

# Multidrug-resistant bacteria in solid organ transplant recipients

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## Abstract

Bacteria are the leading cause of infections after solid organ transplantation. In recent years, a progressive growth in the incidence of multidrug-resistant (MDR) and extensively-drug-resistant (XDR) strains has been observed. While methicillin-resistant *Staphylococcus aureus* (MRSA) infection is declining in non-transplant and SOT patients worldwide, vancomycin-resistant enterococci, MDR/XDR Enterobacteriaceae and MDR/XDR non-fermenters are progressively growing as a cause of infection in solid organ transplant (SOT) patients and represent a global threat. Some SOT patients develop recurrent infections, related to anatomical defects in many cases, which are difficult to treat and predispose patients to the acquisition of MDR pathogens. As the antibiotics active against MDR bacteria have several limitations for their use, which include less clinical experience, higher incidence of adverse effects and less knowledge of the pharmacokinetics of the drug, and, in most cases, are only available for parenteral administration, it is mandatory to know the main characteristics of these drugs to safely treat SOT patients with MDR bacterial infections. Nonetheless, preventive measures are the cornerstone of controlling the spread of these pathogens. Thus, applying the Center for Disease Control and Prevention's and the European Society of Clinical Microbiology and Infectious Diseases's recommended antibiotic policies and strategies to control the transmission of MDR strains in the hospital setting is essential for the management of SOT patients.

**Keywords:** MDR Enterobacteriaceae, MDR non-fermenters, MRSA, multidrug-resistant bacteria, solid organ transplantation, vancomycin-resistant enterococci

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## Hot Topics

- A bacterial strain is defined as multidrug resistant (MDR) when it is not susceptible to one or more agents in three or more antimicrobial categories active against the isolated bacteria.
- To prevent the acquisition of MDR strains during hospitalization, the procedures recommended by the Center for Disease Control and Prevention (CDC) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines should be applied.
- In addition to antibiotic treatment, which is unavoidable in most solid organ transplantation (SOT) recipients, certain features related to the surgical technique of the transplantation alter the risk of bacterial infection.
- While methicillin-resistant *Staphylococcus aureus* (MRSA) infection is declining in non-transplant and SOT patients worldwide, vancomycin-resistant enterococci, MDR/extensively-drug resistant (XDR) Enterobacteriaceae and MDR/XDR non-fermenters are progressively growing as a cause of infection in SOT patients and represent a global threat.
- Some SOT patients develop recurrent infections, related to anatomical defects in many cases, which are difficult to treat

and predispose patients to the acquisition of MDR pathogens.

- The antibiotics active against MDR bacteria have several limitations for their use, which include less clinical experience, higher incidence of adverse effects and less knowledge of the pharmacokinetics of the drug, and, in most cases, are only available for parenteral administration. It is mandatory to know the main characteristics of these drugs to safely treat SOT patients with MDR bacterial infections.

## Main Characteristics of MDR Bacterial Infection after SOT

### Recommendations

- To prevent the acquisition of MDR strains during hospitalization, the procedures recommended by the CDC should be applied (A-I).
- For empirical treatment of suspected bacterial infections in SOT patients, the selection of antimicrobial agents should be based on local epidemiological data and on the patient's history of colonization or infection with antibiotic-resistant organisms (A-II).

### General principles, definitions and risk factors for MDR bacterial infection after solid organ transplantation

Bacteria are the leading cause of infections after solid organ transplantation (SOT). After the surgical procedure, transplant patients should remain in the hospital for a period of time, which varies according to the type of allograft, previous existence of co-morbidities, the underlying disease responsible for transplantation and the development of complications. During prolonged hospitalization, most patients receive broad-spectrum antibiotics and some develop infections with multidrug-resistant (MDR) bacteria. The use of central line and urinary catheters, parenteral nutrition and prolonged intubation and the need for renal replacement therapy all increase the risk of this complication.

