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REVIEW

Updates on urinary tract infections in kidney transplantation

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Abstract
Urinary tract infection (UTI) represents the most common infection after kidney transplantation; it is associated with an increased risk for acute kidney rejection and impaired graft function in the early post-transplant period. Kidney transplant recipients with UTIs are often clinically asymptomatic due to the immunosuppressive therapy; however, asymptomatic bacteriuria may progress to acute pyelonephritis, bacteremia and urosepsis, particularly in the early post-transplant period, that are independent risk factors for short and long-term graft and patient survival. This article reviews the definitions, incidence, risk factors and the management of UTI in kidney transplant recipients; furthermore, the main controversial and still unanswered questions, regarding the causes of recurrent UTIs, adequate use of antibiotics to avoid antibiotic resistance, dosing and timing for prophylaxis and treatment of symptomatic infections, are also discussed. The emerging definition of urinary microbiota introduces new concepts in understanding the complexity of the disease and might represent the future target for therapeutic interventions.

Keywords Urinary tract infection · Kidney transplantation · Graft survival · Urinary microbiota

Introduction

A urinary tract infection (UTI) is a pathologic invasion of the urothelium with a consequent inflammatory response which is clinically characterized by specific signs and symptoms and caused by an infectious agent (mainly bacterial agents). UTIs are the most important and frequent infection in adults and represent the most common problem in patients with kidney transplantation (KTX) and the incidence in these patients is significantly higher than in the general population [1–3]. UTIs not only impacts on the patient's well-being but also increase the risk of further complications in transplanted patients, particularly related to potential drug interactions, development of resistant bacteria [4] and severe sepsis and potential effect on long-term graft survival and even death [5, 6]. Even a single episode of UTI during the post-transplant period can cause a decrease in graft function, measured as iothalamate GFR [7]. Hence, prevention and early diagnosis of UTIs are important to minimize the risk of life-threatening complications and graft loss [8]. However, the real impact of UTIs in this setting is still under debate and several aspects, such as morbidity and mortality from UTIs are controversial.

This article reviews and updates the main controversial aspects related to UTIs in kidney transplantation, mainly focusing on the prevalence and risk factors in this specific subset of patients, their potential influence on short and long-term graft outcome, as well as treatment and prophylaxis recommendations.

Definitions and epidemiology of UTI

UTIs after kidney transplantation may occur either as asymptomatic bacteriuria or as symptomatic infection [9]. An asymptomatic bacteriuria is defined as the presence of $> 10^5$ bacterial colony forming units per milliliter (CFU/ml) on urine culture without local or systemic signs and symptoms [10]. A symptomatic UTI is defined as uncomplicated (presence of $> 10^5$ CFU/ml on urine culture with local urinary symptoms, such as dysuria,

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urgency, but without systemic symptoms) or complicated if the urinary symptoms are associated with systemic ones (allograft pain, fever, chills) [7, 10, 11]. Guidelines define sporadic (less than three episodes/year) or recurrent (more than three episodes/year) UTIs according to the frequency of episodes [9]. Conventionally, a classification based on the severity of UTIs has been proposed by European Association of Urology and distinguishes six different severity grades of infection [cystitis, mild-moderate pyelonephritis, severe pyelonephritis, systemic inflammatory response syndrome (SIRS), severe urosepsis and uroseptic shock] (Table 1) [9].

The prevalence of UTIs in renal allograft recipients is extremely various among studies, ranging from 23 to 75% [3, 12], and accounting for about 40–50% of all infectious complications [13]. This may be ascribed to differences across studies in terms of population characteristics, definitions and diagnostic criteria, centre-specific antibiotic strategies and duration of follow-up. Likewise, the incidence of UTIs after KTX has been estimated to vary across the studies. Many authors reported that infections are more likely to occur in the early post-transplant period, particularly in the first year (74%) [13], while the incidence of UTIs decreases to about 35% during the second year and further to 21% at four post-transplant years [14]. The development of early UTIs is probably related to the surgical trauma, the placement of urinary catheter and ureteral stent, as well as to the higher level of immunosuppression in this post-transplant period. By contrast, Senger et al. showed that in a prospective cohort of kidney transplant recipients only < 30% developed UTIs within the first 3 months [15]. Similarly, a retrospective study of 28,942 kidney transplant recipients in the USA, described a cumulative incidence of early UTIs of 17% in the initial 3 months [16].

