Enferm Infecc Microbiol Clin. 2017;35(4):255–259

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Review article

Urinary tract infection in kidney transplant recipients

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ARTICLE INFO

Article history:
Received 24 November 2015
Accepted 14 March 2016
Available online 21 April 2016

Keywords:
Solid organ transplantation
Kidney transplantation
Urinary tract infection
Pyelonephritis
Graft function

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 from 25% to 75%, varies widely likely due to differences in definition, diagnostic criteria, study design, and length of observation. We sought reviews the incidence and importance of urinary tract infection on graft survival, the microbiology with special emphasis on multidrug resistant microorganisms, the therapeutic management of UTI and the prophylaxis of recurrent UTI among solid organ transplant recipients, highlighting the need for prospective clinical trials to unify the clinical management in this population.

Infección del Tracto Urinario en el Paciente Trasplantado Renal

Palabras clave:
Trasplante de órgano sólido
Trasplante renal
Infección del tracto urinario
Pielonefritis
Función del injerto

RESUMEN

Las complicaciones infecciosas siguen siendo una causa importante de morbimortalidad entre los pacientes trasplantados de órgano sólido. La infección del tracto urinario (ITU) es la complicación infecciosa más frecuente en los trasplantados renales con una incidencia que varía entre el 25 y el 75% según los estudios, debido a diferencias en la definición, criterios diagnósticos, diseño de los estudios y tiempo de seguimiento. Revisamos la incidencia e importancia de la ITU en la supervivencia del injerto, la microbiología, con especial énfasis en los microorganismos multirresistentes, el manejo terapéutico de la ITU y la profilaxis de la infección urinaria recurrente en los receptores de trasplante renal destacando la necesidad de ensayos clínicos prospectivos que unifiquen el manejo clínico en esta población.

Introduction

Despite improved surgical techniques, antimicrobial prophylaxis, new schemes of immunosuppressive therapy 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. Urinary tract infections (UTI) are one of the most common infectious complications among them.[1–5]

One of the largest prospective series described that 4.4% of patients receiving solid organ transplant developed urinary tract infection with an overall incidence of 0.23 episodes per 1000 days of transplant. This incidence varies also significantly depending on the type of transplanted organ. Kidney recipients have the highest risk of developing UTI with an incidence of 7.3%, followed by kidney–pancreas (4.9%), heart (2.2%), liver (1.6%) and lung recipients (0.7%).[1] Other authors described an incidence that ranged from 25% to 75% in renal allograft recipients.[2–5] Moreover, in a Spanish cohort of 867 kidney recipients, 184 (21%) patients developed an UTI during the first year post-transplantation.[6] Another recent study of prevalence in Yemen, has shown that the incidence of bacterial UTI raises to 33.3% in a cohort of 150 renal transplant recipients.[7]

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These differences might be explained by the heterogeneity in the definition of UTI in the different reports, such as asymptomatic bacteriuria, pyuria, acute cystitis, pyelonephritis or bacteremia and by differences in the follow-up period. Most episodes of UTI occur during the first 6 months after the transplant,[2,8] probably secondary to surgical injury, bladder catheterization and the most intensive immunosuppressant regimens.

In a prospective study of 161 renal transplant recipients, 25% were diagnosed of at least one UTI during the monitoring period (median of 180 days), half of the episodes occurring in the first 44 days after transplantation.[9] Furthermore, the different surgical techniques strategies performed, antimicrobial prophylaxis used and immunosuppression regimens employed also influence these differences in incidence.

Impact of urinary tract infection on graft survival

The effect of UTI on graft survival in transplant patients remains controversial. So far it has not been established a consensus on whether the development of UTI in the solid organ recipient carries a higher mortality or graft loss, although it has been suggested a tendency to graft dysfunction.[4,10,11]

Pellé et al.[4] found that acute graft pyelonephritis (AGP) was an independent risk factor for impaired renal function, by analyzing the serum creatinine and creatinine clearance, compared with those renal transplant recipients without UTI or with uncomplicated cystitis. However, it did not increase the risk of graft loss, development of acute rejection or mortality rate during the first year after transplantation. Time to AGP has also been related to graft and recipient outcome. Giral et al.[10] observed that AGP occurring within the first 3 months after transplantation was associated to graft loss. Nevertheless, Abott et al.[11] in a retrospective cohort study of 28,942 renal transplant recipients in the USA observed that UTI occurring after 6 months of the transplant 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.