The most widely accepted definition of MDR includes lack of susceptibility to one or more agents in three or more antimicrobial categories active against the isolated bacteria (Table 1) [1]. In the case of *S. aureus*, methicillin resistance on its own defines the strain as MDR, regardless of resistance to other antimicrobials. Many transplant patients may be infected with extensively-drug resistant (XDR) bacteria, which is defined as susceptibility to no more than two classes of active categories of antimicrobials (Table 1) [1]. In recent years, certain bacterial strains have shown a lack of susceptibility to

all the active drugs for treating the microorganism; in this case, the isolated bacterium is defined as pan-drug resistant (PDR). A group of six organisms representing the paradigm of pathogenesis, transmission and potential antibiotic resistance have been recently defined and labeled as the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) [2,3]. As identifying novel antimicrobial agents with reliable activity against these pathogens is very difficult, special efforts to identify optimal strategies for infection control and antimicrobial use are warranted.

Multidrug-resistant organisms lead to increased use of hospital resources due to extended hospital stays, more frequent physician consultations and laboratory tests, and costly medications [4]. Specifically, their presence increases the costs derived from solid organ transplantation (SOT). In addition, MDR bacterial infection jeopardizes patient and graft survival. Infection is the second leading cause of death in renal transplant recipients, and the incidence of mortality related to bacterial infection in this group of patients has remained stable over the last decade [5]. Approximately 14% of patients with renal transplantation develop an infectious episode caused by MDR bacteria in the post-transplant period, including enteric Gram-negative bacilli, non-fermentative Gram-negative bacilli, enterococci and *S. aureus* [6]. This complication is associated with poorer graft and patient survival [6]. One of the greatest dangers when treating an SOT patient with fever and risk of MDR bacterial infection is the use of inappropriate empirical antibiotic therapy. Several studies have demonstrated an increase in mortality when bacteraemic patients with MDR pathogens receive inappropriate treatment [7,8]. In one retrospective cohort study evaluating empirical antibiotic therapy in SOT patients, inappropriate antibiotic therapy was administered to 54% of patients, resulting in a 3.5-fold increase in mortality compared with those receiving adequate therapy [9]. Therefore, in order to initiate appropriate antibiotic therapy it is important to know the local rates of antimicrobial resistance. Early therapy may also reduce the mortality associated with severe sepsis and septic shock, which occur in nearly 15% of bacteraemic infections in SOT recipients and have a mortality rate of 50% [10].

There are two main strategies for the prevention of MDR transmission in the hospital [11]. Vertical infection-prevention strategies are designed to reduce colonization or infection due to a specific pathogen; they involve a microbiological screening test and carry high resource utilization, direct costs and opportunity costs [12]. Horizontal strategies are population-based, applied universally, and use interventions effective in controlling all pathogens transmitted by means of

**TABLE 1.** Definitions of multidrug-resistant (MDR), extensively-drug-resistant (XDR) and pan-drug-resistant (PDR) bacteria (adapted from Magiorakos et al. [1])