Microbiology

UTIs after KTX is usually caused by gram-negative organisms, accounting for more than 70% and *Escherichia coli* is the most common causative organism in the general population, as well as in kidney transplantation (30–80%) [14, 17]. *Klebsiella, Pseudomonas aeruginosa*, and *Proteus* are other gram-negative bacteria frequently isolated. However, the widespread use of antibiotics in preventing infections or treatment of asymptomatic bacteriuria in kidney transplant recipients has led to a significant increase in resistance to common antibiotics, like trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones, and caused an increase of infections due to multidrug resistant (MDR) and extensively-drug-resistant (XDR) pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* spp.) [15, 18, 19]. Recently, Korth et al. reported a significant increase in antimicrobial resistence of *Klebiella* spp. to TMP-SMX, ciprofloxacin and ceftazidime from 2009 to 2012 [20]. Emergence of MDR pathogens, extended-spectrum β-lactamases (ESBL)- and carbapenemase-producting organisms has been the most important threat in KTX and may be associated with a poorer short- and long-term prognosis [21, 22]. Gram-positive pathogens (*Streptococcus* species, *Staphylococcus saprophyticus*) are less frequent cause of UTIs. Candida species are the most common fungal cause of UTIs in KTX, occurring in about 11% of renal transplant recipients [23]. Since these infections are often asymptomatic, there are no diagnostic tests to differentiate infection from colonization in patients with candiduria. However, candiduria may uncommonly have serious complications, leading to ascending infections, candidemia and obstructing fungal balls at the ureterovescical junction, with a significant impact on graft and patient survival [24].

Table 1 Severity assessment of urinary tract infections (UTIs) according to the European Association of Urology [9]

Cystitis	Frequency, dysuria, urgency, pain, fever
Mild to moderate pyelonephritis	Fever, flank pain (graft pain) and unspecific symptoms
Severe pyelonephritis	As before, but in addition nausea and vomiting
SIRS	This systemic response to clinical insults is manifested by two or more of the following conditions temperature > 38 °C or < 36 °C heart rate > 90 bpm respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg (< 4.3 kPa) WBC > 12,000 cells/mm^3 or < 4000 cells/mm^3 or > 10% immature (band) forms
Severe urosepsis	Sepsis with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or acute alteration of mental status
Uroseptic shock	Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured

Risk factors for UTIs

Risk factors for UTI in KTX are similar to those in the general population as shown in Fig. 1. Female gender is a well-known risk factor for UTIs in the post-transplant period [3, 10, 25] and this is due to the anatomical features of the urinary tract. On the other hand, many authors did not find any gender difference in the incidence and frequency of UTIs in the post-transplant period [18, 26]. Conflicting results have been reported on the association between older age and frequency of UTIs. A higher infection occurrence is generally found in elder kidney transplant recipients [27, 28]; Chaung et al. showed that 55% of patients aged > 60 years developed UTIs compared to only 30% in the younger group [25]. By contrast, other studies did not show significant correlation between age and UTI occurrence [29–31]. An impaired immune system, the low tolerance to immunosuppression and other concurrent co-morbidities are the main determinants of the increased risk for UTIs observed in older transplant recipients. A number of recipient co-morbidities and factors, such as diabetes mellitus, polycystic kidney disease, uropathies and poor hygiene, have been indicated as significant risk factors for UTI [3, 16, 25]. Patients with chronic kidney disease (CKD) are typically characterized by alterations in host protective functions and functional disorders of the urinary tract: the loss of antibacterial properties of the urine, the reduction of the production of protective mucosa in the urothelium and the immunosuppression in the setting of uraemia and KTX are the main reasons for the higher risk of UTIs [32].

Transplant-related factors might also be associated with an increased risk for UTI, as for example the type of donor (living or deceased), episodes of delayed graft function (DGF), acute rejection, cytomegalovirus infection, and urological complications (duration of catheterisation and stenting, vescicoureteric reflux) [33]. In a recent meta-analysis of 13 studies that evaluated the prevalence and risk factors for UTIs, more than one-third of patients had at least one episode of UTI after KTX. Female gender, older recipient age, long duration of catheterisation, acute rejection episodes and cadaveric donor were significantly associated with an increased risk for UTI [34].

