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UTI in renal transplant patients

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Abstract

Urinary tract infection (UTI) is the most common infectious complication following kidney transplantation. The incidence in adults is about 20% in the first six months and 50% in the first three years, despite the common use of antibiotic prophylaxis. Risk factors include more intensive immunosuppression (especially the use of depleting induction antibodies and sirolimus), extremes of age, diabetes, prolonged time on dialysis, abnormal or reconstructed lower urinary tract and prolonged use of urinary catheters and stents. Diagnosis may be complicated by other conditions causing urinary symptoms and fever in transplant recipients, as well as immunosuppression masking the typical presentation and lack of symptoms in a denervated kidney. Infection may involve the graft or native kidneys. Typical uropathogens are commonly involved but UTI's may also be caused by commensal and fastidious bacteria, fungus, mycobacteria and viruses. Some studies suggest post transplant UTI has a negative impact on graft survival and function, although causality has not been established. There is a paucity of prospective controlled data that can guide UTI prophylaxis or therapy in terms of agent or duration although most programs will routinely use prophylaxis for at least six months.

Summary of recommendations

1. Antimicrobial prophylaxis following renal transplantation reduces bacteriuria (GoR A) and incidence of early urinary tract infection (GoR B)
2. While there are kidney and recipient factors that increase the risk of UTI post-transplant, the value of more intensive or greater duration prophylaxis is unproven (GoR C)
3. Post-transplant UTI risk can be reduced by early removal of urinary foreign bodies (foley catheters, stents, percutaneous nephrostomies) (GoR B)
4. Asymptomatic bacteriuria post-kidney transplant does not require therapy beyond standard prophylaxis (GoR C)
5. Therapy of post-transplant UTI should be guided by culture, sensitivities and antibiotic characteristics, favoring bacteriocidal antibiotics rather than bacteriostatic antibiotics with poor tissue penetration (GoR C)

Introduction

Urinary tract infection (UTI) is the commonest infectious complication following renal transplantation. It is a potential source of severe systemic illness but its contribution to permanent graft dysfunction remains controversial.

This chapter is an update of the previous 2010 edition, discussing the definitions, epidemiology, microbiology, risk factors, therapy and impact of post-transplant UTI. Recommendations are made based on the previous chapter and evidence derived from studies which have been published since then.

Methods

The consensus was reached after a systematic Pubmed review of reports published in the last 20 years using the following keywords: kidney or renal, transplantation, complications (urinary tract infection or bacteriuria). This search yielded 1,429 studies of which 155 were review articles. The studies were rated according to the level of evidence (LoE) and the grade of recommendation (Gor) using ICUD standards.

Results

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1 Definitions in post-transplant UTI

The definition of post-transplant UTI in literature can vary significantly. Asymptomatic bacteriuria (ASB), which is the presence of bacteria in the urine without the presence of clinical symptoms (dysuria, urinary frequency, hematuria, graft tenderness etc.), is often considered a UTI. A UTI requires pathological invasion of the urothelium with microorganisms resulting in tissue injury and an inflammatory response. This inflammatory response, which may be local and/or systemic, produces the clinical syndrome of infection. One should keep in mind that the common signs and symptoms of UTI may be absent in the immunosuppressed transplant recipient or may be mimicked by normal post-transplant conditions (e.g. hematuria from the ureteral stent, polyuria due to early loss of urinary concentrating ability and urinary frequency from a small defunctionalized bladder). All UTIs in renal allograft recipients are considered complicated UTIs because of the immunocompromised status of the patient and the altered anatomy of the urogenital tract. It is therefore important to distinguish the definitions used when reviewing transplant literature. Also, UTI can be further subdivided into cystitis, graft pyelonephritis and urosepsis.

Most laboratories will report a positive urine culture with isolation of a single bacterial strain in quantitative counts $\geq 10^5$ cfu/ml of fresh unspun midstream urine. This definition is based on studies in the 1970s of college age females which tried to find an appropriate cutoff to diagnose pyelonephritis in the absence of lower urinary tract symptoms. In a symptomatic patient however, 10^2 cfu/ml is a sufficient threshold. Furthermore, in transplant patients, the diagnosis of UTI may be equivocal and ideally the lab should be asked to provide a numerical bacterial count and not merely report "no significant bacterial growth". Conversely, in a patient with a Foley catheter, urine may have counts over 10^{10} and not be infected [1].

Finally, the classification and definitions of repeat UTI give important etiologic information in transplant recipients. They may be unresolved (remain active despite therapy), persistent (resolve with therapy but recur soon after with the same bacteria) or recurrent (resolve with therapy but recurs later with a different bacteria). Unresolved UTI usually indicates wrong antibiotic therapy or multiple organisms. In transplant patients, bacteriostatic antibiotics may be insufficient as the immune system cannot eradicate the dormant bacteria. Recurrent UTIs often point to bacterial reintroduction, commonly following intercourse in women; however, in transplant patients it may point to over-immunosuppression. Persistent infections are usually clues to an unresolved bacterial nidus, and should prompt a search for foreign bodies, inefficient bladder emptying or a source from the native kidneys (e.g. reflux, stones).