<i>S. aureus</i>	<i>Enterococcus spp.</i>	<i>Enterobacteriaceae</i>	<i>P. aeruginosa</i>
Active agents: Antimicrobial category (agents) <ul style="list-style-type: none"> <li>• Aminoglycosides (gentamicin)</li> <li>• Ansamycins (rifampin/rifampicin)</li> <li>• Cephalosporins (ceftaroline)</li> <li>• Anti-staphylococcal <math>\beta</math>-lactams (oxacillin)</li> <li>• Cephamycins (cefoxitin)</li> <li>• Fluorquinolones (cipro/moxifloxacin)</li> <li>• Folate pathway inhibitors (sulfamethoxazole-trimethoprim)</li> <li>• Fucidanes (fusidic acid)</li> <li>• Glycopeptides (vancomycin, teicoplanin, telavancin)</li> <li>• Glycylcyclines (tigecycline)</li> <li>• Lincosamides (clindamycin)</li> <li>• Lipopeptides (daptomycin)</li> <li>• Macrolides (erythromycin)</li> <li>• Oxazolidinones (linezolid)</li> <li>• Phenolics (chloramphenicol)</li> <li>• Phosphonic acids (fosfomicin)</li> <li>• Streptogramins (quinupristin-dalfopristin)</li> <li>• Tetracyclines (tetracycline, doxycycline, minocycline)</li> </ul>	Active agents: Antimicrobial category (agents) <ul style="list-style-type: none"> <li>• Aminoglycosides, except streptomycin (high-level resistance gentamicin)</li> <li>• Streptomycin (high-level resistance streptomycin)</li> <li>• Carbapenems (imipenem, meropenem, doripenem)</li> <li>• Fluorquinolones (ciprofloxacin, levofloxacin, moxifloxacin)</li> <li>• Glycopeptides (vancomycin, teicoplanin)</li> <li>• Glycylcyclines (tigecycline)</li> <li>• Lipopeptides (daptomycin)</li> <li>• Oxazolidinones (linezolid)</li> <li>• Penicillins (ampicillin)</li> <li>• Streptogramins (quinupristin-dalfopristin)</li> <li>• Tetracycline (doxycycline, minocycline)</li> </ul>	Active agents: Antimicrobial category (agents) <ul style="list-style-type: none"> <li>• Aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin)</li> <li>• Anti-MRSA cephalosporins (ceftaroline)</li> <li>• Anti-pseudomonal penicillins + <math>\beta</math>-lactamase inhibitors (ticarcillin-clavulanic acid, piperacillin-tazobactam)</li> <li>• Carbapenems (imipenem, meropenem, ertapenem, doripenem)</li> <li>• Non-extended spectrum cephalosporins; 1st and 2nd generation cephalosporins (cefazolin, cefuroxime)</li> <li>• Extended-spectrum cephalosporins; 3rd and 4th generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime)</li> <li>• Cephamycins (cefoxitin, cefotetan)</li> <li>• Fluorquinolones (ciprofloxacin)</li> <li>• Folate pathway inhibitors (sulfamethoxazole-trimethoprim)</li> <li>• Glycylcyclines (tigecycline)</li> <li>• Monobactams (aztreonam)</li> <li>• Penicillins (ampicillin)</li> <li>• Penicillins + <math>\beta</math>-lactamase inhibitors (amoxicillin-clavulanic acid, ampicillin-sulbactam)</li> <li>• Phenolics (chloramphenicol)</li> <li>• Phosphonic acids (fosfomicin)</li> <li>• Polymyxins (colistin)</li> <li>• Tetracyclines (tetracycline, doxycycline, minocycline)</li> </ul>	Active agents: Antimicrobial category (agents) <ul style="list-style-type: none"> <li>• Aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin)</li> <li>• Anti-pseudomonals carbapenems (imipenem, meropenem, doripenem)</li> <li>• Anti-pseudomonals cephalosporins (ceftazidime, cefepime)</li> <li>• Anti-pseudomonals fluorquinolones (ciprofloxacin, levofloxacin)</li> <li>• Anti-pseudomonal penicillins + <math>\beta</math>-lactamase inhibitors (ticarcillin-clavulanic acid, piperacillin-tazobactam)</li> <li>• Monobactams (aztreonam)</li> <li>• Phosphonic acids (fosfomicin)</li> <li>• Polymyxins (colistin polymyxin B)</li> </ul>
Criteria for multidrug-resistant (MDR): non-susceptible to $\geq 1$ agent in $\geq 3$ antimicrobial categories or methicillin resistance in the case of <i>S. aureus</i> . Criteria for extensively drug-resistant (XDR): non-susceptible to $\geq 1$ agent in all but $\leq 2$ categories. Criteria for pan-drug-resistant (PDR): non-susceptible to all the antimicrobials.			

