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Multidrug-resistant bacterial infection in solid organ transplant recipients

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A B S T R A C T

The most frequent complication from infection after solid organ transplantation is bacterial infection. This complication is more frequent in organ transplantation involving the abdominal cavity, such as liver or pancreas transplantation, and less frequent in heart transplant recipients. The sources, clinical characteristics, antibiotic resistance and clinical outcomes vary according to the time of onset after transplantation. Most bacterial infections during the first month post-transplantation are hospital acquired, and there is usually a high incidence of multidrug-resistant bacterial infections. The higher incidence of complications from bacterial infection in the first month post-transplantation may be associated with high morbidity. Of special interest due to their frequency are infections by *S. aureus*, enterococci, Gram-negative enteric and non-fermentative bacilli. Opportunistic bacterial infections may occur at any time on the post-transplant timeline, but are more frequent between months two and six, the period in which immunosuppression is higher. The most frequent bacterial species causing opportunistic infections in organ transplant recipients are *Listeria monocytogenes* and *Nocardia* spp. After month six, post-transplantation solid organ transplant patients usually develop conventional community-acquired bacterial infections, especially urinary tract infections by *E. coli* and *S. pneumoniae* pneumonia. In this article we review the clinical characteristics, epidemiology, diagnosis and prognosis of bacterial infections in solid organ transplant patients.

Infección bacteriana en receptores de trasplante de órgano sólido. Bacterias multirresistentes a fármacos

Palabras clave:
Infecciones bacterianas nosocomiales
Infecciones bacterianas oportunistas
Multirresistencia
Trasplante de órgano sólido

R E S U M E N

La infección bacteriana es la complicación infecciosa más frecuente tras el trasplante de órgano sólido. Esta complicación es más frecuente en el trasplante de órgano que involucra la cavidad abdominal, como por ejemplo el trasplante de hígado o de páncreas, y menos frecuente en los receptores de trasplante cardíaco. Las fuentes, características clínicas, resistencia a antibiótico y resultados clínicos varían de acuerdo con el momento del comienzo de la infección tras el trasplante. Muchas infecciones bacterianas durante el primer mes tras el trasplante son adquiridas en el hospital, habitualmente asociadas con una alta incidencia de infecciones por bacterias multirresistentes. La mayor incidencia de infección bacteriana ocurre durante el primer mes tras el trasplante y esta complicación puede amenazar la vida del paciente y estar asociada a una alta mortalidad. Debido a su frecuencia son de especial interés las infecciones por *S. aureus*, enterococos, Gram-negativos entéricos y bacilos no fermentativos. Las infecciones bacterianas oportunistas pueden ocurrir en cualquier momento tras el trasplante, pero son más frecuentes de los 2 a los 6 meses, período en el cual la inmunosupresión es más alta. Las especies bacterianas causantes de infección oportunista en los receptores de trasplante de órgano más frecuentes son *Listeria monocytogenes* y *Nocardia* spp. Tras el sexto mes después del trasplante los pacientes sometidos a trasplante de órgano sólido habitualmente desarrollan las convencionales infecciones bacterianas adquiridas en la comunidad, especialmente infecciones del tracto urinario por *E. coli* y neumonía por *S. pneumoniae.* En este artículo revisamos las características clínicas, epidemiología, diagnóstico y pronóstico de las infecciones bacterianas en los pacientes sometidos a trasplante de órgano sólido.

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Introduction

The most frequent complication from infection after solid organ transplantation is due to infection from bacteria. The incidence rate of bacterial infections after renal transplantation has been estimated to be 23.2 cases per 100 transplant/years in North America.[1] The incidence rate in liver recipients is 4.4 cases per patient per year during the first year, decreasing thereafter.[2] In general, organ transplantation involving intra-abdominal surgery, such as liver, pancreas and intestinal transplantation have the highest risk of bacterial infection. Heart transplantation has a lower risk of these infections in comparison with other types of transplantation.

Bacterial infection can appear during all post-transplantation periods (Fig. 1). The first two months after transplantation is when the risk of bacterial infection, mainly hospital acquired, is higher for two main reasons: 1) surgical aggression inherent in the transplantation procedure; and 2) the requirement for intravascular catheters, urinary catheterization and orotracheal intubation. The risk of opportunistic bacterial infection during the fist month is low, as is the net state of immunosuppression, progressively increasing from month two to month six, in which a maximum plateau is established, decreasing thereafter. In recent years, due to the emergence of new mechanisms of antibiotic resistance, organ transplant patients most often develop infections from hospital-acquired multidrug resistant bacteria. This can lead to the requirement for second-line antimicrobial agents for treatment of these complications, which usually produce more side-effects, such as renal toxicity, worsening the prognosis of the graft and the patient. During the first month, the most relevant sources of bacterial infection include intravascular catheters, urinary indwelling catheters, surgical sites and ventilator-associated pneumonia. Among all post-transplant periods, the rate of immunosuppression is highest between months two and six, ,when the patient can develop either conventional community-acquired or opportunistic bacterial infections. Most infections during this period are urinary tract infections or community-acquired pneumonia. After month six post-transplant, the risk of opportunistic bacterial infections is very low and patients are more likely to develop conventional bacterial infections. The subgroup of patients with allograft dysfunction has a greater risk of bacterial infection and may develop opportunistic complications in later post-transplantation periods (more than six months post-transplantation).