Finally, the type of immunosuppression is strongly related to the development of UTI. It is well known that immunosuppression may influence the resistance of enterococcal spp. to β-lactam-based antibiotics affecting the expression of penicillin-binding proteins (PBPs). Many studies showed that azathioprine [25], mycophenolate mofetil [25, 31] and

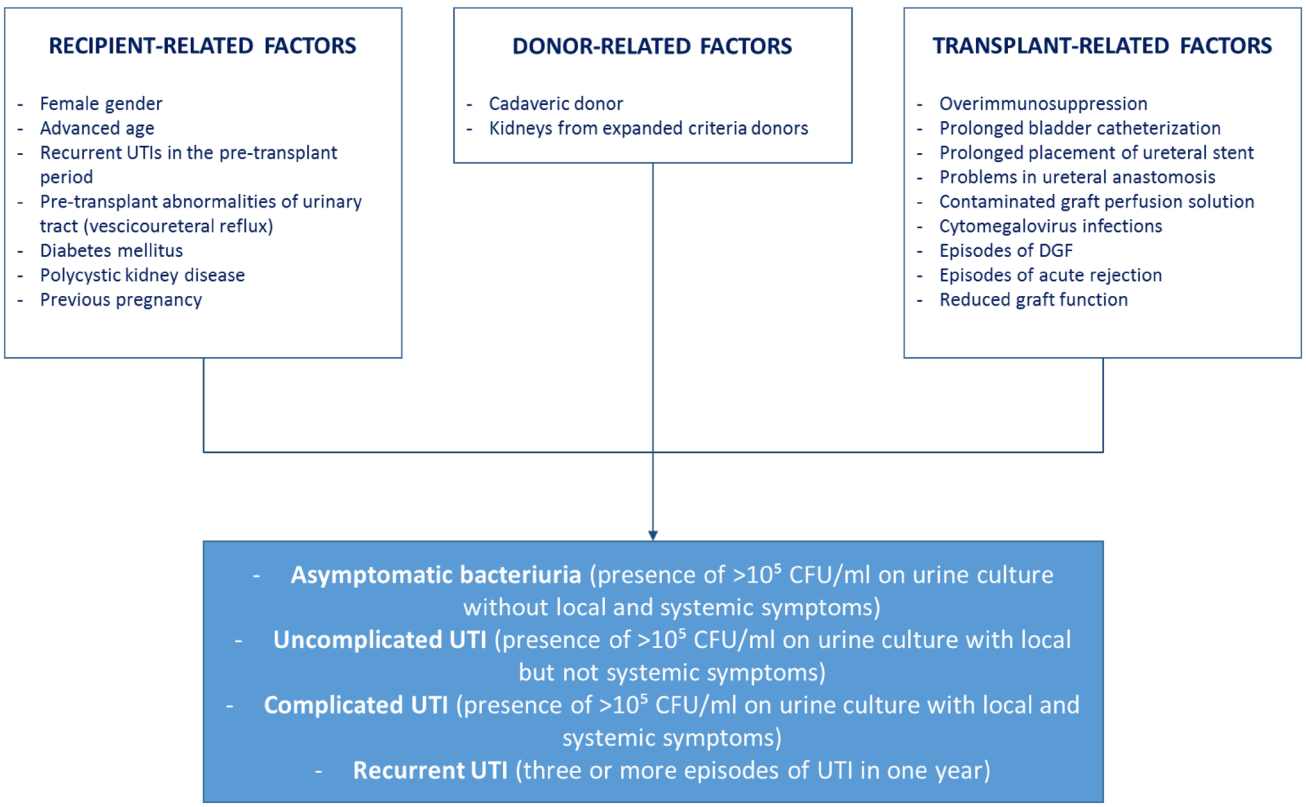

Fig. 1 Risk factors for UTI in kidney transplantation

anti-thymocyte globulin [3] are associated with higher rate of UTIs in the post-transplant period, while other drugs (calcineurin inhibitors, everolimus) seems not to affect the risk; moreover, steroid withdrawal did not have any effect on the risk of UTI [35]. In a cohort of patients with chronic allograft nephropathy commenced on mycophenolate for calcineurin inhibitors withdrawal, Hanvesakul et al. showed a significant increase in infections after conversion (26.7% vs 66.6%, $p < 0.0005$), especially for both urinary tract and respiratory tract infections [36]. Although several studies showed no differences between calcineurin inhibitors, β-lactam-based antibiotics seem to be more effective in tacrolimus-based immunosuppression [37].

