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.