Major Clinical Syndromes of Bacterial Infection in Solid Organ Transplant Recipients

Bloodstream infection

Bloodstream infection is the most severe expression of bacterial infection. Clinical symptoms range from asymptomatic to the most life-threatening complications, such as septic shock. Regarding prognosis, the risk of mortality is influenced by several factors. The development of septic shock is associated with higher mortality, reaching 50% of cases in solid organ transplant recipients.[3] Catheter-related bacteremia generally has a better prognosis, while bacteremia from a pulmonary source is associated with higher mortality.[4] Some virulence factors intrinsic to the causative bacteria can influence the outcome. In addition, antibiotic resistance of the isolate and the use

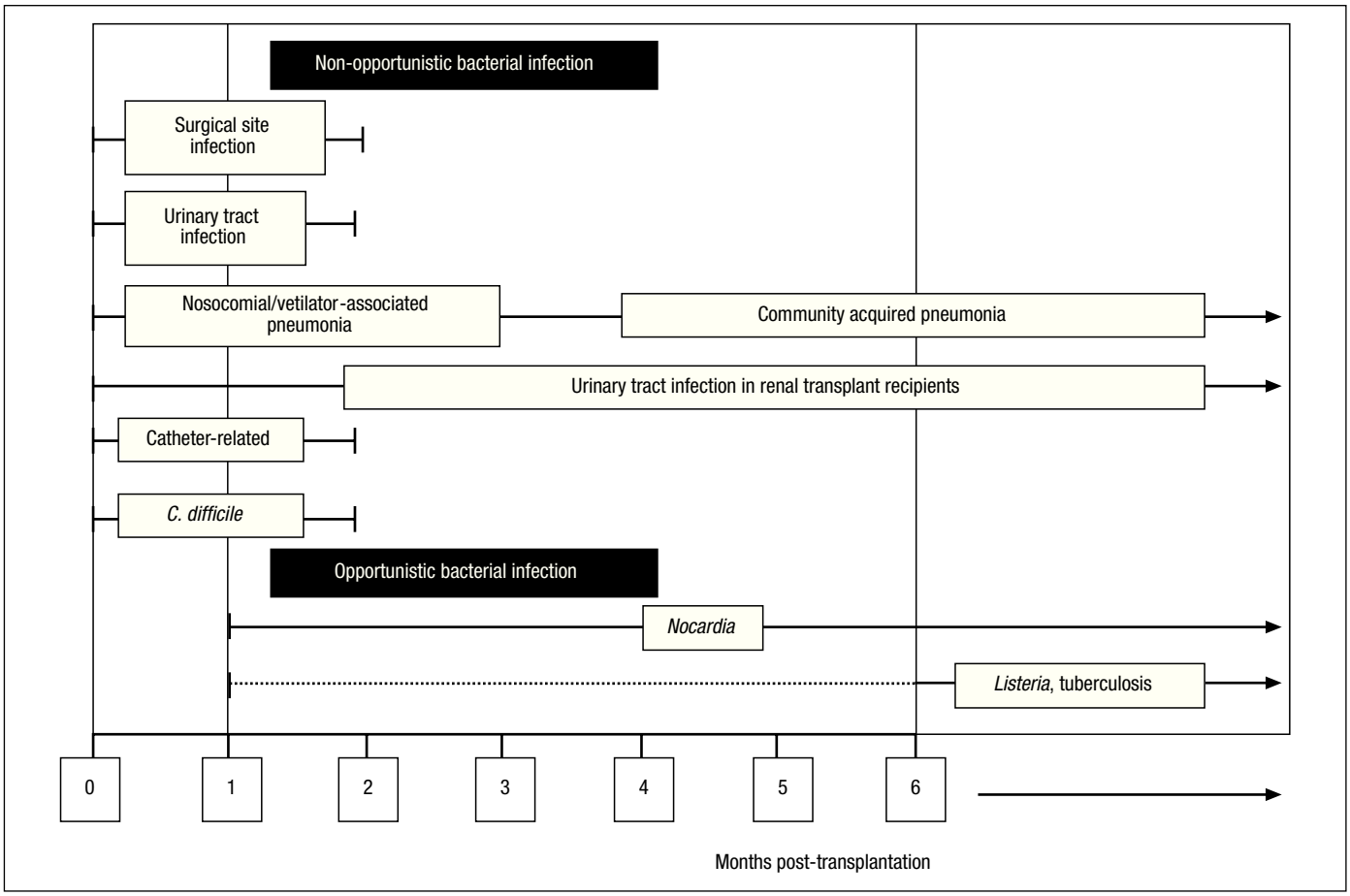

Figure 1. Chronology of bacterial infections after solid organ transplantation.

of inappropriate therapy are also associated with higher mortality.[5] Therefore, it is critical to have detailed knowledge of the local epidemiology of bacteremia in the transplant patient in order to apply appropriate early treatment based on the most prevalent causative agents and rates of bacterial resistance.

After initial evaluation of a transplant patient with bacteremia, the time of onset in the post-transplant period must be taken into account. Most cases of bacteremia occurring during the first month after transplantation are hospital-acquired. The most frequent source is intravascular catheters, and the most frequent isolates are coagulase-negative staphylococci and *Staphylococcus aureus*.

The second most frequent source is urine, especially in recipients of simultaneous renal and kidney pancreas transplantation. Bacteremia in patients on mechanical ventilation can be secondary to pulmonary infection, although the rate of bacteremia from nosocomial pneumonia in transplant recipients is very low (3% of patients).[6] Another possible source is the surgical site, but this occurs less frequently.