Pathogenesis of UTIs: bacteria virulence and host defence mechanisms

UTIs are tipically related to the presence of uropathogenic bacteria ascending to the bladder from the urethra (ascending route). Uropathogens initially adhere to and colonize urothelium of the distal urethra; then, up to 50% of infections may ascend into the upper urinary tracts and bacteria reach the renal pelvis, penetrate the renal parenchyma leading to pyelonephritis. The heamatogenous route is more frequent than in healthy individuals because of immunosuppression. Bacteria virulence factors play a significant role in the invasion of the urothelium. Adherence of micro-organisms is related to the presence of specific adhesins found on the surface of bacterial membrane [38]. Adhesins are surface glycoproteins that work as ligands for specific glycoprotein and glycolipid receptors on uroepithelial cells. After penetrating the cell membrane, uropathogens proliferate within the cytosol to form cluster [39]; furthermore, bacteria develop specific protective structures, as biofilm matrix, that allow them to change their phenotypes and avoid host's immune response [40]. Overall, these processes stimulate epithelial cells to produce proinflammatory factors leading to an inflammatory response.

In this setting, several host defence mechanisms may also play a pathogenic role in UTIs onset, particularly in the transplant setting, including alterations in vaginal mucosa in female recipients, regular bladder emptying, urine flow, specific urine characteristics, such as high concentration of urea, that inhibits bacterial growth [41]. Other urine conditions that increase the susceptibility to pathogens are urinary pH between 6 and 7, glicosuria, idiopathic hypercalciuria and elevated urinary iron [32]. The absence of a sphincter between the transplanted ureter and the native bladder can increase the risk of transplant pyelonephritis: furthermore, ureteral stents placed during transplantation and the presence of renal cysts in patients with history of polycystic disease may predispose patients to develop recurrent UTIs [10, 11, 25]. Innate immunity represents a first line of defence against the invasion of urinary pathogens, counteracting the penetration of microrganisms into urethelial cells. Numerous cell types such as neutrophils, macrophages, natural killer cells are activated as the uropathogen invades, mediating several effects to limit pathogens penetration and damage. Several studies showed that specific genetic backgrounds are implicated in recurrence and persistence of UTIs and genetic variations of innate immunity modifying specific aspects of the immune response can result in a compromised urinary immunity and an higher susceptibility to UTIs [42]. Many of the identified genes are involved in neutrophils function. Interleukin-8 is an inflammatory cytokine promoting neutrophils migration across infected urothelial cells; absence of CXCR1, the interleukin-8 receptor, have been shown to promote bacteremia within the urinary tract. A genetic predisposition to UTIs has been identified in pediatric patients with recurrent pyelonephritis (mutation of CXCR1 gene) and expression of CXCR1 is usually lower in these patients compared with controls [43]. Moreover, patients with asymptomatic bacteriuria carry TLR4 promoter genotype variants that lower TLR4 expression [42]. Finally, a promoter sequence variants that reduce the expression of Irf3, a key transcription factor that controls the TLR4-dependent response to uropathogenic bacteria, has been reported [42].

Impact on short and long-term outcomes

It was long believed that UTIs could be considered "benign" in kidney transplant patients; however, in the recent years, accumulating evidence suggested that UTIs could significantly impact on graft function and long-term outcomes. Although kidney transplant recipients with UTIs are often clinically asymptomatic due to the inability to mount an adequate inflammatory response to infection compared to the general population, UTIs can complicate in acute pyelonephritis (APN) and potential urosepsis, particularly in the early post-transplant period, when the mortality associated to bacteremia is higher [13, 14, 44]. Infections are the main indication for emergency department admission during the early post-transplant period and UTI represents the main cause of sepsis in this setting [45]. While lower UTIs did not affect graft function over the time, post-transplant APN can lead to a decreased graft function and increased mortality [14]. Conflicting results have been reported on late and recurrent post-transplant UTIs; although late UTIs were often considered as benign in the past [46], other studies suggested something different [47]. Abbott et al. found in a large cohort study that the adjusted relative risk for graft failure in patients with late UTIs was 2.35 times higher than in patients without UTI [16]; moreover, recipients who developed septicaemia are at higher risk of death due to cardiovascular events compared to recipients without infections.