the same mechanism. Horizontal interventions include hand hygiene, chlorhexidine bathing and care bundles [11]. In the transplant population, as the risk of acquiring MDR pathogens is higher than in other hospitalized patients, both strategies are probably required to control the spread of these microorganisms. During admission the international recommendations for infection control should be followed (appropriate hand washing, contact isolation, antibiotic policy, and so on). In the case of catheter-related bacteraemia, the application of the evidence-based procedures recommended by the CDC [13] (hand-washing, the use of full-barrier precautions during the insertion of central venous catheters avoiding the femoral site, cleaning the skin with chlorhexidine, and removing unnecessary catheters) has been shown to diminish the risk of catheter-related bacteraemia [14]. In addition, improved hand hygiene plus unit-wide chlorhexidine body-washing reduces acquisition of antimicrobial-resistant bacteria in the intensive care unit [15]. Here, vertical

prevention strategies for each MDR microorganism will be discussed. Finally, limiting unnecessary uses of antimicrobial agents through multidisciplinary stewardship programmes is critical to minimize the emergence of MDR bacteria in solid organ transplant patients, as has been proved in non-transplant hospitalized patients.

Multidrug-resistant infections can be acquired by the recipient through the donor's graft in the setting of organ transplantation. Although this issue is addressed in another chapter of this monograph, it should be noted that transmission of MDR bacteria through the donor may be difficult to diagnose, leading to delayed treatments and high mortality. Proper diagnosis and treatment of a donor's infection and accurate screening of the preservation fluid for bacterial or fungal colonization is essential to prevent this complication.

Another important point is the fact that MDR strains have to be treated with second- or third-line antibiotics, the use of

which tends to present major difficulties. First, physicians have less experience with their use. Second, the incidence of adverse effects is high (renal toxicity in the case of aminoglycosides and colistin, neurological toxicity in the case of colistin, etc.). Third, they are available only in parenteral formulations (usually accompanied by a prolonged hospital stay due to the impossibility of discharge). In general, little is known about the pharmacokinetics and pharmacodynamics of these second-line drugs. In addition, as in many cases the serum levels of the drug cannot be monitored, dosing has to be based on data obtained from clinical cohorts. The incidence of adverse effects using second-line antibiotics may be increased in SOT patients because of the concomitant use of nephrotoxic agents (such as calcineurin inhibitors), decreased glomerular filtration rate in most SOT patients, or because of the need for renal replacement therapies. Finally, infection with MDR pathogens increases the length of hospitalization [16], which in turn increases the risk of additional hospital-acquired infections.

#### **Main principles of the microbiological diagnosis of MDR bacterial infections in SOT patients**

In order to optimize the management of patients with bacterial infection the isolation of the responsible strain is important, and in organ transplant patients with a suspected infection with an MDR pathogen this is mandatory. This will allow not only its identification and the study of antimicrobial susceptibility, but also the obtaining of information on epidemiological molecular markers. The majority of MDR bacteria implicated in SOT infections (Table 1) usually grow in ordinary culture media at a temperature of 37°C, in a conventional aerobic atmosphere.

The determination of the MDR 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).

Proteomics-based methods have recently emerged in microbiology laboratories, improving the microbiological diagnosis of isolates. One of the most widely used techniques in proteomics is mass spectrometry, a technique used to analyse the precise chemical composition of different elements by measuring their molecular ions, separating them according to their mass/charge. The acronym MALDI-TOF is derived from the terms matrix-assisted laser desorption/ionization and time of flight. One of its 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 multi-drug-resistant isolates. The main advantage over conventional phenotypic methods is the ability to obtain rapid diagnosis, capable of identifying species within minutes.

An additional issue in the diagnosis of infection with MDR organisms is the possibility of heteroresistance, defined as the presence of mixed populations of drug-resistant and drug-sensitive strains in a single clinical specimen. *Staphylococcus aureus* is the species in which heteroresistance has been described more often, especially to vancomycin [17]. Heteroresistance has been described also for vancomycin in *E. faecium* [18], colistin and meropenem in carbapenemase-producing *K. pneumoniae* [19,20], polymyxin-B in carbapenem-resistant *P. aeruginosa* [21] and colistin in *A. baumannii* [22], among others. The clinical consequences of heteroresistance have been mainly evaluated for heteroresistant vancomycin-intermediate *S. aureus*, which is associated with prolonged bacteraemia duration, greater rates of complications, and emergence of rifampin resistance [23]. The reference standard for the diagnosis of heteroresistance requires a population analysis profile, which is labour intensive, costly and unsuitable for routine use in daily practice. Other techniques for diagnosis are being evaluated to improve the practicability of heteroresistance diagnosis [24].