Bacteremia after the first month post-transplantation is much less frequent than during the first month. After discharge from the hospital, solid organ transplant recipients can develop bacteremia due to community-acquired bacteria, of which *Streptococcus pneumoniae* is the leading cause. The incidence of *S. pneumoniae* bacteremia is higher than in the general population (146 versus 11.5 cases per 100,000 persons/year) with a hospital mortality of 29%.[7] Community-acquired *Listeria monocytogenes* bacteremia is more frequent in solid organ transplant recipients than in the general population. In one study, listeriosis in solid organ transplant recipients was accompanied by bacteremia in 86% of cases, the onset starting a median of 202 days after transplantation. The risk factors for its acquisition were diabetes mellitus, the use of high doses of steroids, previous infection or disease from cytomegalovirus and the absence of prophylaxis with cotrimoxazole.[8] The most severe complication of *L. monocytogenes* bacteremia is meningitis, with a mortality of 50% in liver transplant recipients.[9] For this reason, a lumbar puncture should be performed for a transplant patient with bacteremia from *Listeria*.

The measures to prevent bloodstream infection in patients with solid organ transplantation are the same as those in non-immunosuppressed hospitalized patients. Catheters are the main source of bacteremic infections in organ transplantation patients, and the most easily preventable complication. Simply applying the measures recommended by the CDC on management of intravascular catheters (hand washing, use of barrier precautions and avoiding the femoral site during insertion of central venous lines, skin antisepsis with clorhexidine and removal of all unnecessary catheters),[10] dramatically reduces the incidence of catheter-related bacteremia.[11] In many transplant patients, especially those receiving renal transplantation, the urinary catheter is also a frequent source of bacteremia, and early removal of urinary catheterization is associated with a lower incidence of urinary tract infection.[12] Regarding other sources such as surgical site infection, prevention measures are the same as with other hospitalized patients. With respect to pneumococcal bacteremia, vaccination administered before transplantation is an effective preventive strategy in solid organ transplant patients.[13] In the case of listeriosis, we must identify those patients at risk, such as in the case of patients requiring high doses of steroids, and reintroduce cotrimoxazole prophylaxis.

Surgical site infection

The incidence rate of surgical site infection in liver transplant recipients is higher than that registered in other solid organ transplantations and is accompanied by notable morbidity and mortality.[14] It includes incisional and organ space infection, intra-abdominal abscesses and peritonitis.[15] In a recent Spanish study, surgical site infection occurred in nearly 9% of liver transplant recipients with a related mortality of 10%.[16] In this study, the most frequent etiologic agent was *Enterococcus* spp. followed by *Escherichia coli* and *S. aureus*. The risk factors associated to this complication were choledoc or hepatic-jejunostomy biliary reconstruction, a history of previous organ transplantation and the requirement for transfusion with four or more units of red blood cells during surgery.[16]

In renal transplant patients the incidence of surgical site infection reaches almost 4%, predominantly *E. coli* (32%), *Pseudomonas aeruginosa* (13%), *Enterococcus faecalis* (12%), *Enterobacter* spp. (10%) and coagulase-negative staphylococci (8%).[17] Pre-transplant diabetes and the use of mTOR inhibitors as immunosuppressants were associated with increased risk.[17]

In patients undergoing simultaneous kidney-pancreas transplantation the incidence of surgical site infection has been reported to be as high as 46%, and the main pathogens responsible are Gram-negative bacilli.[18] Identified risk factors include acute tubular necrosis, the development of post-transplant fistulae and graft rejection.[18]

In heart transplant recipients the incidence of incisional surgical site infection occurs in 5% of patients, predominantly Gram-positive cocci, although in some cases Gram-negative bacilli and *Candida* spp. may be isolated.[19] The most life-threatening complication in heart and/or lung transplant recipients is the development of mediastinitis, which occurs in 2%-7% of cases, with very high mortality.[19,20]

Lower respiratory tract infections: pneumonia

Pneumonia is a frequent cause of morbidity and mortality in solid organ transplant recipients, with a mortality rate of 30% when it appears during the first 3 months after transplantation,[21,22] and higher when it occurs during the first month.[23] Pneumonia in organ transplant recipients has a poorer prognosis when it is acquired during hospitalization.[6]

In liver transplant recipients, the etiology of pulmonary infiltrates is infectious in 48% of the cases, consisting predominantly of Gram-negative bacilli in the early post-transplant period, and mechanical ventilation and opportunistic infections after the first month post-transplantation.[22] In recent years, multidrug-resistant Gram-negative bacilli have emerged as causative agents for early pulmonary infections in liver transplant recipients, especially in patients with grade II-IV encephalopathy, who require prolonged orotracheal intubation and/or tracheostomy, and when a major surgical reintervention is required in the post-transplant period.[24] Pneumonia caused by multidrug-resistant Gram-negative bacilli has higher mortality rates than Gram-positive bacteria.[24]

In renal transplantation patients, the most frequent pneumonia-causing agents are *S. aureus*, *P. aeruginosa*, *Acinetobacter* spp. and *Haemophilus influenzae*.[21,25] Community-acquired pneumonia in renal transplant recipients is more frequently caused by *S. pneumoniae*.[26]

