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## REVIEW ARTICLE

# Review of Bacterial Urinary Tract Infection in Kidney Transplant Recipients: Incidence, Risk Factors and Impact on the Graft Survival

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### Abstract

Infectious complications remain a major cause of morbidity and mortality among transplant recipients. Urinary tract infection (UTI) is the most common infectious complication in kidney transplant recipients with a reported incidence of between 25%-75%. This varies widely likely due to differences in definition, diagnostic criteria, study design, and length of observation. We sought to review the incidence and importance of urinary tract infection on graft survival, related risk factors for UTI, and its impact on renal graft, showing the uncertainty that still exists in these issues because of the lack of prospective data and clinical trials.

### Keywords

Solid organ transplantation, Urinary tract infection, Asymptomatic bacteriuria, Kidney transplantation

## Introduction

### Incidence and burden of urinary tract infection in solid organ transplantation patients

Despite improved surgical techniques, antimicrobial prophylaxis, new immunosuppressive therapies and hygiene measures in the management of transplant patients, infectious complications remain a major cause of morbidity and mortality in solid organ transplantation (SOT) patients, and urinary tract infections (UTI) are one of the most common infectious complications among them [1-5]. Urinary tract infections explain the main use of antibiotics in these patients [6]. It has been described that 25%-47% of renal recipients have at least one symptomatic UTI [7,8].

One of the largest prospective series, reported that 4.4% of patients receiving solid organ transplants developed UTI with an overall incidence of 0.23 episodes per 1000 days of transplant. This incidence varies significantly depending on the type of transplanted organ. Kidney recipients have the highest risk of developing UTI, with an incidence of 0.45 episodes per 1000 days of transplant and a frequency of 7.3%, followed by kidney-pancreas (5%), heart (2.2%), liver (1.6%) and lung recipients (0.7%) [1]. Other authors described an incidence that ranged from 4% to 75% in renal allograft recipients [2-5,8-11]. These differences might be explained by the heterogeneity at establishing the definition of UTI and its clinical manifestations-asymptomatic bacteriuria (AB), acute pyelonephritis (APN), lower UTI, urosepsis, etc., different frequency of routine urine culture testing, different follow-up times, different surgical techniques strategies, diversity in the use of antimicrobial prophylaxis, and in the immunosuppression regimens employed and the retrospective design of most of the studies.

### Risk factors of UTI In transplant recipients

Most episodes of UTI occur during the first 6 months after the transplant [2], being, the first month the main period of events [6]. During the first month, asymptomatic bacteriuria (AB) occurs in 22%-71% of the patients [9,12-14], and symptomatic UTI in 12%-34% [7,13]. The study with the longer follow-up time, 36 months, recorded an incidence of APN during the first 6 months of 6.4%, with an incidence of 10% at the end of follow up. The rates of urosepsis in the first six months and 36



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months from transplantation were 0.6% and 5%, respectively [12]. In a prospective study of 161 renal transplant recipients half of the episodes occurred in the first 44 days after transplantation [15].

Furthermore, very few authors stratify the incidence by type of UTI. In the RESITRA cohort the distribution of UTI during the first three months of the transplant were 82% cystitis and 18% APN [1]. While other studies, the distribution of UTI during the first 6 years after transplantation were: AB 18.4 and 38%, cystitis 7.6 and 25%, APN 12.5 and 22%, and urosepsis 4% [16,17].

Risk factors of APN are: female sex, acute rejection, use of mycophenolate as immunosuppressor agent, age, days of bladder catheterization, genitourinary structural or functional abnormalities, UTI the month prior to the transplant, ureteral stent, frequent episodes of acute rejection, cytomegalovirus (CMV) disease, illness of the native kidney, cadaveric donor graft, urological catheter, more than 2 AB episodes, and advanced age of the donor [16,18-22].

Reported risk factors of acute cystitis are: female sex, over a week of bladder catheterization, no preoperative prophylactic antibiotic, immunosuppressor induction, recurrent UTI before transplantation, acute rejection, CMV disease, AB, age, haemodialysis just after transplant (reflecting delayed graft function), and BMI of recipient [10,16,18,22-26].

Risk factors of AB are female sex, immunosuppressor induction, morbidity by Charlson index, past acute rejection episodes, CMV disease, acute glomerulonephritis and double transplant [12,20,21,27].

Elderly patients and those with long bladder catheterization are at higher risk of UTI-related bacteraemia [18].

### **Impact of urinary tract infection on graft survival**

The effect of UTI on graft survival in transplant patients remains controversial. So far a consensus has not been established as to whether the development of UTI in the solid organ recipient carries a higher mortality or graft loss, although a tendency to graft dysfunction has been suggested. Prior to 2008, it was associated to chronic rejection, papilar necrosis, mortality and graft dysfunction [4,22,23].