#### **Surgical features according to type of allograft and their involvement in the development of MDR infection**

Most SOT patients require central venous lines, urinary catheterization, abdominal drainages or mechanical ventilation, which are all sources of bacterial infection. In addition, the use of broad-spectrum antibiotics is unavoidable in the majority of patients. All these issues are common to all SOT recipients. However, certain features related to the surgical technique alter the risk of bacterial infection after SOT.

Renal grafts are usually implanted in the iliac fossa without removing the native kidneys and the ureter is directly connected to the native bladder. Urinary tract infection is the most common infectious complication after renal transplantation. After the procedure, urine flow alterations may develop because of ureteral stenosis or vesicoureteral reflux. In addition, some renal transplant patients have underlying urological abnormalities (e.g. neurogenic bladder or chronic vesicoureteral reflux) that increase the risk of post-transplant urinary tract infection. There are three types of kidney donor: living, deceased and cardiac death (non-heart-beating). Renal transplantation from cardiac-death donors develop delayed

graft function more frequently than other types of renal transplantation [25], which in turn increases the need for dialysis and the incidence of infection [26].

The liver graft is usually placed orthotopically, as heterotopic liver transplantation is associated with worse outcome at 1 year [27]. As in the case of renal transplantation, liver grafts may come from deceased, cardiac-death or living donors. Living donor livers are used in adult-to-adult right lobe liver transplantation, which is more frequently associated with biliary complications such as leaks and anastomotic and non-anastomotic strictures [28]. Liver transplantation from cardiac-death donors has an increased risk of ischaemic cholangiopathy [29]. Both living donor and cardiac-death donor liver transplantation have an increased risk of bile infections. Bile reconstruction after liver transplantation can be performed in three ways: duct-to-duct reconstruction (by far the most frequent one), choledoco-jejunostomy and hepatico-jejunostomy. Bile reconstructions other than duct-to-duct carry a higher risk of bile infections and peritonitis [30].

Regarding pancreas transplantation, simultaneous kidney-pancreas transplantation from a deceased donor is the most frequent technique used for young diabetic patients with end-stage renal failure. Exocrine drainage of the donor's pancreas is made through a duodenal stump from the donor that can be drained to the jejunum (intestinal drainage) or to the bladder (bladder drainage). Bladder drainage is associated with a higher risk of infection than intestinal drainage [31]. As pancreas transplantation involves intestinal manipulation, the risk of peritonitis and abdominal collections is high.

Small bowel transplantation (intestinal transplantation) is the treatment of choice in patients with intestinal failure and complications of parenteral nutrition. Many of the patients who undergo intestinal transplantation will have a heavily scarred abdominal wall from multiple abdominal procedures and previous bowel resections, which may cause technical difficulties during surgery and complications later on. Very often, small bowel and liver transplantation are combined when irreversible liver damage develops due to long-term parenteral nutrition. The small bowel is rich in lymphoid tissue, which increases the risk of allograft rejection. Patients undergoing small-bowel transplantation have a higher incidence of infectious complications than other SOT recipients because of a very high load of microorganisms in the intestinal graft and because they require higher degrees of immunosuppression [32,33]. Intra-abdominal abscesses also occur often as a consequence of bacterial translocation or peritoneal contamination during surgery [34].

Heart grafts are placed orthotopically and, for obvious reasons, always come from heart-beating deceased donors. Surgical anatomy does not predispose heart transplant recip-

ients to higher risk of infectious complications, as the heart graft does not come into contact with the environment. However, the surgical technique requires performance of a sternotomy, which can be complicated by postoperative mediastinitis.