In lung transplant recipients the general incidence of respiratory tract infections, particularly pneumonia, is higher than in other solid organ transplant recipients, reaching an incidence rate of 72 cases per 100 lung transplants/year.[27] The most frequent etiological agent of pneumonia after lung transplantation is *P. aeruginosa*.[27]

Urinary tract infection

The urinary tract is the most frequent site of infection in renal transplant recipients, and its development is influenced by several factors, such as the presence of pre-transplantation diabetes, history of recurrent urinary tract infections, recipient's age, female gender and others.[28] The need for urinary catheterization in the post-transplant period is the main factor responsible for the high incidence of urinary tract infections after solid organ transplantation. The most

frequent etiologic agent is Gram-negative enteric bacilli, especially *E. coli* and *Klebsiella* spp., followed by *P. aeruginosa* and *Enterococcus* spp.[29] In recent years, a progressive increase in the rate of urinary tract infections caused by extended-spectrum beta-lactamase producing enteric bacilli has been noted in organ transplant recipients, and can reach around 20% of all cases.[30,31]

In solid organ transplant recipients other than renal, the pattern of urinary tract infections is similar to that of non-transplanted populations. However, renal transplant recipients can develop either acute graft pyelonephritis or infection of their own kidney, each infection with a specific management and prognosis.

Asymptomatic bacteriuria is associated with a much higher risk of renal transplant recipients developing acute pyelonephritis.[32] Cystitis is the most frequent infectious complication in organ transplantation patients. The most efficacious measure for its prevention is early withdrawal of urinary catheters. In general, a course of treatment for 7 to 10 days is recommended in the case of uncomplicated cystitis, with prolonged treatments (6 weeks) reserved for recurrent urinary tract infections.[33] The decision whether or not to treat asymptomatic bacteriuria in renal transplant recipients is still unresolved.

The development of acute graft pyelonephritis is associated with more frequent bacteremia and acute rejection induction, although its association with graft loss is controversial.[32,34,35] The severity of acute graft pyelonephritis from *E. coli* is associated with the expression of virulence factors (serotypes O:H, expression of P fimbriae and adhesins).[36]

Patients receiving kidney transplantation due to polycystic disease have more frequent urinary tract infections than patients receiving a transplant with other etiologies. Some authors have proposed bilateral nephrectomy during transplantation surgery to minimize the incidence of infectious complications.[37]

Empirical antibiotic therapy for urinary tract infections in solid organ transplant recipients depends on the antibiotic resistance rates of each center. In general, an antibiotic regimen active against *P. aeruginosa* is recommended in early infections (during the first month after transplantation). As the incidence of infection from enteric bacilli producing extended-spectrum beta-lactamases is high in these patients, an active drug against these isolates is recommended, especially in the case of severe infection.

Infections Caused by Multidrug-Resistant Bacteria

Epidemiology and risk factors

Antibiotic resistance is a global and dynamic process that leads us to constantly reevaluate the therapeutic regimens for the treatment of patients with infection. The use of inappropriate antimicrobial therapy or a delay in initiating appropriate therapy is associated with higher mortality in solid organ transplant recipients with bacterial infection.[38] Nearly 15% of bacteremic infections in solid organ transplant recipients develop septic shock, with a mortality higher than 50%.[3] Therefore, in order to initiate appropriate antibiotic therapy it is important to know the local rates of antimicrobial resistance. Moreover, to avoid the development of resistant strains, it is necessary to follow international recommendations for infection control (appropriate hand washing, contact isolation, antibiotic policy, etc.)

Infection with multidrug-resistant strains in organ transplant recipients may have several implications for the outcome of the graft and the patient. Infection is the second leading cause of death in renal transplant recipients, and the incidence rate of mortality related to bacterial infection in this group of patients has remained stable during the last decade.[39] Approximately 14% of patients with renal transplantation develop an infectious episode caused by multidrug-resistant bacteria in the post-transplant period, including enteric Gram-negative bacilli, non-fermentative Gram-negative bacilli, enterococci and *S. aureus*. The development of this complication is associated with poorer graft and patient survival.[40] Another important fact is that multidrug-resistant strains need to be treated with second or third line antibiotics that usually have considerable drawbacks: 1) less experience with their use; 2) higher incidence of adverse effects (renal toxicity such as aminoglycosides and colistin, neurologic toxicity such as colistin, etc.); and 3) sole availability of parenteral formulations (usually accompanied by prolonged hospital stay due to the impossibility of discharge).

Most infections with multidrug-resistant strains are acquired during hospitalization. However, most patients undergoing solid organ transplantation have chronic underlying diseases that lead to multiple hospital admissions and continuous contact with health care devices prior to transplantation (e.g. hemodialysis, outpatient parenteral antimicrobial therapy, etc.), increasing the risk of health-care associated infections that have a bacterial etiology closer to hospital than to community infections.[41] Pre-transplant colonization by multidrug-resistant strains (bowel, oral, etc.) may represent a major risk factor for infection with multidrug-resistant bacteria in the post-transplant period.

Diagnosis of multidrug-resistant bacterial infection

It is essential for the microbiology laboratory to make a correct diagnosis to identify the etiologic agent, the epidemiology of the infection, the possible pathogenic role of the organism and the clinical aspects of infection, in order to select the most optimal antibiotics. There are several steps required to correctly identify isolated bacteria.[42] Traditional methods are based on the phenotypic characteristics of the bacteria. These are based on the bacteria's "visible" characteristics, such as morphology, growth conditions, biochemical and metabolic properties. It is important to consider that isolation of bacteria in the culture media is essential, as this will allow for its identification and the study of its sensitivity to antimicrobials, as well as to obtain information on epidemiological molecular markers. The majority of multidrug-resistant bacteria implicated in hospital infections (Table 1) usually grow in ordinary culture media at a temperature of 37°C in a conventional aerobic atmosphere.