Pellé, et al. [4] found that graft APN, which is defined by hiperleucocytosis, fever or allograft tenderness which can be accompanied by renal failure, was an independent risk factor for impaired renal function compared with those renal transplant recipients without UTI or with acute cystitis; however, it did not increase the risk of graft loss, acute rejection and mortality during the first year after transplantation. Time to APN has also been related to graft and recipient outcome. Giral, et al. [22] observed that APN occurring within the first 3 months of the transplant was associated to graft loss. Nevertheless, Abott, et al. [23] in a retrospective cohort study of 28.942 renal transplant recipients in the USA observed that UTI occurring 6 months after the trans-

plant was associated with death and graft loss. However, among patients who died, primary specific causes of death were missing or unknown for 61% of the patients [19].

Other authors did not observe any association between graft survival and UTI. Fiorante, et al. [12] reported 19 episodes of graft APN among 189 renal transplant patients and did not find relationship between the development of UTI and graft dysfunction. More recently, Ariza, et al. [28] did not find a worsening of renal function in patients without UTI compared with patients who developed at least one episode of UTI in the first year post-transplant. In the Spanish cohort RESITRA, UTI was not associated with an increased graft loss or increased mortality, even with a related bacteraemia rate of 20% [1]. Lee, et al. [29] conducted a retrospective study of 1166 renal transplant patients with an incidence of UTI-related bacteraemia of 12%. In this study, treated UTI was not associated to acute graft rejection however the absence of antimicrobial therapy was associated with a higher rate of acute graft rejection. Capocasale, et al. conducted a retrospective cohort study of 24 years follow-up in 1000 renal transplants, and they did not observe an increased in mortality, allograft dysfunction, even during the first month after transplantation [10].

A review by Singh, et al. showed that although UTI didn't impact significantly on renal function, an early detection of the graft injury was observed using nuclear techniques. All enphisematose APN had an impact on renal function, but results are more controversial where simple APN take place [19]. El Amari, et al. show that APN could decrease the renal function or decrease the allograft functionality [30]. On the other hand, the hazard ratio to get insufficiency of the allograft tripled when bloodstream infections set, irrespective of the source of the primary infection site [19].

Although there is no absolute observational statement, Golebiewska [16] suggests that UTI can be a cause and consequence of acute rejection. His group observed that UTI happening just after the transplant deteriorated the renal function from the early time, explaining it by a scarring process which lead to unrecuperate the basal creatinine, even though this event did not increase the mortality or the rejection. Furthermore, these patients would have more UTI consequently.

Green, et al. [31] found that recurrent AB is linked to acute rejection, but was not harmful by itself. Abbott [23] reported a 5 years follow-up study where chronic rejection recipients had more UTI, with an over expression of TNF- $\alpha$ , Il-6 and IF- $\delta$ . Also, Cizek, et al. show AB as a cause of subclinical damage due to proinflammatory pathways, but without clinical significance at the first year of monitoring [32].

Some authors [12] suggest that prolonged presence of microorganism in urine might allow the invasion of

the urinary tract, but only a clinical trial has addressed this matter, showing that although in the untreated group, 14% of patients the AB persisted for 7 months, and none developed symptomatic UTI [8].

Other authors propose AB as a risk marker of ulterior UTI caused by the same or different microorganism, independently of antibiotic therapy [27]. Coussment, et al. suggest that AB are caused by low-virulence microorganisms, so keeping them untreated compete with the ones causing symptomatic episodes. They called this kind of preventive strategy bacterial interference [6].

Although in some studies AB produce molecular and subclinical damage, there is no impact on the survival of the allograft, rejection or renal function. One of the most robust retrospective study showed no difference on acute rejection development on 334 AB when treated or not [30]. In a prospective Iranian study, which is a case-control study set about AB in SOT recipients, changes in serum creatinine levels were not found comparing treated and untreated events [26]. A trial pointing the AB in renal recipients did not find differences in acute rejection, graft function and all-cause short term mortality [8].

Finally, APN of native kidneys has been reported, but no studies confirm its impact on the graft.

## Conclusions

In summary, urinary tract infection remains a major problem in solid organ transplantation patients because of the high frequency and the unlikely impact on graft survival. Definitive effects of UTI on a kidney transplant patient are controversial, but recent studies demonstrate no risk at all for at least AB and acute cystitis in terms of: graft and recipient survival, rejection neither renal function. The APN impact is not clear, but as far as we know, graft APN set in a short period from the transplant is more dangerous than the ones set further. More studies with prospective data are needed to clarify this issue.

On the other hand, urinary tract infection remains a main cause of morbidity among renal recipients. Its incidence it's still high despite of the improvement of medical treatments and surgery techniques. We need more information to get a better management of AB and UTI, so we can avoid future episodes and low the recurrent infections.

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