Other authors did not observe any association between graft survival and UTI. Fiorante et al.[12] reported 25 episodes of AGP among 189 renal transplant patients and did not find any relationship between the development of UTI and graft dysfunction. More recently, Ariza et al.[13] 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 when kidney function was measured by eGFR. However, when using iothalamate clearance (iGFR) to determine allograft function, the predicted difference in iGFR was 5.09% lower in patients who had at least one UTI than in those who did not. In the Spanish cohort RESITRA,[1] UTI was not associated with increased graft loss or increased mortality, even with a related pyelonephritis bacteremia rate of 18.9%. Lee et al.[14] conducted a retrospective study of 1166 renal transplant patients with an incidence of UTI-related bacteremia of 12.1%. 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. In the study of Bodro et al., 867 kidney recipients were included retrospectively to analyze the clinical impact of UTI on graft function and one year post-transplantation graft survival. They found that presenting with one or more episodes of AGP was significantly associated with impaired kidney graft function and graft loss one year after transplantation. Furthermore, patients with AGP caused by resistant strains, extended spectrum betalactamase (ESBL) producing *Enterobacteriaceae* and MDR *Pseudomonas aeruginosa*, had worse graft function along the monitoring, with the difference almost reaching statistical significance.[6]

In summary, definitive effects of UTI on a kidney transplant patient are controversial, thus more studies are needed to clarify this issue.

Management of urinary tract infections in renal transplant recipients. Multirresistant microorganisms urinary tract infection

Epidemiologically, the most frequent microorganisms causing UTI in the SOT setting are, as in the general population, gram-negative bacilli, mainly *Escherichia coli*, followed by *Klebsiella* spp., *Pseudomonas aeruginosa* and *Enterococcus* spp. Current data indicate an increasing rate of multidrug-resistant (MDR) strains of urinary pathogens worldwide. The RESITRA cohort reported an ESBL-producing *E. coli* rate of 26.3% and resistance to quinolones was achieved in 38–45% of *E. coli*, 25–31% of *Klebsiella* spp., and 21% of *P. aeruginosa* isolates. The resistance of *E. coli* isolates to cotrimoxazole was 77%.[1] Senger et al.[15] found a resistance of *E. coli* strains to ciprofloxacin in 50% of the UTI that occurred during the first month post-transplant and in 32.4% of those occurring after 6 months of transplantation. Furthermore the rate of resistance of *E. coli* to trimethoprim–sulfamethoxazole (TMP–SMX) was 70.6% in UTI occurring during the first 6 months after transplantation. This resistance to TMP–SMX can be explained by its use for the prophylaxis of *Pneumocystis jiroveci* pneumonia during the first 6 months after transplantation.[15] In a Polish study where 295 renal transplant patients were analyzed, the proportion of ESBL-producing *Enterobacteriaceae* was 52.5%, attributing this finding to the use of prolonged prophylaxis with ceftriaxone.[16] Similar results were obtained in Turkey, where 124 patients were retrospectively analyzed and found that *E. coli* was the most frequent isolate, with a rate of 52.8% of *E. coli* and *Klebsiella* spp. producing ESBL.[17]

This high incidence of multidrug-resistant microorganisms is associated with increased mortality and graft failure[18] and favors the recurrence of UTI.[19]

A growing problem is the current spread of carbapenem resistant *Klebsiella pneumoniae* (CRKP). Brizendine et al.[20] described 108 urinary tract infections in SOT recipients caused by *Klebsiella pneumoniae* and compared three groups: carbapenem resistant *K. pneumoniae* (22 cases, 20%), ESBL-producing *K. pneumoniae* (22 cases, 20%) and susceptible *K. pneumoniae* (64 cases, 60%). Among overall transplant recipients with UTI due to CRKP, 64% received combined antibiotic therapy with at least 2 different classes of drugs, 45% received fosfomycin. Compared to susceptible *K. pneumoniae*, patients with UTI due to CRKP or ESBL-producing *K. pneumoniae* were more likely to have a prolonged stay in the intensive care unit (ICU) and CRKP was associated with microbiological failure among SOT patients with UTI, though no association with mortality was found.