Pellè et al. confirmed that late UTIs were associated with worse long-term patient survival and APN is an independent risk factor for worse outcomes in KTX [14]. By contrast, in a cohort of kidney transplant recipients with recurrent UTIs, Dupont et al. found that more than 75% of patients have focal renal cortical scarring in a DMSA single-photon emission CT evaluation, independent of the presence of vescicoureteral reflux; however, no significantly different impairment in graft function was found between patients with or without these findings [48]. Recently, in an observational study of 1019 kidney transplant recipients in Kuwait, the Authors found that female gender, older age, thymoglobulin induction, pretransplant urological abnormalities and hepatitis C infection were significant risk factors for recurrent UTIs, but no difference in patient and graft survival was shown between patients with recurrent UTIs and those without UTIs or with no-recurrent UTIs [49]. In both studies, the favorable outcomes for patients with recurrent UTIs have been ascribed to a prompt prophylactic intervention and treatment with intravenous antibiotics to avoid further complications (i.e. sepsis). Finally, in a retrospective study based on 380 patients from our Transplant Center, we demonstrated that recurrent UTIs during the first year post-transplantation is an independent predictor of graft function at 3 years (hazard ratio 2.2; 95% CI 1.3–3.5; $p = 0.001$) [50]. Hence, the idea of UTIs as "benign" needs to be revised and it seems more reasonable to define each episode of UTI as potentially dangerous for graft and patient survival.

Diagnosis, prophylaxis and treatment of UTI

UTIs can present as either uncomplicated (characterized by urinary signs and symptoms like dysuria, frequency, urgency, hematuria) or complicated UTIs (the signs and symptoms above are associated with those of systemic inflammation, like fever, allograft pain, chills, nausea, fatigue). The diagnosis is based on a positive urine culture with $> 10^5$ CFU/ml in presence of clinical symptoms. Patients also present a urine dipstick positive for nitrites, blood, protein, and leukocyte esterase. About 16% of patients with complicated UTIs present also a positive blood cultures [11]. Additional evaluation (renal and bladder ultrasounds, CT scan of urinary tract, cystoscopy, urodynamic studies) should be considered in patients with recurrent UTIs to detect potential structural or functional abnormalities of the urinary tract, stones, complex cysts [51]. Considering the relevant impact on graft outcomes, early detection of UTIs among transplant recipients is important, particularly in the early post-transplant period. Untreated UTIs in the first 3 months post-transplantation have been found to significantly increase the risk of allograft rejection [10]. Most transplant centers routinely screen for asymptomatic bacteriuria and use an antimicrobial prophylaxis within the first 6 months of transplantation to prevent symptomatic UTIs and potential early graft dysfunction [52]. A meta-analysis of six randomized clinical trials in 545 patients, showed that TMP-SMX prophylaxis significantly reduced the risk of sepsis, septicemia by 87% and bacteriuria by 60%, although no differences in graft loss and mortality were reported [53]. However, no consensus is achieved among transplant clinicians on the optimal prophylactic regimen and duration; a prophylaxis with TMP-SMX 160 + 800 mg orally daily is effective and strongly suggested [53]. KDIGO guidelines suggested a prophylaxis based on TMP-SMX for at least 6 months post-transplantation that is helpful even in preventing other opportunistic infections (Pneumocystis) [54]. Long-term prophylaxis has been demonstrated as an effective and inexpensive approach to reduce the incidence of UTIs and sepsis [55]; nevertheless, it is still doubtful whether the long-term antimicrobial prophylaxis could increase the risk of resistance in this subset of patients as already demonstrated in the general population, and consequently affect graft and patient survival [3, 15]. Alternative agents should be used for patients known to be allergic to TMP-SMX (cephalexin, phosphomycin, nitrofurantoin) [53, 54]. Since UTI may not be clinically evident but may evolve to APN, bacteremia, urosepsis and potential risk for allograft rejection [10], a general consensus suggests to treat all transplant recipients with asymptomatic bacteriuria in the first 3 months after transplantation; an initial administration of empiric antibiotics should be followed by a specific antibiotic therapy based on the pathogen and its susceptibility pattern identified in the urine culture. Uncomplicated UTIs may be managed on an outpatient basis and common antibiotics regimes are based on ciprofloxacin 250 mg orally twice daily, levofloxacin 500 mg orally once daily, amoxicillin 500 mg orally three times daily, nitrofurantoin 100 mg orally twice daily [54]. The duration of the therapy should be modulated according to patient's characteristics and the timing of transplantation (10–14 days treatment in the early post-transplant period, 5–7 days after 6 months) [13] and the dosing must be adjusted in patients with reduced graft function. The suspicion of APN or other complications requires hospitalization and intravenous therapy covering both gram-negative and gram-positive organisms (piperacillin-tazobactam 4.5 g IV every 6 h, meropenem 1 g IV every 8 h, cefepime 1 g IV every 8 h), adjusted for graft function [54]. As for uncomplicated UTI, urine culture samples must be collected before initiating empiric antibiotic treatment and treatment should be modified according to the urine culture results. There is no consensus on optimal duration and general recommendations suggest to treat all patients with complicated UTIs for 14–21 days and a switch to oral treatment may be suggested after the resolution of symptoms [13]. Patients with relapses or recurrent UTIs (more than three episodes in 1 year) should be evaluated for potential predisposing factors

