantation [8, 15, 28-30]. This highly variable incidence rate of post renal transplantation UTIs was attributed mainly to variations in the study design, infection outburst and investigation criteria. Whilst, UTIs are associated with less morbidity than other nosocomial infections, many reviews have reported that nosocomial UTIs in RTRs are associated with significant morbidity and mortality [31, 32]. Nosocomial UTIs are so troublesome in RTRs since their health is already compromised by the condition for which they were originally hospitalized. Nosocomial infections can occasionally lead to septicaemia and death. The most common cause of septicaemia in RTRs is UTIs which are usually related to the early rejection problems [3].

UTIs are generally defined by means of microbiological measures as a positive quantitative urine culture of ≥ 100,000 colony-forming units per milliliter (c.f.u/ml) of clean voided mid-stream urine specimen. While this definition is general, the diagnosis of UTIs in female is defined as microorganisms (bacteria) count ≥ 10,000 c.f.u/ml urine, in addition to a microscopical inspection of the urine to dismiss vaginal contamination, which may result in false-positive cultures [33]. Some studies have suggested that low bacterial counts between 100 and 10,000 c.f.u/ml in majority of patients might be an early phase of UTIs [34]. UTIs are characterized by a wide range of clinical symptoms ranging from asymptomatic bacteriuria to mild irritative voiding to severe septic shock [35]. UTIs after renal transplan-
tation exist commonly as asymptomatic bacteriuria [21, 36]. The term UTIs applies to a heterogeneous group of clinical syndromes including the infections of the lower urinary tract involves the bladder (cystitis), the urethra (urethritis), and prostate gland (prostatitis) and infections of the upper urinary tract involving the kidneys (pyelonephritis). Cystitis is the most common type of UTI and occurs most frequently in women.

**Timing of UTI after renal transplantation**

Most studies have reported that the highest incidence of UTIs in RTRs occur during the first 3 to 6 months after renal transplantation [27, 37-39]. Interestingly, it has been reported that the risk of UTIs was comparable in both men and women during the first 6 months post-transplantation, but significantly higher for female recipients than males after 6 months post transplantation period [31].

However, Di Cocco et al. [24] have reported that UTIs most frequently occurred within the first month after renal transplantation. A consistent result has been reached in a surveillance by Parapiboon et al. [30] for bacteriuria by urine culture in RTRs, who reported that most of bacteriuria, whether it is symptomatic on not, occur at 1 month post transplantation period. A similar conclusion was reached by a recent study by Alkatheri [15], who has confirmed that most of the UTIs were detected within the first month post transplantation.

Although many RTRs have asymptomatic bacteriuria during the first year post transplantation, there is still no solid evidences for the benefit of long term antibacterial treatment [36, 40]. According to the Infectious Diseases Society of America Guidelines; there is no recommendations available for monitoring or treating of asymptomatic infections in organ recipients [41]. Moreover, the common screening of bacteriuria for asymptomatic RTRs, which is regularly done by transplant centers to determine the efficacy of antibacterial prophylaxis did not demonstrate benefits in reducing the incidence of UTIs [42]. Therefore, an efficient antibacterial prophylaxis against UTIs should be continued for at least one month and not exceeding three months after renal transplantation, since most studies did not reveal significant advantage of long-term antibacterial prophylaxis after renal transplantation.

**Recurrent of UTI after renal transplantation**

Recurrent UTIs was usually defined as at least two symptomatic UTIs with more than 2 weeks apart between each episode in the interval of 12 months [16]. Many reports have stated that the highest incidence of recurrent UTIs was apparent during the first six months after renal transplantation, despite antibacterial prophylaxis treatment [12, 16, 17, 40]. This usually coincides with the greatest immune depressing effects of the immunosuppressive regimens [29]. This is also probably due to recurrent bacteremia caused by a mixed population of Gram-negative microorganisms namely, *Escherichia coli* and *Enterobacteriaceae* bacteria, which can develop resistance to the antibacterial therapy during that time [43]. This might increase the burden on the health team in the determining of the best antibacterial therapy in such immunocompromised hosts.