Forms of lung transplantation comprise basically double-lung (sequential or in-block), single lung or double heart-lung transplantation. The most frequent site of infection is the lung, as the graft is exposed to the environment through the airway. Bacteria are the most frequent pathogens causing respiratory infections after lung transplantation, but environment-acquired tracheobronchial aspergillosis and aspergillosis of the bronchial anastomosis are other complications related to the anatomy of lung transplantation [35].

## MDR Pathogens in Solid Organ Transplant Recipients

### Recommendations for the management of MRSA in solid organ transplant patients

- Pre-transplant screening for MRSA nasal carriage and decolonization with mupirocin in carriers is recommended prior to transplantation in areas with low or moderate prevalence of MRSA (B-II).
- Universal decolonization with nasal mupirocin should be considered along with daily bathing with chlorhexidine-impregnated cloths during the ICU stay after transplantation in areas with high prevalence of MRSA (A-I).
- Vancomycin or daptomycin are the recommended drugs for the treatment of MRSA bacteraemia with vancomycin minimum inhibitory concentration (MIC) of 1.0 mg/L or below (A-I).
- For the treatment of MRSA bacteraemia with vancomycin MIC >1.0 mg/L, the use of daptomycin (B-I) or antibiotic combinations with daptomycin is recommended in cases in which bacteraemia persists during monotherapy (B-II).

### Gram-positive bacteria

*Methicillin-resistant Staphylococcus aureus*. Multidrug resistance is defined for *S. aureus* by the existence of methicillin resistance or lack of susceptibility to  $\geq 1$  active agent in  $\geq 3$  antimicrobial categories (Table 1). However, most epidemiological studies focus on methicillin-resistant *S. aureus* (MRSA), which represents almost all studies of multidrug resistance of *S. aureus*.

Although *S. aureus* is the second most important aetiological cause of bacteraemia in the population [36] and the leading cause of nosocomial bacteraemia in Europe [37], in invasive

infections in solid organ transplant recipients it falls to sixth place [38]. In addition, the rate of methicillin resistance among *S. aureus* isolates has been decreasing in recent years in Europe [39] and in the United States [40]. Nevertheless, the occurrence of invasive *S. aureus* infection in organ transplant patients is associated with very high mortality [41].

The most frequent source of *S. aureus* infections is nasal colonization. Between 20 and 30% of healthy adults are colonized and are persistent or intermittent carriers of *S. aureus* [42], and 1.5–3.0% are persistently colonized with MRSA [43–45]. In patients undergoing organ transplantation, the prevalence of MRSA nasal carriage may be higher due to permanent contact with healthcare resources (dialysis, hospital admissions, etc.). One study found a prevalence of *S. aureus* nasal colonization in patients undergoing liver transplantation of 44% (9 out of 21 strains were MRSA), with a 30% prevalence of MRSA nasal carriage [46]. Another study demonstrated that MRSA colonization after liver transplantation is not unusual and occurred in 15% of patients who were not colonized prior to transplantation [47]. In addition to nasal colonization, intestinal carriage of *S. aureus* can be a potential source of infection; the prevalence of MRSA intestinal colonization varies in different studies from 5 to 33% [48]. Intestinal carriage may increase the risk of MRSA infection. In one study performed in intensive care and liver transplant units, patients with both nasal and intestinal colonization had significantly increased rates of *S. aureus* infection (40%) compared with patients with nasal but not intestinal carriage (18%) [49]. In organ transplant patients, nasal colonization is, however, the main risk factor for MRSA infection in the post-transplant period [50,51]. Patients who underwent a liver transplantation with MRSA nasal colonization had an almost 16-fold higher risk of infection with this bacterium, although the presence of nasal colonization was not associated with an increase in mortality [52]. In a surveillance study of liver transplant recipients with nasal carriage of MRSA, the rates of infection decreased from 40.4% to 4.1% and the rate of bacteraemia from 25.5% to 4.1% after decolonization with topical mupirocin [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 with mupirocin-susceptible strains treated with topical mupirocin, mainly because of recolonization [46].