However, definitive identification may not be possible using phenotypic methods because there is sometimes a lack of correlation between the phenotypic characteristics of the strain and those observed in the pattern strain. Identification is also complicated by the apparent lack of biochemical reactivity of some bacterial species, the variability of phenotypic expression of some isolates and database limitations. Therefore, molecular and genotypic methods have been progressively introduced as complementary or alternative procedures. Using these methods, a wide variety of genes have been used as molecular targets in phylogeny and taxonomic studies, with the most important being ARNr 16S. Other molecular markers include the 16S-23S rRNA intergenic spacer and the genes 23S rRNA, rpoB and gyrB. However, molecular methods are expensive and require specialized personnel.

Multidrug-resistant bacteria of greater clinical impact (Table 1) are easily identified by phenotypic methods, so only in very specific situations is there a need for diagnosis by molecular methods.

Proteomics-based methods have recently emerged in microbiology laboratories, improving the microbiological diagnosis of isolates. Proteomics is the study and characterization of all proteins expressed by a genome (proteome). One of the most widely used techniques in proteomics is mass spectrometry, a technique used to analyze the precise chemical composition of different elements by measuring their molecular ions, separating them according to their mass/charge (m/z). The acronym MALDI-TOF is derived from the terms Matrix-Assisted Laser Desorption/Ionization and Time of Flight. One of its

Table 1
Multidrug-resistant bacteria (MDR)

Bacteria	Multidrug-resistant bacteria
Gram-positive	
Staphylococcus aureus	*S. aureus* resistant to methicillin (MRSA) is considered by itself as MDR. The isolate is not sensitive to at least 1 antibiotic in a number equal to or more than 3 categories of antimicrobials[a]
Enterococcus spp.	The isolate is not sensitive to at least 1 antibiotic in a number equal to or more than 3 categories of antimicrobials[b]
Gram-negative	
Enterobacteriaceae	The isolate is not sensitive to at least 1 antibiotic in a number equal to or more than 3 categories of antimicrobials[c]
Pseudomonas aeruginosa	The isolate is not sensitive to at least 1 antibiotic in a number equal to or more than 3 categories of antimicrobials[d]
Acinetobacter baumannii	The isolate is not sensitive to at least 1 antibiotic in a number equal to or more than 3 categories of antimicrobials[e]

[a]*Staphylococcus aureus*: aminoglycosides (gentamicin), rifampin, anti-MRSA cephalosporins (ceftaroline), beta-lactam anti-staphylococcal (or cephamycins), fluoroquinolones (ciprofloxacin, levofloxacin), trimethoprim-sulfamethoxazole, fusidic acid, glycopeptides (vancomin, teicoplanin, telavancin), tigecycline, clindamycin, daptomycin, eritromycin, linezolid, chloramphenicol, fosfomycin, quinupristin-dalfopristin, and tetracyclines (tetracycline, doxicycline, and minocycline).
[b]*Enterococcus* spp.: high levels of resistance to gentamicin and streptomycin, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), glycopeptides (vancomycin, teicoplanin), tigecycline, daptomycin, linezolid, ampicillin, quinupristin-dalfopristin and tetracyclines (doxycycline, minocycline). When a species has intrinsic resistance to an antibiotic such as carbapenems in *E. faecium*, or quinupristin-dalfopristin with *E. faecalis*, this category is removed in order to calculate the estimated number of categories to which the bacterial isolate is not sensitive.
[c]*Enterobacteriaceae*: aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin), anti-MRSA cephalosporins (ceftaroline), penicillin inhibitors (ticarcillin-clavulanate, piperacillin-tazobactam), carbapenems (imipenem, meropenem, ertapenem, doripenem), 1st and 2nd generation cephalosporins (cefazoline, cefuroxime), 3rd and 4th generation cephalosporins (cefotaxime, ceftazidime, cefepime), cephamycins (cefoxitin and cefotetan), ciprofloxacin, trimethoprim-sulfamethoxazole, tigecycline, aztreonam, ampicillin, penicillin and inhibitors (amoxicillin-clavulanate , ampicillin-sulbactam), chloramphenicol, fosfomycin, and colistine. When a species has intrinsic resistance to an antibiotic, such as in the case of colistine and *M. morganii, Proteus* spp., *P. stuartii* and *S. marcescens*, this category is removed in order to calculate the estimated number of categories to which the bacterial isolate is not sensitive.
[d]*Pseudomonas aeruginosa*: aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin), carbapenems (imipenem, meropenem, doripenem), antipseudomonal cephalosporins (ceftazidime, cefepime), fluoroquinolones (ciprofloxacin, levofloxacin), penicillin inhibitors (ticarcillin-clavulanate, piperacillin-tazobactam), aztreonam, fosfomycin, and polymyxins (colistin and polymyxin B).
[e]*Acinetobacter baumannii*: aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin), carbapenems (imipenem, meropenem, doripenem), extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime), fluoroquinolones (ciprofloxacin, levofloxacin), penicillin plus inhibitor (ampicillin-sulbactam), trimethoprim-sulfamethoxazole, tetracyclines (tetracycline, doxycycline, minocycline) and polymyxins (colistin and polymyxin B).

main applications is the identification of microorganisms. At present there are different MALDI-TOF platforms for microbial identification. Most conventional bacteria responsible for human diseases are very accurately identified by MALDI-TOF systems, which also identify multidrug-resistant isolates. The main advantage over conventional phenotypic methods is rapid diagnosis, capable of identifying species within minutes.