Consequently, early recognition of UTIs in symptomatic patients during the first 3 to 6 months after renal transplantation to initiate antibacterial therapy could be a better option than long-term antibacterial prophylaxis for asymptomatic bacteriuria that increases the risk of developing bacterial resistance.

**Cadaveric vs. Living Kidney Transplantation**

Most of the reviewed studies have implied that recipients of cadaveric kidneys may be at higher risk of post-transplant UTIs than the recipients of grafts.
from living donors [7, 30, 32, 44-46]. However, none of these studies have given a rational explanation for this risk except for the fact that kidneys from cadaveric donors may be more susceptible to UTIs due to the prolonged ischemia time leading to major harm of the kidney [32]. This might result in reduced/delayed graft function and/or survival as indicate in a recent review by van der Vliet and Warlé [47] rather than increasing the likelihood of UTIs. Nevertheless, Outerelo et al. [18] has reported a controversial results in which renal transplantation using organs from infected donors was not associated with a greater risk of UTIs. Outerelo et al. (2013) has justified these eccentric results owing to the antibacterial therapy initiated in the donor, which perhaps reducing infectious complications in the recipient. However, almost all the studies have agreed on the importance of other risk factors, such as gender, bladder catheter and the impaired immune responses due to immunosuppressive drugs.

**Caustic Microorganisms of UTIs**

It had been recognized that the most predominant caustic agents of UTIs in RTRs are similar to the general population (see Figure 1). *Escherichia coli* (*E. coli*) is being usually emerged from the individual’s own fecal flora either normal or acquired in hospital [32, 42, 48]. Other bacterial pathogens include *Enterococcus, Staphylococcus, Klebsiella, and Pseudomonas* species [28, 42, 49, 50]. Interestingly, unlike most reports, a recent report by Golebiewska et al. [21] has implied that most of UTIs diagnosed before patient discharge or during the first month

**Figure 1.** Proportion of Causative microorganisms of urinary tract infections identified in urine of RTRs. Data taken from [16], [29], [20], [67], [89], [26], [90], [91] and [31].
post-transplantation were due to bacteria other than *E. coli* such as *Enterococcus faecium* and *Serratia marcescens*. Whereas, *E. coli* is the most common bacterium responsible for UTIs after patients being discharged [21]. Although many reports have shown that *E. coli* is the most common isolate in the urine of RTRs, followed by many organisms such as *Enterococcus, Staphylococcus, Klebsiella* and others, no study has identified the difference in causific agents of UTI between recipients of cadaveric kidneys and living kidneys recipients or between genders.

**Antibacterial Prophylaxis**

According to the Centers for Disease Control and Prevention (CDC), 40% of nosocomial infections are preventable through strict adherence of health care workers to the infection control guidelines when caring for patients [6]. Recurrent or relapsing UTIs are common in the early post-transplant period in RTRs [40]. Additionally, the use of intensified immunosuppressive therapy, postoperatively, in organ transplant recipients to treat or prevent acute rejection of the donor organ also renders patients vulnerable to infections. Therefore, in light of the increased incidence of infections in RTRs [21], it is essential to use of antibacterial drugs to prevent frequent hospitalizations as a result of infectious complications. In an earlier retrospective study which including all the adult RTRs at two US transplant centers, it was found that UTIs are associated with an increased risk of mortality and preventing these infections is necessary to decrease post-transplant mortality [32].

Many studies have reported that most RTRs received postoperative antibacterial prophylaxis for a period ranging from 3 to 6 month have significantly reduced the incidence of UTI after renal transplantation [51-54]. Nevertheless, it is has been reported that even late UTIs occurring 6 months after renal transplantation can produce serious risks, such as bacterial septicemia [31]. This might necessitates the use of an efficient antibacterial prophylaxis for 12-month period. Since, UTIs are most likely caused by Gram-negative bacteria, (see Figure 1), empiric antibacterial drugs selected to all RTRs should cover Gram-negative bacteria. Additional consideration of Gram-positive management should be handled in the first year post-transplantation [6]. However, several important differences should also be considered, such as the immunocompromise status of RTRs and the heterogeneity of pathogens responsible for UTIs in those vulnerable patients.