(structural and functional abnormalities of the urinary tract) as previously mentioned, and the duration of therapy might be prolonged (up to 3 months); in other cases, patients can be switched to prophylactic antibiotics after a short period of antibiotic treatment [13, 54]. Treatment of patients with asymptomatic candiduria is not universally accepted: many of these patients are treated for the risk of severe graft and patient complications. However, some evidences suggested to discourage this approach, unless the patient is neutropenic or undergoing an urological procedure [24]. The preferred agent is fluconazole, 200–400 mg orally per day per 14 days and adjustment of calcineurin inhibitors dosage may be necessary [21]. Intravenous amphotericin B (0.3–1 mg/kg/day) should be used with caution for its nephrotoxicity, while lipid formulations should be not used given their limited urine concentration. Alternative approaches (flucytosine, voriconazole, echinocandins) can be considered in selected cases, especially in the treatment of transplant pyelonephritis [21].

Challenges in UTIs treatment

Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) infections remain a critical challenge. Pre-transplant colonization is common (about 10%) and transplant recipients are at high risk for MRSA infection due to surgical procedure, ICU stay and immunosuppression [56]. Infection control strategies, including hard hygiene, active surveillance with screening for MRSA before KTX (nasal/cutaneous swab cultures) and decolonization of carriers, are still matter of debate [57]: a typical decolonization protocol includes intranasal application of 2% topical mupirocin twice daily for 5 days combined with chlorhexidine baths for 7 days, while long-term use of antistaphylococcal agents is not recommended for decolonization [57]. Vancomycin is the best choice for the treatment of severe MRSA infections and dosage should be calculated based on actual body weight and renal function: in patients with normal renal function, a dose of 15–20 mg/kg every 8–12 h should be considered with a serum trough concentrations of 15–20 µg/ml. However, vancomycin MIC value ≥ 1.5 µg/ml are strongly predictive of treatment failure; daptomycin, a bactericidal agent, should be considered in complicated MRSA infections and bacteremia at the dose of 6 mg/kg/day in patients with normal renal function [58].

VRE is hystorically considered as low pathogenic; however, VRE colonization and infections have been linked with increased mortality in patients with solid organ transplant [59]. Infection control strategies are pivotal in management of VRE infections; treatment of VRE infections remain a critical clinical situation, as the use of linezolid, quinupristin/dalfopristin (Q/D) and daptomycin is also associated with adverse effects [60]. Meta-analyses showed a modest advantage for linezolid over daptomycin, although the heterogeneity of the studies did not allow definitive conclusions [61].

While MRSA and VRE infections are declining worldwide, MDR/XDR Enterobacteriaceae and MDR/XDR nonfermenters are progressively growing as a cause of infection and represent a global threat [62]. While ESBL-producing *E. coli* do not need isolation in the majority of cases, ESBL-producing *K. pneumoniae* and Enterobacteriaceae producing derepressed β-lactamases or carbapenemases may require single-bed isolation and contact precautions: no active surveillance to detect colonization is recommended [63]. Carbapenems are the cornerstone of treatment for MDR Enterobacteriaceae as they are often resistant to quinolones and cotrimoxazole: the use of ertapenem should be preferred as this can downscale the use of imipenem and improve susceptibility of non-fermentative Gram-negative bacteria [64]. A combination of antibiotics is a standard of care in carbapenemase-producing Enterobacteriaceae infections and colistin is the most active agent against these strains [63]. In most cases, combination antibiotic therapy with polymyxin B, tigecycline, aminoglycosides, fosfomycin is an optimal choice [63]. Finally, clinical experience in the treatment of MDR/XDR non-fermatative bacilli (*Pseudomonas aeruginosa*) is limited; combination therapies using different antibiotic classes on the base of resistance phenotypes (beta-lactam + aminoglycoside ± fluoroquinolone) should be considered for at least 10–14 days [63].