Usually carried out in a microbiology laboratory, the determination of the multidrug-resistant phenotype is inferred from the data regarding sensitivity to various antibiotics, using highly standardized methods such as disk diffusion, antibiotic gradient strips (such as E-test), agar dilution and microdilution, usually by automated processes. Among the most important break points used in the interpretation of antimicrobial susceptibility are those indicated by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Multidrug-resistant bacteria with greater clinical impact are described in Table 1. The criteria recently reviewed by Magiorakos, et al.[43] to define multidrug resistance is detailed at the bottom of Table 1.

Infection by multidrug-resistant Gram-positive bacteria

1. Methicillin-resistant *Staphylococcus aureus* (MRSA): *S. aureus* is the second-leading etiological cause of bacteremia in the population,[44] and the leading cause of nosocomial bacteremia in Europe.[45] In solid organ transplant recipients, however, *S. aureus* is the sixth-leading cause of bacteremia after the coagulase-negative staphylococci, *E. coli*, *A. baumanii*, *P. aeruginosa* and *Enterococcus* spp.[4] Nevertheless, *S. aureus* in liver transplant recipients is associated with very high mortality.[46] The most frequent source of MRSA infections is nasal colonization, present in 1.5%-3% of the general population. In liver transplant recipients, the incidence of nasal colonization has reached 43%-44% in some studies.[47,48] In addition to nasal colonization, bowel colonization by *S. aureus* can be a potential source of infection in critically-ill patients.[49] There is no doubt that nasal colonization is the main risk factor for MRSA infection in the post-transplant period.[50,51] Patients who underwent a liver transplantation with nasal colonization with MRSA had an increased risk of infection with this bacteria (OR 15.6; CI 95% 6.6-36.9), although the presence of nasal colonization was not associated with an increase in mortality.[52] A surveillance study of liver transplant recipients who had nasal colonization with MRSA, in which patients were treated with topical mupirocin, found the rates of infection decreased from 40.4% to 4.1% and the rate of bacteremia decreased from 25.5% to 4.1%.[53] However, the results of this control strategy are controversial, and one study did not find a decrease in MRSA infection in patients with nasal colonization by mupirocin-susceptible strains treated with topical mupirocin, mainly due to nasal re-colonization.[48]

2. Vancomycin-resistant enterococci: enterococci are an emerging cause of infection in solid organ transplant recipients. Therapeutic options for the treatment of vancomycin-resistant *E. faecium* are limited in many cases to the use of linezolid and daptomycin. A recent report of a new mechanism associated with resistance to daptomycin in strains of vancomycin-resistant enterococci has increased concern regarding the treatment for these bacteria.[54] Although the incidence of infections by vancomycin-resistant *E. faecium* in Spain is very low, there is the likelihood of a significant increase in the future.[55] Most infections by vancomycin-resistant enterococci occur in patients with previous colonization by these bacteria. Liver transplant recipients with pre-transplant colonization of vancomycin-resistant enterococci have an increased risk of infection by these bacteria (OR 3.6; 95% CI 2.0-6.5) and colonization was associated with higher mortality (OR 2.1; 95% CI 1.3-3.5).[52]

Gram-negative bacilli infection caused by extended-spectrum beta-lactamases (ESBL) or chromosomic beta-lactamases (AmpC)

Gram-negative bacilli with resistance to cephalosporins due to extended-spectrum or chromosomic beta-lactamases represent a

major cause of hospital infections, although there are increasing reports of community-acquired infections. *E. coli* and *Klebsiella pneumoniae* are the main pathogens producing extended-spectrum beta-lactamases (ESBL), and *Enterobacter* spp., *Citrobacter freundii* and *Morganella morganii* usually express inducible chromosomal beta-lactamases (AmpC). These bacteria are resistant to penicillin and cephalosporins and are susceptible to carbapenems. Usually they have other mechanisms of resistance (e.g., DNA gyrase mutations conferring resistance to quinolones, etc.). Tigecycline, aminoglycosides and colistin are effective against these bacteria. ESBL-producing *E. coli* is usually susceptible to nitrofurantoin; however many strains of *Klebsiella* spp. are intrinsically resistant to this antibiotic.

One of the most important risk factors for *Enterobacteriaceae* infection from ESBL or AmpC is bowel colonization. One study of hospitalized patients during an outbreak of ESBL-producing *K. pneumoniae* infection showed a 38% incidence of colonization in an intensive care unit,[56] with the most important risk factors being clinical severity at admission, arterial catheterization, parenteral nutrition, urinary catheterization, mechanical ventilation and previous antibiotic treatment.[56] In Spain, a dramatic increase in bowel colonization by these bacteria has been found in non-epidemic periods and in outpatients.[57] In organ transplant patients, epidemiological information is scarce. One study showed a 14% incidence of pre-transplant bowel colonization by ESBL-producing *E. coli* in renal transplant patients, which resulted in higher risk of infection.[58] In another study of hospitalized patients, having renal transplantation was an independent risk factor for developing bacteremic infection by ESBL-producing *E. coli* or *Klebsiella* spp.[59] Moreover, patients admitted to a renal transplant unit had higher risk of infection by ESBL-producing enteric bacilli with quinolone-associated resistance.[60] In the pediatric renal transplantation population, ESBL-producing *E. coli* has been shown to be the most frequent etiologic agent of infection, especially urinary.[61] Although data are scarce, renal transplant recipients seem to be at higher risk of infection with these bacteria, especially in the cases of simultaneous pancreas transplantation, previous use of antibiotics, post-transplant dialysis and post-transplant urinary obstruction.[30]