Cotrimoxazole has been routinely used as the first-line prophylaxis in immunocompromized renal transplant recipient. A study by Khosroshahi et al. [13] which investigated the efficacy of cotrimoxazole for prophylaxis of early UTIs in RTRs found that high-dose of cotrimoxazole (1600/320mg) is required for RTRs to reduce the UTI occurrence during the first month post-transplantation. Other antibiotics have been also used such as amoxicillin-clavulanate or ciprofloxacin [21].

On the other hand, it has been suggested that the use of cephalosporins such as cefoxitin or cefazolin [55] or cotrimoxazole [24] for surgical perioperative antibacterial prophylaxis is effective in reducing the frequency of UTIs. A recent study by Salehipour et al. [38] has suggested that a perioperative intravesicular application of antibiotic (e.g., amikacin) solution into the patient bladder with a mean of a catheter could also provide an efficient prophylaxis against UTIs for at least 3 months after renal transplantation. However, it has been suggested that the increased emergence of resistant bacteria isolates in RTRs was due to the use of perioperative prophylaxis regimen [56].

Interestingly, a recent study has reported that Uromune®, a novel sublingual bacterial vaccine, used to prevent recurrent UTIs showed a significant superior effect compared to cotrimoxazole [57]. Uromune®

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contains inactivated bacteria of selected bacterial strains, such as *E. coli*, *K. pneumonia*, *P. vulgaris*, and *E. faecalis*. The significant reduction in UTIs of this vaccine was observed up to 15 months.

Although bacterial infections account for the majority of cases of UTIs in RTRs, fungal UTI also have been reported in these patients [58]. Fungal UTIs represents a high-risk event posing a difficult therapeutic problem. Invasive fungal infections, although rare, were associated with greatly increased mortality [28]. The most common antifungal agents currently used to treat fungal UTIs are the azole derivatives; such as fluconazole and ketoconazole. These agents have always been considered safe and effective antifungal agents for the treatment of fungal infections such as candidiasis [58]. However, due to common fungal resistance to azoles, other antifungal agents have been used such as amphotericin B [59], and caspofungin [60]. Although caspofungin is well-tolerated and highly effective alternative for the treatment of azole-resistant fungal infections in RTRs, caspofungin is not use as first-line treatment for fungal infections due to its high cost [60].

In contrast, other studies have reported that there is a lack of reliable evidence that the widespread antibacterial prophylaxis can reduce the risk of UTI recurrence [46, 61-64]. A recent systematic review about the use of antibacterial prophylaxis for UTIs in RTRs suggested that there is not any advantage for such prophylactic treatment during the first months after renal transplantation, other than preventing severe bacteremic sepsis [12]. A similar conclusion was reached in a recent Cochrane review, which stated that long-term antibacterial prophylaxis is not justified, since most UTIs, especially in children, are asymptomatic and do not affect the general health of the patient [65]. Moreover, it has been proposed that no further antibacterial is required in case of asymptomatic UTIs, since no benefit for the antibacterial treatment had been observed for preventing future UTIs or preserving graft function [36]. The guidelines published in 2007 by the National Institute for Health and Clinical Excellence in England and Wales have also stated that “antibacterial prophylaxis should not be routinely recommended in infants and children following first-time UTI.” [66]. This was mainly attributed to the drawbacks of antibacterial prophylaxis such as increasing risk of resistant infections [67].