2 Epidemiology

UTIs are the most common infectious complication (45%) following kidney transplantation [2]. While seldom causing mortality, UTIs can still cause significant morbidity and possibly impact graft survival. Publications addressing its incidence are limited by being single center with small numbers, heterogeneity in UTI definitions/diagnosis, follow up and inpatient vs outpatient records (LoE 3).

Up to 71% of bacteriuria occurring within 1 month of transplantation is ASB [3]. Another study reported that half of renal transplant recipients developed at least one episode of ASB within 36 months of their transplant [4].

In a large retrospective database study of almost 29,000 patients (USRDS with Medicare billing codes from 1996 to 2000), the cumulative incidence of UTI during the first 6 months after renal transplantation was 17% (equivalent for men and women). At three years, the UTI incidence was 60% for women and 47% for men [5].

Another study analyzed UTIs as cystitis and pyelonephritis and reported the incidence of UTI as 0.45 episodes/1000 transplantation days [6]. In this cohort, 7.3% of renal transplant recipients developed a UTI, of which 82% had cystitis and 18% had pyelonephritis. In a 12-year study looking at gram negative bacteremia in renal transplant recipients, 75% of the 6.6% who developed bacteremia had UTI as the primary source of infection [7].

3 Etiology and risk factors

The etiology of UTI following renal transplantation is usually multifactorial. The risk factors include patient factors and transplant related factors i.e. donor factors, immunosuppression and the presence of foreign bodies.

3.1 Patient factors

Age correlates with post-transplant UTI in a bimodal distribution, with the highest incidences in the pediatric and elderly population. In the previously mentioned USRDS review, age was found to be independently associated with late UTIs (>6 months following renal transplantation) in men >55 years when compared with those <55 years [5]. Similarly, Chuang et al. reported that 55% of patients >65 years vs 38% of patients <30 years at transplantation developed post-transplant UTIs [9]. Older patients may be at higher risk due to inefficient voiding as a result of poor bladder contractility (e.g. diabetic cystopathy) or outflow obstruction (e.g. prostatic hyperplasia).

At the other end of the spectrum, pediatric renal allograft recipients represent a special population with respect to post transplant UTI. In this group, the higher incidence of UTI is often related to the etiology of ESRD. Urinary tract malformations and lower urinary tract dysfunction are present in up to 25% of children with renal failure. John et al., in their retrospective review of three centers found a UTI rate of 36% (median time one year) and 28% of patients had recurrent UTI [10]. Bacteriuria was also more common in patients transplanted into a reconstructed lower urinary tract than in recipients with normal bladders (83% vs 17%) [11].

Female gender is a UTI risk factor in adult transplant recipients [6]. 68% of female recipients vs 30% of male recipients had at least one UTI post-transplant and 71% of patients with recurrent UTI were females in Chuang's study [9]. In the pediatric group however, boys had more frequent post-transplant UTIs, again likely related to the etiology of ESRD [5].

Comorbid conditions such as diabetes mellitus (DM) may impact the frequency of infections post-transplant. DM recipients had a higher readmission rate due to infections (45% vs 2%) and an increased risk of fungal UTI [12], [13].

Prolonged ESRD with dialysis pre-transplant has also been correlated with higher risk of UTI in renal transplant recipients [5]. This may be related to a higher incidence of complicated UTI in recipients with prolonged anuria prior to transplant [14].

The presence of ASB has also been described as a risk factor for UTI. Other risk factors described include recurrent UTIs prior to transplantation and glomerulonephritis as the primary renal disease [3], [4].

3.2 Transplant related factors

3.2.1 Donor type

Several studies have suggested that the incidence of UTI is higher following cadaveric transplant [2]. This is unlikely due to donor contamination or ischemia but rather due to shorter waiting times for living donors and less intensive immunosuppression. One study showed an increased risk for UTI in expanded criteria donors, despite normal preimplantation biopsy findings and comparable outcomes to standard deceased donors [15]. Other studies have shown dual kidney transplants and delayed graft function to be risk factors for UTI, and these may be another reflection of expanded criteria donors [4], [6].

3.2.2 Immunosuppression

It is axiomatic that more intensive immunosuppression increases the risk of infection. Unfortunately, since there are no reliable tests of degree of immune compromise, clinical management of based upon drug levels and weight-based dosages will often lead to over- and under-treatment, which would not be evident until acute rejection or infection develops. One study which looked at infectious complications based on drug selection found more bacterial infections in patients receiving anti-thymocyte globulin (vs basiliximab) and sirolimus (vs tacrolimus) [16].