The best prevention for these infections is to apply the measures recommended for hospitalized patients, such as hand washing. While ESBL-producing *K. pneumoniae* strains are highly transmissible, it seems that most ESBL-producing *E. coli* strains are much less contagious, thus many centres do not apply isolation measures to patients infected with ESBL-producing *E. coli*.[62] Patients infected with ESBL-*K. pneumoniae* must always be admitted under contact isolation. Carbapenems are the cornerstone of treatment for these infections. We should administer an aminoglycoside in hemodynamically unstable or critically ill patients. Other therapeutic options include tigecycline, and cotrimoxazole, quinolones, nitrofurantoin and fosfomycin in the case of proven susceptibility.

Infection by multidrug-resistant non-fermentative Gram-negative bacilli

The most important non-fermentative Gram-negative bacilli species causing diseases in organ transplant recipients are *P. aeruginosa, Acinetobacter baumanii* and *Stenotrophomonas maltophilia*. *P. aeruginosa* is a highly virulent, aggressive and drug-resistant microorganism due to its constitutive expression of beta-lactamases and efflux pumps, combined with the low permeability of its outer membrane and a high ability to generate acquired antibiotic resistance.[63] Non-fermentative Gram-negative bacilli mainly cause hospital infections.

P. aeruginosa is the fourth-leading microorganism causing bloodstream infections in solid organ transplant recipients.[4] *P. aeruginosa* represents 14% of bacteremia in patients with renal, 6.5% of liver, 5% of pancreas and 6% of lung transplantation.[4] This rate of bacteremia is similar to that reported 13 years ago, in which *P. aeruginosa* was responsible for nearly 15% of all bloodstream infections.[64] In liver transplant recipients, *P. aeruginosa* is the cause of approximately 6% of surgical site infections[16] and 18% of nosocomial pneumonia cases.[6] In lung transplant recipients, *P. aeruginosa* caused 25% of post-transplant pneumonia cases.[27]

Multidrug-resistant *A. baumanii* is a common cause of epidemic outbreaks of severe infection in patients admitted to the intensive care unit. It is currently the third-leading cause of bloodstream infection in transplant patients in Spain, and is responsible for 3% of bacteremia in renal, 14% in liver, 16% in pancreas, 3% in heart and 12% in lung transplant recipients.[4] It is a frequent cause of surgical site infection in liver transplant recipients, and is responsible for about 13% of the cases[16] and in lung transplant recipients of 14% of the cases of pneumonia with microbiological diagnosis.[27]

Stenotrophomonas maltophilia is the cause of 1% of all bacteremia in solid organ transplant recipients.[4] This microorganism usually appears in critically ill patients on treatment with carbapenems. It has been recognized as the causative agent for several types of infections, but typically it causes bacteremia and pneumonia. *S. maltophilia* is a multidrug-resistant bacteria.

It must be taken into account that bloodstream infection with multi-drug non-fermentative Gram-negative bacilli in solid organ transplant patients is associated with higher mortality compared with bacteremia caused by non-multidrug-resistant counterparts.[4]

Prevention of infection with non-fermentative bacilli is always based on isolation measures and appropriate hand washing. To prevent the emergence of multidrug-resistant strains it has been shown that restricted use of quinolones and antibiotic schedule rotation are useful measures in intensive care.[65] The treatment of these infections should always be guided by antibiogram, watching for possible pharmacological interactions and monitoring side effects of the treatment, especially renal toxicity with the use of aminoglycosides or colistin. Colistin has been considered a highly nephrotoxic antibiotic, however, recent studies demonstrate that colistin is less toxic than it was once believed.[66] Cotrimoxazole is the drug of choice to treat infections caused by *S. maltophilia*.

Clostridium Difficile **Infections**

The incidence of *Clostridium difficile*-associated diarrhea in hospitalized patients has been progressively increasing in frequency.[67] Many factors have contributed to this increase, such as the massive use of broad-spectrum antibiotics, the increase in the population of fragile and immunosuppressed patients, and the widespread use of proton pump inhibitors.[68] Other microbiological and environmental factors have been described that may also explain this increase.[68]

From an epidemiological and clinical point of view, *C. difficile* infection and *C. difficile*-associated diarrhea must be differentiated. Infection is defined as the isolation of *C. difficile* toxin in faeces without considering the clinical symptoms of the patient. *C. difficile*-associated disease symptoms can vary from mild to severe diarrhea and toxic megacolon, including the classical picture of pseudomembranous colitis with high associated mortality.[69] In recent years, a new strain of *C. difficile* producing a hypervirulent type III ribotype O27 has been described in the U.S.A. and Canada reaching a mortality rate up to 20% in the 30 first days after diagnosis.[70]