**Antibacterial Resistance**

It had been well recognized that the haphazard use of antibacterial prophylaxis could result in the appearance of resistant microbial strains thus leads to treatment failure and recurrent infections [65]. It has been also reported that, the prevalence of antibacterial resistance among UTIs pathogenic bacteria is increasing due to long-term use of these agents [68]. In a retrospective study by Waller and Beattie [62], it has been concluded that the daily antibacterial use to prevent recurrent UTIs was associated with an increased risk of resistant infections. A similar conclusion was reached by Kawecki et al. [56] and Silva et al. [17], who reported that recurrent UTIs in RTRs attributed to the increased proportion of isolates of multidrug-resistant bacteria was probably due to frequent use of postoperative antibacterial prophylaxis. Moreover, the increased bacterial resistance can be also attributed to the impaired immunity of RTRs resulting from the use of immunosuppressants [16].

Being the most predominant pathogen of UTIs, *E. coli* was frequently studied by many researchers (see Figure 2). It has been found that *E. coli* isolate showed considerable varying resistance patterns among regions and countries [50]. Senger et al. [26] had managed to recover resistant *E. coli* isolates in 76% of patients on cotrimoxazole prophylaxis. However, *E. coli* strains did not show a significant resistance against ciprofloxacin. On the other hand,
nitrofurantoin has been suggested to be considered as an empirical therapy of lower tract UTI, since the incidence of nitrofurantoin resistance was not statistically significant [69]. Interestingly, it has been reported that there was no significant difference in antibacterial resistance in \textit{E. coli} isolates from either symptomatic or asymptomatic UTIs patients [69].

**Clinical Risk Factors**

There is always a high risk for nosocomial infections among all hospitalized patients. However, certain patients are at greater risk than others, particularly young children, elderly and immunocompromised patients. The risk of acquiring infections in RTRs depends on many factors including epidemiologic factors, surgical consequences and the recipient’s immunosuppression state [29].

Most postoperative UTIs are related to the use of an indwelling urinary catheters, which can expose a hospitalized patient to the possibility of infection [70]. A strong association was suggested between postoperative duration of an indwelling urinary catheterization and UTIs, which has been considered as the most important risk factor for the development of UTIs [71]. The catheter-associated UTIs were accounted for more than 80% of the most common nosocomial UTIs [10]. In a retrospective cohort study in US hospitals, Wald et al. [72] has reported that a postoperative duration of an indwelling urinary...
catheterization of more than two days was associated with an increased likelihood of nosocomial UTIs. However, in RTRs or in patients underwent urologic surgery, urinary catheter might be needed for extended periods. Therefore, catheter-associated UTIs could be prohibited by the appropriate use of infection prevention policies according to the guideline issued in 2009 by the CDC for prevention of catheter-associated UTIs [73]. Other possible risk factors of UTIs, which impose some therapeutic difficulty in RTRs, were also identified. Prior antibiotic therapy [59], urinary tract abnormalities [22], diabetes mellitus [48], female gender [74] and advanced age [15]. However, a recent study by Lim et al. [19] has not established female gender as an important risk factor for recurrent UTIs in RTRs, in spite of the fact that females showed a high incidences in both nonrecurrent (70.4%) and recurrent (73.9%) UTIs. Unlike Lim et al. [19], most studies have agreed on the finding that female gender was the only consistent independent risk factor of UTIs after renal transplantation. The high risk of UTIs in female patients is most probably due to distinct anatomical difference of female genitals. The estimated odd ratio of the pooled data from some studies was consistent with studies which reported the female gender as an independent risk factor of UTI in RTRs (Figure 3).

**Immunosuppressive therapy**

The use of immunosuppressive therapy in the post-operative period in organ transplant recipients is always necessary to avoid rejection of the donor organ [75]. However, suppressing the immune system functions render patients susceptible for higher rate of infectious complications [76]. In a recent retrospective observational study which involved 245 RTRs, the infections highest incidence was noticeable by the sixth month after renal transplantation, which coincided with the most immune suppressive effect of the treatment regimen used [29].

Patients typically receive a three-drug immunosuppression regimen, which frequently include a combination of a calcineurin inhibitor, a corticosteroid and an antiproliferative agent (e.g., azathioprine) [75].
Traditionally, corticosteroids were used as the main regimens in RTRs because of their value in reducing rejection and enhancing organ survival [77]. However, it has been recognized that the prolong corticosteroids therapy was associated with increased patient morbidity and mortality [78]. Numerous adverse effects of steroid treatment are widely recognized including an increased vulnerability to infection; glucose intolerance; hyperlipidemia; osteoporosis; cataracts; myopathy; sodium retention; weight gain, and impaired growth [79].