Acute rejection episodes have also been shown to be a risk factor for post-transplant UTI in a few studies [17], [18]. This may reflect the effect of increased immunosuppression used to treat the rejection episodes, or conversely, a reduction of immunosuppression in patients with recurrent UTI leading to subsequent acute rejection. A temporal analysis is required to establish the cause/consequence of UTI and rejection.

3.2.3 Foreign bodies

All patients following transplant require bladder drainage, both to closely monitor urine output and to allow the ureteroneocystostomy to heal; however, bacterial colonization and biofilm formation are inevitable over time. For patients with otherwise normal bladders and uneventful ureteral reimplant, Foley removal as early as post-operative day 2 appears safe and reduces early UTI rates [19]. Prolonged catheter use has also been linked to increased risk for bacteremia [20]. For patients whose bladders do not empty, clean intermittent catheterization is preferable to prolonged Foley drainage [21]. The microbiological implications of suprapubic catheters in transplant patients have not been studied.

Ureteral stents are often placed at the time of transplant, either routinely or in patients considered at higher risk for urologic complications. Meta-analysis of published trials confirm that stents reduce the incidence of ureteral complications but increases the risk for UTI. This is especially so with longer stents (≥20 cm) and when left in longer than six weeks [22]. Studies support the removal of stents within two to four weeks to minimize UTI risk while not compromising anastomotic healing [23], [24].

Prolonged use of percutaneous nephrostomy tubes for management of urologic complications after kidney transplant is associated with multi-drug resistant bacteria and fungal infection [25].

4 Microbiology

Bacterial UTI pathogens in renal transplant recipients are similar to that in the general population. Gram negative bacterial infections (*Escherichia coli, Enterobacter, Pseudomonas* and *Klebsiella*) are the most common followed by Gram positive organisms (*Enterococcus, staphylococcus* and *streptococcus*) and fungi [26]. Due to the routine use of antibiotics and exposure to hospital-acquired organisms, infecting strains are increasingly resistant to commonly used first line antibiotics [27].

Fungal infections are more common in immunosuppressed patients, especially those with diabetes and urinary foreign bodies [28]. Locally, fungal balls lead to ureteral obstruction [29] and systemic spread is associated with high mortality rates [16].

The BK polyoma virus was first described in 1971 after a renal transplant recipient presented with ureteral stenosis (BK was the initials of the patient) [30]. A quarter of a century later, it is increasingly recognized as a cause for graft nephropathy and subsequent graft loss, besides causing ureteral injury and strictures. BK virus exists latently in within the renal epithelial and urothelial cells in the immunocompetent host. Urinary 'decoy cells', although highly specific, lack sensitivity in diagnosing BK virus nephropathy and transplant biopsy remains the gold standard for diagnosis [31]. It may cause hemorrhagic cystitis, although this is more commonly seen in bone marrow transplant recipients. Specifically to renal transplant recipients, BK virus leads to ureteral fibrosis and ischemia with subsequent stricture formation [32].

The parasite *Schistosoma haematobium* is endemic in certain African countries. Bacterial UTI, renal stones and ureteric complications were found to be greater among kidney transplant recipients with schistosomiasis than among controls. However this did not impact patients or graft outcomes [33]. *Mycobacterium tuberculosis* can be contracted by or reactivated in immunosuppressed patients leading to UTI, epididymitis or prostatic abscess [34].

5 Presentation and evaluation

Symptomatic UTI post-renal transplant has a wide clinical spectrum including acute cystitis, transplant/native kidney pyelonephritis and bacteremia. As mentioned previously, typical signs and symptoms of UTI may be mimicked by other common post-transplant conditions. Furthermore, common UTI features may not be evident. Immunosuppression can suppress fever, primarily through blockade of IL-1 and tumor necrosis factor. Blood WBC counts may not be elevated due to bone marrow suppression. The transplant kidney is denervated and may not be tender even in the face of pyelonephritis.

Given the high prevalence and atypical presentation and microbial diversity in transplant UTI, lower urinary tract symptoms (LUTS), fever and unexplained leukocytosis should prompt immediate urine culture. If fungal infection is suspected, microscopy and cytology may give a more rapid result than culture. Blood cultures should be included if fever or systemic symptoms are present. LUTS should be evaluated to include assessment of the post void residual by ultrasound, especially in diabetics, elderly

men and in those with known urologic abnormalities. Acute prostatitis should be considered in febrile infections in men and can be confirmed by prostate exam without prostatic massage. Particularly if the patient was transplanted elsewhere, consider a KUB to ensure that a ureteric stent has not been inadvertently overlooked.