The only available antibacterial agents with activity against CPKP are polymyxins (colistin and polymyxin B), tigecycline, fosfomycin, gentamicin, and amikacin but there are several limitations to each of these agents and little evidence. Therefore, combination therapy for carbapenem resistant enterobacteria should be considered.[21]

In vitro activity of fosfomycin against CRKP has been demonstrated,[22] however data supporting its efficacy for carbapenem resistant enterobacteria infection are limited, resistance may develop rapidly and optimal dosage and duration of fosfomycin treatment is unknown in this setting.[23] Avibactam is a non-β-lactam, β-lactamase inhibitor with activity against class A carbapenemases. Recently, a case of CPKP urinary tract infection in a kidney transplant recipient successfully treated with ceftazidime–avibactam has been described.[24] Although there is still little evidence, it can be a promising new drug in this setting.

Most infections due to multidrug-resistant strains are acquired during hospitalization, but most patients undergoing solid organ transplantation have previous risk factors that predispose to these infections, such as chronic underlying diseases that lead to multiple hospital admissions and continuous contact with health care devices.

In the general population, relationship with health care services or nursing home residency, prolonged hospital stay, intensive care unit admission, prior antimicrobial therapy and recurrent UTI are some of the factors that have been associated with the risk of ESBL-producing enterobacteria UTI.[20,25,26] SOT recipients accomplish many of these factors, due to concomitant comorbidities and continuous contact with the health care environment.

Empirical antibiotic therapy for UTI in SOT patients as well as their optimal duration is based on the established recommendations for the general population due to the lack of randomized clinical trials in this setting. To guide empirical therapy it is necessary to consider host clinical characteristics, including infection severity, local epidemiological data, patient's history of resistant microorganisms and prior antibiotic therapies.

Due to the high frequency of sepsis and bacteremia secondary to UTI in the transplant setting,[11,14] the empirical treatment of severe graft acute pyelonephritis should be active against gram negative bacilli, including *P. aeruginosa*, as well as gram positive cocci. Antibiotic should be simplified once the susceptibility analysis is available. Uncomplicated cystitis can be treated as outpatients while suspected acute pyelonephritis requires hospitalization and intravenous treatment should begin as soon as possible.[27,28]

Although no conclusive evidence is available on the optimal duration of therapy for pyelonephritis in SOT recipients, cystitis should usually be treated empirically with a single oral antibiotic like ciprofloxacin, amoxicillin–clavulanate or an oral third generation cephalosporin (e.g. cefixime) for 5–7 days.[29] Others authors recommend that even uncomplicated cystitis occurring early post-transplant (e.g. within the first 6 months), should be treated for 7–10 days. Removal or replacement of urinary tract instruments such as urethral catheters and urologic stents is recommended.[27]

Few data exist on the treatment of non-complicated UTI with fosfomycin trometamol. A meta-analysis of 27 randomized controlled trials in the general population compared a single 3 g oral dose of fosfomycin trometamole with regimens of 3–7 days of fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, pefloxacin), pipemidic acid, trimethoprim, cotrimoxazole, betalactams (cefalexin, amoxicillin) and nitrofurantoin for the treatment of cystitis. The study demonstrated no difference in microbiological success between these regimens. The fosfomycin single-dose was associated with fewer adverse effects in comparison with longer regimens in pregnant women.[30]

A Greek study evaluated the in vitro activity of fosfomycin against 578 urinary isolates. They found 29 cases of ESBL-producing *E. coli* and *K. pneumoniae* isolates and fosfomycin was active against all them. Furthermore, 60% of isolates of *Klebsiella pneumoniae* non-susceptible to carbapenem were susceptible to fosfomycin.[31] Falagas et al.[32] reviewed 17 studies evaluating the antimicrobial activity or the clinical effectiveness of fosfomycin. 5057 clinical isolates of *Enterobacteriaceae* with advanced resistance to antimicrobial drugs were analyzed and 96.8% of *Escherichia coli* isolates producing ESBL were susceptible to fosfomycin. Therefore, a single 3 g oral dose of fosfomycin-trometamole may be a good option in uncomplicated cystitis but studies in the transplant population are necessary.