Although the use of corticosteroids has been a mainstay for the management of acute organ rejection, there had been a rational tendency to employ steroid-sparing immunosuppression protocols to minimize adverse effects [78]. Since the introduction of immunosuppressive therapy in the early 1980s, a new approach has been established that allowed either early withdrawal of steroids or sparing steroids altogether. Some studies have demonstrated that newer steroid-free immunosuppression regimes were associated with lower incidence of infection.

**Figure 4.** Summary of A) CsA, B) MMF (p=0.0222), C) TAC, and D) ATG Induction therapy (p=0.0365) risk factor of UTIs in RTRs, expressed as odd ratio with 95% confidence intervals were computed with Fisher’s exact test using Graphpad Prism version 6 software package. Where, CsA: Cyclosporine A; MMF: Mycophenolate mofetil; TAC: Tacrolimus; ATG, antithymocyte globulin.
infectious complications and equivalent organ survival rates [80]. However, removal of corticosteroids has not been always free of acute rejection risk. Some studies have indicated that steroid-free protocols were associated with a significant increase in the rate of the incidence of acute rejection episodes [2, 81]. Thus, the main challenge nowadays is to identify the renal transplant candidates who may benefit from steroid-free regimens without increasing the risk of acute rejection. Peculiarity, a study by Alangaden et al. [28] has reported that the use of newer immunosuppressive agents was associated with a number of changes in the epidemiology of infections in transplant recipients. Enterococci have become the predominant pathogen responsible for UTIs. Therefore, further studies are required to establish the impact of steroid avoidance in these protocols before drawing a firm conclusion.

Although many published studies have reported that immunosuppressive drugs, including cyclosporin A, azathioprine, mycophenolate mofetil, tacrolimus, and induction regimens (antithymocyte globulin), do not show any significant risk factor for UTIs in RTRs. The estimated odd ratio of the pooled data (Figure 4) shows an ambiguous significant value in both mycophenolate mofetil (p=0.0222) and antithymocyte globulin (p=0.0365).

On the other hand, Golebiewska et al. [21] has indicated that the increased proliferation of cytomegalovirus (CMV) in UTIs patients was due to the reactivation of latent CMV by proinflammatory cytokines. Moreover, many reports have demonstrated that CMV increases the net immunosuppression status after organ transplantation by undermining the immune responses, which predispose the patient to different infections [21, 82]. However, only few studies have reported a significant effect of CMV on UTIs in RTRs. The estimated odd ratio of the pooled data again shows a significant value due to CMV infection (see Figure 5).
Other Risk Factors

Additional risk factors were also recognized in hospitalized patients that increase the opportunity of acquiring infections. For example, prolonged hospital stay, underlying disease severity, nutritional deficiencies, and failure of health care workers to follow good hygiene practices [83]. Nevertheless, some factors which are critically important in RTRs such as bladder dysfunction or residual urine were not considered as predisposing factors of recurrent UTIs [25]. However, recent reports have found that vesicoureteric reflux (VUR), presence of ureteric stents and urological malformations are represented as risk factors of recurrent UTIs in RTRs throughout the post-transplantation period [4, 84].

On the other hand, it has been reported that organ transplant recipients are at a high risk of hyperuricemia [85]. Hyperuricaemia has been suggested to be an early sign of acute cellular rejection in RTRs [86] or it could be attributed to the use of immunosuppressant cyclosporine and/or to the impairment of renal functions. Hyperuricaemia is a challenging clinical problem that adversely affects organ transplant patients’ quality of life, which underlines the importance of prompt treatment of hyperuricemia [85]. However, treatment of hyperuricemia and/or gout in RTRs has always been difficult due to the risk of adverse effects and possible drug interactions with the immunosuppressive regimen [87]. Allopurinol has a serious interaction with azathioprine, but not with mycophenylate mofetil, which might result in bone marrow suppression. Moreover, uricosuric medications, such as probenecid, are ineffective in patients with kidney malady [85]. However, the rate of having hyperuricemia and gout was significantly lower in patients receiving tacrolimus [88]. Therefore the improper choice of immunosuppressants could make organ transplant recipients vulnerable to develop gout, which imposes additional risk in RTRs.