Urosepsis and uroseptic shock

Urosepsis is common in both community-acquired and in hospital associated infections; it is diagnosed when clinical evidence of infection is associated to a systemic inflammatory response (fever, tachycardia, tachypnoea, leukopenia) (Table 1). Severe urosepsis is characterized by the presence of multi organ dysfunction, while uroseptic shock is defined by the persistence of hypotension despite adequate resuscitation approaches and represents the most frequent cause of death for nosocomial infection [9]. Urosepsis treatment requires a combination of adequate life-supporting care, prompt antibiotic therapy and the optimal management of urinary tract disorders; a strong collaboration between urologists, nephrologists, intensive care and infectious disease specialists are required for the best management of these patients [21, 32]. An empirical initial antibiotic treatment should be provided early and adapted on the basis of the culture results later. The antibiotic dosage should be generally higher than in uncomplicated UTIs, but adequately reduced in presence of renal failure. The prompt management of fluid

and volume balance, as well as the respiratory support, is crucial in patients with septic shock; the goal is to maintain adequate tissue perfusion, oxygen delivery, stabilization of arterial pressure, effective in reducing mortality among these patients [65]. The most effective preventive measures for urosepsis include isolation of all patients with multi-resistant organisms, early removal of indwelling urethral catheters, reduction of hospital stay, minimization of immunosuppressive therapy. A clinical algorithm for the management of these conditions are reported in Fig. 2. Patients with septic shock are more likely to develop renal failure and require renal replacement therapy in intensive care units: moreover, continuous treatment should be preferred because of the hemodynamic instability. Furthermore, specific extracorporeal therapies for sepsis should be considered: techniques based on adsorption or the combination of plasma filtration and absorption (CPFA) may reduce the deadly systemic inflammatory response in sepsis, improving hemodynamics, stabilizing patients and reducing the severity of disease [66].

Urinary microbiota and non-antibiotic approaches for UTIs

Recent studies suggested that the urinary tract is characterized by a unique specific urinary microbiota, completely different from that of the gut and vagina [41, 67]. As described for the gut, the composition and the balance between certain microbial organisms may have a critical role in the maintenance of health and the development of disease in the urinary tract [67]: in fact, although the urinary microbiota is not fully characterized, differences between patients and healthy volunteers have been linked to several urological diseases [68–70]. However, the extent of this relation is still unclear. Several factors have been implicated in changes of urinary microbiota during an individual's life [71]. Hormonal changes during puberty and adolescence, as well as the sexual activity are associated with changes in the bacterial composition of the urinary microbiota in both men and women [72, 73]. Dietary habits are well known risk factors for UTIs and specific urinary components may have a pivotal role in determining the colonization of the urinary tract. For example, Habash et al. demonstrated that high water intake may lead to the dilution of specific factors that usually inhibits microbial deposition, and this lead to an increased adherence of *E. coli* and *E. faecalis* to silicon rubber [74]. Furthermore, drugs, like antibiotics, may significantly alter the microbiota composition, leading to an increased risk for infections [75]. In this scenario, several non-antibiotic options have been proposed for recurrent UTIs in the last years with controversial results [76]. No RCTs supported the utility of urinary alkalinisation with potassium citrate in reducing UTIs symptoms [77]. Probiotic organisms (e.g. *Lactobacillus* spp.) modulate host defences by reducing pathogen adherence and their ability to cause infections: a Cochrane systematic review did not show significant differences between the probiotic arm and placebo, although the small sample size may limit the significance of this analysis [78]. In post-menopausal women with recurrent UTIs, the use of topical estrogen has been shown to reduce the events of UTIs, improving vaginal atrophia and increasing vaginal lactobacilli [79]. Several evidences suggest the use of cranberry juice for patients with chronic recurrent post-transplant UTIs in order to prevent the adhesion of uropathogenic micro-organisms to the urothelium [80]; however, the role of these products is still controversial, as a recent Cochrane systematic review and meta-analysis points out that cranberry juice is less effective than previously indicated [81]. Moreover, D-mannose have shown promising results in reducing the risk for UTIs, inhibiting the attachment of bacterial type 1 fimbriae to cell surfaces and reducing their ability to infect the host, but its efficacy has not been evaluated in RCTs yet [82].

Finally, it is notable that several UTIs resolve without antibiotic interventions, probably related to the ability to restore the urinary microbiota after the acute infection [83]. If so, why do not all UTIs resolve in this way? Are changes in the urinary microbiota related to this specific pathway and the restore of the urinary microbiota has a pivotal role for IVUs outcomes? These questions are still unanswered and future studies focusing on differences in urinary metabolites in healthy and pathological conditions might help in characterizing urinary microbiota in both conditions and identifying markers of disease. Future alternative therapeutic strategies targeting the urinary microbiota might be useful tools for the correct management of symptoms and reducing the risk for complications.