6 Prevention and therapy

It is standard practice at most centers to use antimicrobial prophylaxis peri-operatively for the wound (commonly cephalosporins) and long term against Pneumocystis pneumonia (trimethoprim-sulphamethoxazole [TMP-SMX]). Therefore, most of the UTIs within 6 months were almost certainly 'breakthrough infections' with resistant strains.

A meta-analysis and systematic review, including only randomized controlled trials, of antibiotic prophylaxis in renal transplant recipients concluded that antimicrobial prophylaxis reduces bacteriuria and bacteremia [8]. TMP-SMZ or ciprofloxacin was used as prophylaxis in these studies with variable dosing and duration of administration. Higher dose of TMP/SMX was superior to lower dose and ciprofloxacin was superior to TMP/SMX. However, ciprofloxacin has no prophylaxis against *Pneumocystis jiroveci, Nocardia* and *Listeria species* unlike TMP/SMX. In contrast to the studies in this meta-analysis, the RESITRA cohort did not show prevention of UTI (cystitis and allograft pyelonephritis) with the use of TMP-SMX [6].

The need for treatment of ASB is controversial. There are no published prospective studies evaluating the effectiveness of ASB treatment for prevention of UTI in renal transplant recipients. However, three trials are currently ongoing and data of these studies are eagerly awaited [35], [36], [37]. In a retrospective study of 196 renal allograft recipients, spontaneous bacterial clearance occurred in 59% of untreated episodes of ASB [38]. In another retrospective study, the authors interestingly reported that the risk of developing symptomatic UTI was almost three times higher and the total number of hospitalization days was also higher after treatment of ASB in comparison to no treatment [8].

Therapy can range from oral outpatient antibiotics to multidrug inpatient intravenous therapy depending on the clinical circumstance. Bacteriocidal antibiotics are preferred since the compromised innate immune cells may not be able to efficiently clear live bacteria treated with bacteriostatic drugs. Avoid drugs with primary urinary excretion and low tissue penetration (e.g. nitrofurantoin).

Predisposing/contributing factors should be corrected if possible (e.g. optimal diabetic control, removal or change of stents and catheters, minimize immunosuppression).

Interactions exist between antibiotics and immunosuppression drugs. Ciprofloxacin may raise calcineurin inhibitor (CNI) levels, but levofloxacin and ofloxacin usually do not [39]. Erythromycin and antifungal agents inhibit cytochrome p450 and increase CNI levels. Rifampin, imipenem and cephalosporins can reduce CNi levels. Nephrotoxic antibiotics (e.g. aminoglycosides, amphotericin) may have synergistic effects with CNIs, increasing renal damage.

The ideal duration of antibiotic therapy for post-transplant UTI is not firmly established. It has been suggested that early (<6 months) relapsing post-transplant UTI be treated at least 6 weeks. Persistent or recurrent UTIs should prompt the search for a surgically cause such as stones, urinary stenosis, reflux, abscess, leak or infection in the native kidneys.

UTI can co-exist with common post-transplant viral illnesses (e.g. cytomegalovirus). Transplant pyelonephritis may cause elevated creatinine. However, it should be kept in mind that there may be other causes for declining renal function (e.g. obstruction, rejection, drug toxicity) and a lack of response to antibiotic therapy should prompt an allograft biopsy.

7 Impact of UTI on graft survival

Data on the long term impact of post-transplant UTI on graft function and survival is mixed, reflecting the variations in definition and difficulty in separating causality from association. ASB itself does not seem to impair graft function. However, frequent episodes of ASB may provoke an acute rejection episode, which itself threatens the renal allograft function [4].

One recently published study reported that UTI did not impair allograft function based on creatinine levels, but a tendency towards impairment was shown when measured by nuclear studies [40].

When looking at the effect of graft pyelonephritis, the results are again conflicting. One group reported a negative impact on long term serum creatinine [18], however, another did not [4]. The data on emphysematous allograft pyelonephritis, which is rare, is more univocal. In one study of 23 cases, 12 cases (52%) required allograft nephrectomy, while 7 cases were recovered by a combination of percutaneous drainage and antibiotic treatment. Only 4 cases could be managed by antibiotic therapy alone [41].

In addition to this, bacteremia among renal allograft recipients, regardless of the primary source, jeopardize renal allograft function by raising the hazard ratio of graft failure three times [12].

In adults, the USRDS database review reported that late UTI (>6 months) was associated with increased risk of death, even after adjusting for cardiac or other infectious complications. The authors did state that UTI might simply be a clinical marker for serious underlying illness [5].

In an analysis of the USRDS data for pediatric recipients, risk for graft loss was higher for early but not late UTI, and neither impacted patient survival [42].

It is likely that pathogenic factors of the infecting bacteria play a role in renal injury which may also account for disparities in published studies [43].

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