Discussion and recommendations

Although renal transplantation had saved many patients lives with end-stage renal disease, post-transplantation infections are considered common causes of morbidity and mortality among RTRs. It is alarming that infections have been considered the second cause of fatality in RTRs after cardiovascular complications [89]. In spite of the fact that UTIs are the most common infections in RTRs, there are limited treatment guidelines on antibacterial prophylaxis for UTIs in this population. This may be due to the shortage of published data that examine antibacterial susceptibility in renal pathogens among RTRs.

However, in the face of lack of strong evidence to support the use of antibacterial prophylaxis to prevent recurrence of UTI, it continues to be a very common medical practice nowadays [6]. Although mortality rate after renal transplantation has been fairly diminished to less than 5% [29], infection-related complications still pose a serious challenge that attenuate organ survival opportunity. The use of antibacterial prophylaxis is still considered indispensable in order to achieve successful outcomes following renal transplantation and overcome infection impediments.

The following critically important issues, in the authors’ opinion, should be of concern by health practitioners for the well-being of RTRs to avoid the avertable lethal consequences and to minimize risk factors for UTIs:

- Investigating regularly the UTIs caustic pathogens, antibacterial susceptibility and the local pattern of resistance to optimize the initial empiric antibacterial selection and update the treatment protocols.
• Choosing narrow spectrum antibacterial according to antibacterial sensitivities, to minimize the opportunity of invasive fungal or parasitic infections.

• Selecting the correct balanced therapy of the immunosuppressant agents and the use of antimicrobial prophylactic regimens that will significantly reduce the incidence of early opportunistic infections.

• Avoiding unnecessary prolonged urethral catheterization in RTRs since it has been found that long catheterization was frequently associated with high rate of UTIs which could increase mortality or at least delay discharges to home.

• Recognizing promptly the occurrence of serious infections that require meticulous management of immunosuppressive therapy

• Encouraging living kidney donations, since most investigators have reported that UTIs risk was considerably higher in RTR of grafts from deceased donors. However, this requires a thorough medical examination of living-related donors to reduce the incidence of UTIs in recipients of kidneys from these donors.

• Development of potent therapeutic strategies, in light of the decreased efficacy of existing antibacterial regimes, for better management of infections.

• Commitment regimens to the use of hand sanitizers as lack of general hygiene is considered a serious threat of nosocomial infections.

• Health care practitioners should be alert for different risk factors that participate in the occurrence of UTIs which can undermine the function and survival of transplanted organ in critically ill patients.

• Finally, it is essential to conduct larger prospective studies involving multiple centers to evaluate the microbiology and treatment of post-transplantation infections hopefully to develop guidelines for monitoring and preventing organ transplant associated infections.

Conclusions

In summary, the high infection rate associated with the use of immunosuppressive agents currently used necessitates the use of antibacterial prophylaxis. The UTI-related mortality and morbidity in the first year post-transplantation can be substantially reduced by elegant integration of antibacterial prophylactic regimens in the therapy practice early after renal transplantations. However, the optimal antibacterial therapy duration to prevent recurrent UTIs in RTRs remains uncertain.

However, despite routine antibacterial therapy, recurrent UTIs remain common; besides, there was not enough evidence to support the beneficial effect of prophylactic antibacterial drugs other than reducing the risk of bacterial sepsis. Therefore, it is essential to establish a long-term prospective observational study with a sample sufficient to determine evidence to support the potential benefits and risks associated with the long-term antibacterial prophylaxis in RTRs. Such study is indispensable to determine the optimal duration of antibacterial therapy for recurrent UTIs in RTRs.
References