The increasing incidence of *C. difficile*-associated disease in organ transplant patients is of concern.[71] A prospective study of liver transplant recipients with active surveillance of toxin A and B in feces detected the presence of the toxin in 8% of patients, almost all of whom developed *C. difficile*-associated diarrhea during the first year post-transplant.[72] Another study of recipients of kidney and simultaneous kidney-pancreas transplantation in adult and pediatric populations showed an incidence of 3.5% in adults and 16% in

pediatric patients.[73] In lung transplant patients the incidence of positive toxin has been reported to be 7.4%, and all had a history of previous hospital admission, use of antibiotics and increased steroid dosages.[74] In intestinal transplantation recipients the incidence of *C. difficile*-associated diarrhea occurred in 23% of patients with post-transplant diarrhea, representing 9% of all intestinal transplant patients.[75]

Regarding treatment, a possible interaction between tacrolimus and metronidazole must be considered,[76] but this interaction probably has little relevance in clinical practice. *C. difficile*-associated diarrhea can be treated with oral metronidazole for 10 to 14 days with good clinical response in most cases. For patients with severe diarrhea the use of oral vancomycin for 10-14 days is recommended.[67] Recurrences should be treated with tapering doses of vancomycin, rifaximin or intravenous immunoglobulins.[67]

Other Bacterial Infections Including Opportunistic Bacteria

Nocardia

Nocardia spp. belongs to the group of aerobic actinomycetes, a group of Gram-positive bacteria with the appearance of filamentous ramified cells.[77] Of 16 species causing disease in humans, *Nocardia asteroides*, *N. brasiliensis*, *N. farcinica* and *N. nova* are the most frequently isolated. *Nocardia* is considered an opportunistic pathogen and usually causes disease in immunosuppressed patients, with solid organ transplantation as one of the main risk factors. A Spanish study carried out in a single centre reviewed 27 cases of nocardiosis over a 7-year period in immunosuppressed patients and in those with chronic pulmonary disease, of which 3 cases (11%) occurred in solid organ transplant recipients.[78] Pulmonary disease is the most frequent clinical presentation (more than 40% of reported cases), and includes endobronchial inflammatory masses, pneumonia, lung abscess and cavitary lesions that can evolve into pleural effusion and empyema.[77] After a diagnosis of nocardiosis, the possibility of concurrent central nervous system involvement should always be considered, even in patients without neurological symptoms. In a large series of nocardiosis cases, central nervous system involvement occurred in 44%.[79] In the very early development of transplant programs, cases of infection in solid organ transplant patients with *Nocardia* spp. were described. A case-control study published in 1981 identified 21 cases of nocardiosis in heart transplant recipients in one hospital.[80] The use of systematic prophylaxis with cotrimoxazole for the prevention of *Pneumocystis jirovecii* pneumonia contributed to a decrease in the incidence of this disease. However, for the prevention of *Pneumocystis jirovecii* pneumonia, cotrimoxazole prophylaxis at the standard dose may be insufficient to prevent nocardiosis in all cases.[81]

Rhodococcus equi

Rhodococcus equi are Gram-positive bacilli that usually grow well in all culture media, and the infection usually involves the lungs in immunosuppressed patients, although some atypical cases of paravertebral abscesses and purulent pericarditis in patients with transplantation have been described.[82] In a review of 30 published cases of *R. equi* infection in transplant patients, except for one case of bone marrow transplantation, almost all cases occurred in solid organ transplant recipients, with renal and heart transplantation being the most common. Frequently, this infection appears in later post-transplant phases, with a median of 49 months post-transplantation.[83] Interestingly, 43% of patients required surgical resection of pulmonary lesions, but the cure rate of this complication was very high (88% of cases).[83] Several antibiotic combinations have been proposed for the treatment of this infection such as vancomycin and levofloxacin or imipenem; or rifampin and eritromicin or imipenem. Another promising option is the use of linezolid, which can allow for a prolonged treatment if the drug is well tolerated. Its efficacy has been shown in a case of recurrent infection in a heart transplantation patient.[84]

Listeria monocytogenes

Listeriosis is usually a late opportunistic infection after solid organ transplantation. As previously noted, infection by *L. monocytogenes* usually causes bacteremia and meningitis,[8] although it is currently not a frequent infection after solid organ transplantation due to the generalized use of prophylactic cotrimoxazole. In liver transplant recipients 15 cases of listeriosis have been described with a related mortality of 14%.[85] In other types of organ transplantation the evidence is limited to isolated published cases. The prevention of listeriosis in solid organ transplant recipients is based on the administration of cotrimoxazole for 6 to 12 months after transplantation and in those patients who require additional immunosuppression (especially with high doses of steroids) in any post-transplant period.

Legionella pneumophila

Several cases of sporadic infections from *Legionella pneumophila* have been described in liver,[86,87] heart and/or lung,[88,89] and renal[90] transplant recipients. In one series of pneumonia in these patients, *L. pneumophila* represented 2.4% of cases[6]. Usually, the development of *L. pneumophila* pneumonia was considered to be hospital-acquired. One study demonstrated that 5.3% of renal, 12.2% of liver and 7.5% of pancreas transplant recipients had DNA of *L. pneumophila* in oropharingeal samples just before transplantation. Although all patients received ciprofloxacin before surgery, 3 out of 47 patients with positive DNA developed *L. pneumophila* pneumonia in the post-transplant period.[91] *Legionella* infection may be difficult to diagnose due to the coexistence of other infections, thus this pathogen must be included in the differential diagnosis of the febrile patient with solid organ transplantation.[89]

Conflicts of interest

The authors declare that they have no conflicts of interest.

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