In case of acute graft pyelonephritis or urosepsis, longer treatment, 14–21 days, with extended spectrum intravenous antibiotics such as piperacillin–tazobactam or cefepime are recommended.[29] Clinical trials are in progress to determine whether shorter courses of antibiotic therapy are effective and safe in bacteremic UTI.[33]

In cases of suspecting multirresistant microorganisms and severe disease, the use of a carbapenem with or without vancomycin may be considered.[29] Once susceptibility data are available, the most narrow-spectrum antibiotic should be used to complete course of therapy. Complicated pyelonephritis with a renal or perinephric abscess or emphysematous pyelonephritis may occur and usually requires a multidisciplinary approach for percutaneous or surgical drainage of abscesses. Duration of treatment should be at least 2 weeks, and should be extended until an adequate drainage of abscesses and clinical resolution of infection has been achieved.[29]

Recurrent urinary tract infection prophylaxis

Recurrent UTI is defined as the presence of three or more episodes of symptomatic UTI over a 12-month period, or two episodes in the previous 6 months.[34] It is not an infrequent problem in renal transplant recipients, with an incidence of 2.9–27% of kidney recipients.[35–39] Indeed, it is not exceptional in other SOT recipients, with a rate of 2.7%.[1] Recurrent UTI has been related to an increased risk for subsequent UTI[4] but the long term effect on graft function or survival has not been conclusively established.

Risk factors for recurrent UTI are not well defined. A randomized trial of 201 kidney transplant recipients in the United Kingdom evaluating the effectiveness of ureteral stenting found a significant increase in urinary tract infection in patients with ureteral stent beyond 30 days after transplantation.[40]

Further, female gender, diabetes mellitus, concomitant cytomegalovirus (CMV) disease, vesico-ureteral reflux, native kidney disease with urological malformations, and retransplantation have been associated with recurrent UTI throughout the post-kidney transplant period.[36,38] Recently, two observational studies have shown that multidrug resistant bacteria UTI was a risk factor for recurrent UTI. However, they did not observed an impact of recurrent UTI in graft function.[19,41]

Recurrent UTI must be promptly investigated in kidney transplant patients in order to rule out the existence of any anatomical or functional abnormalities of the urinary tract such as urinary tract obstruction, strictures, stenosis, vesico-ureteral reflux, renal calculi, neurogenic bladder or complex cysts with a meticulous exam including imaging studies of the urinary tract, cystoscopy, cystogram, uroflowmetry and other urodynamic techniques, if necessary.[8,27,42]

Knowledge of the etiology of previous UTI should be used to guide the selection of the empiric antibiotic regimen in the recurrent UTI. The duration of therapy is controversial because of the lack of controlled studies that analyze the length of antimicrobial treatment. Some studies propose a 6-week treatment period[42,43] while others suggest prolonging it for at least three months[27] or even indefinitely. Anatomical changes must be corrected if possible, as this action has been associated with recurrent UTI resolution.[44]

Secondary antimicrobial prophylaxis for prevention of recurrent UTI in SOT recipients has not been well studied. In a Turkish study of 136 renal transplant recipients, 15 of 34 patients with recurrent UTI received nitrofurantoin for 10 weeks to 3 months, but this strategy seemed to lack efficiency for its prevention.[37] It can be extrapolated from the literature in general population that treatment should be designed according to antibiotic susceptibility of previous isolates.[45] However, the use of long-term antibiotic regimens may develop secondary resistances.[28,46] Some authors recommended indefinite treatment, equivalent to secondary prophylaxis, in selected cases such as diabetic patients, prior history of UTIs before transplantation or nearly after, and those receiving high dose immunosuppressive treatment.[47] In the general population, fosfomycin 3 g weekly, has demonstrated non-inferiority in

prevention of recurrent UTI in comparison with a fluoroquinolone agent.[48] Due to the increase resistance of the main uropathogens to TMP–SMX and fluorquinolones, studies are required in SOT population about the use of fosfomycin in this setting.

There is little information about non-pharmacological antimicrobial prophylaxis strategies to prevent the development of UTI in transplant recipients. Pagonas et al.[49] retrospectively studied the prophylactic use of cranberry extract and L-Methionine in transplant population with recurrent UTI finding that using cranberry and/or methionine led to an overall reduction in the incidence of recurrent UTI by 50% of the patients in the study. Its mechanism is not well defined, but it is speculated that it interferes with the adhesion of uropathogenic bacteria, primarily *E. coli*, to the uroepithelial cells.[50]

In conclusion, urinary tract infection remains a major problem in solid organ transplantation patients because of the high frequency and the unknown impact on graft survival. Many issues need to be studied in this population, such as the empiric antibiotic treatment of choice, the safety of short regimens of treatment, the use of new drugs and the prevention of recurrent UTI. A growing problem in this population is the current spread of ESBL-enterobacteria and carbapenem resistant enterobacteria, requiring the use of combined therapy and research of new drugs.

Conflict of interest

The authors declare no conflict of interest.

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