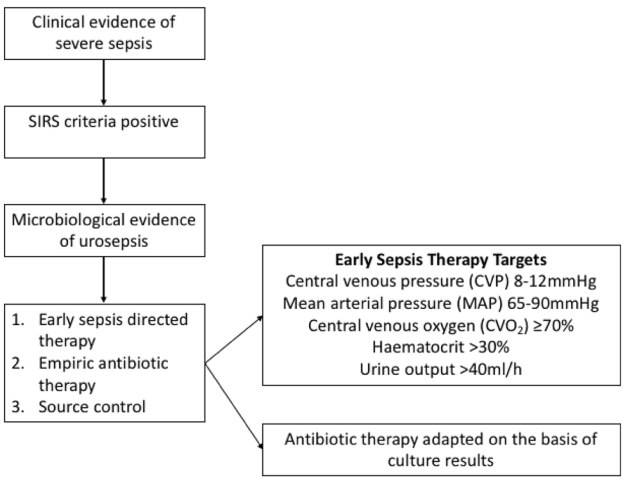

Fig. 2 Clinical management of urosepsis and uroseptic shock in kidney transplantation

Table 2 Current recommendations for the management of UTI in kidney transplantation

Screening and diagnosis of UTI in kidney transplant patients
Adequate screening urine culture in the first 3 months' post-transplant
Antibiotic prophylaxis with double-strength tablet of TMP-SMX orally daily for at least 6 months to 1-year post-transplant
Testing with a urine dipstick, urine microscopy and urine culture in presence of signs and symptoms of UTI
Patients with recurrent UTIs should undergo further evaluation to assess the presence of structural and/or functional abnormalities of the urinary tract (ultrasound imaging, urodynamic studies, etc.)
Treatment of UTI in kidney transplant patients
For patients with asymptomatic bacteriuria in the first 3 months' post-transplant, treatment with oral antibiotics (up to 7 days) based on urine culture results
For patients with uncomplicated UTIs, empiric oral antibiotic therapy should be initiated and then switched according to the bacteria's susceptibility (10–14 days in the first 6 months, 5–7 days after 6 months' post-transplant)
For patients with complicated UTI, hospitalization treatment with intravenous antibiotics is required. The initial empiric treatment should be replaced by a definitive therapy based on causative organism and its antibiotic susceptibility (duration 14–21 days, possible switch to oral treatment after resolution of signs and symptoms)
For patients with recurrent UTI, antibiotic treatment duration may be longer or switched to a prophylactic antibiotic treatment after the usual course (14–21 days). Investigations about the underlying cause of chronic recurrent UTIs should be performed
Vancomycin is the recommended drug for MRSA infections, while for bacteremiae with vancomycin MIC > 1.0 mg/l, daptomycin, alone or in combination, is suggested
Carbapenemes are required for the treatment of ESBL-producting Gram negative bacilla, while colistin, alone or in combination with tigecycline, polymyxin B, aminoglycosides, fosfomycin, is strongly suggested for carbapenamase-producting Enterobacteriaceae

Conclusions

UTI remains a common and challenging problem in kidney transplantation, affecting both short and long-term outcomes in kidney transplant recipients. Various factors may influence the incidence and severity of UTIs in this particular setting and their recognition is important to identify kidney transplant recipients who are more likely to develop UTIs and therefore minimize the risk with a personalized management (e.g. adequate screening and prophylaxis, avoid overimmunosuppression, etc.). A summary of the current recommendations in the management of UTIs in kidney transplantation is showed in Table 2. However, several issues still need to be addressed: the identification of underlying causes of recurrent UTIs, the role of long-term prophylaxis, the need for treating asymptomatic bacteriuria, careful and selective use of antibiotics to avoid the incidence of MDR/XDR micro-organisms, the dosing and timing for prophylaxis and treatment of symptomatic infections. The lack of definitive answers to these issues strongly highlights the need for future well-planned studies of post-transplant UTIs, focusing on the urinary microbiota and alternative non-antibiotic treatments for UTIs. Due to the complexity of the disease, the identification of a multidisciplinary team (nephrologists, urologists, intensive care and infectious disease specialists) in managing UTIs in transplant centers is strongly recommended.

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Compliance with ethical standards

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Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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