The spectrum of MRSA infection in solid organ transplant patients mainly includes bacteraemia (catheter-related or primary), surgical-site infection and pneumonia. Other sites of infection are less frequent. As mentioned above, *S. aureus* was found to be the sixth leading pathogen causing bacteraemia in solid organ transplant patients in a Spanish study

performed in 16 hospitals [38]. Around 16% of the isolates were resistant to methicillin and MRSA bacteraemia did not have a worse prognosis [38]. In a multicentre study in Spain, MRSA was the second cause of incisional surgical-site infection after heart transplantation [54]. However, in other types of transplantation such as kidney [55] or liver [56], *S. aureus* has declined as a causative pathogen of surgical-site infection, in which Gram-negative bacilli predominate. *Staphylococcus aureus* is a frequent cause of pneumonia in solid organ transplant patients [35]. In a single-centre study including mainly non-pulmonary solid organ transplant patients, *S. aureus* was the leading bacterium, representing 16% of all isolations, of which 81% were MRSA [57]. In lung transplantation patients, *S. aureus* is the leading cause of low-tract respiratory infection. In one study, mortality due to MRSA infection in lung transplant patients reached 23.5% [58].

To prevent MRSA transmission in hospital wards, several strategies have been implemented and tested. Hand hygiene, active surveillance and decolonization and patient isolation are the most accepted. Staff hand hygiene compliance appears to be the most successful strategy for reducing the prevalence and incidence of MRSA [59–61]. Mathematical models suggest that isolation of patients carrying MRSA in single-bed rooms could be efficacious in reducing the incidence of MRSA infection [62,63]. However, in one study performed in several ICUs with a high prevalence of MRSA, universal decolonization was more effective than active surveillance and isolation and targeted decolonization in reducing the number of infections with MRSA [64]. Table 2 summarizes the recommendations for infection control in patients with MRSA colonization or infection.

The guidelines for the treatment of MRSA bacteraemia and endocarditis in the general population state that vancomycin is the treatment of choice [65,66]. However, daptomycin has been shown to be non-inferior to the comparator (vancomycin or betalactam) for the treatment of *S. aureus* bacteraemia or endocarditis [67] and is less nephrotoxic. Recently, several studies have shown that a higher vancomycin minimum inhibitory concentration (MIC) confers a worse prognosis for MRSA bacteraemia [68,69]. For the treatment of MRSA with a high vancomycin MIC (>1.0 mg/L), the early use of daptomycin reduced 30-day mortality and persistent bacteraemia compared with vancomycin [70]. Some cases of persistent bacteraemia by MRSA, which did not clear by switching to daptomycin with or without gentamicin, were cured with the combined use of daptomycin plus antistaphylococcal  $\beta$ -lactams [71]. This synergistic effect seems to be achieved by a seesaw effect on daptomycin MIC induced by the use of antistaphylococcal  $\beta$ -lactams [72], increasing the incorporation of daptomycin in the *S. aureus* cellular wall [71]. Finally, the combination of daptomycin plus fosfomicin

**TABLE 2.** Summary of the infection control policies recommended when managing SOT patients with MDR infections

	Contact precautions	Isolation room	Screening cultures	Decolonization	Environment cleaning
Methicillin-resistant <i>S. aureus</i>	Recommended	Recommended	Recommended prior to transplantation	Consider chlorhexidin bathing in areas of high prevalence during ICU stay Consider nasal mupirocin for colonized patients in conventional wards	Recommended
Vancomycin-resistant enterococci	Recommended	Recommended	Only recommended during outbreaks or in areas with high prevalence of VRE	Not recommended	Recommended
ESBL-producing <i>E. coli</i>	Recommended	Not recommended	Not recommended	Not recommended	Recommended during outbreaks and optional when infections are epidemic
ESBL or ampC-producing Enterobacteriaceae (other than ESBL-producing <i>E. coli</i> )	Recommended	Recommended	Not recommended	Not recommended	Recommended
KPC-producing <i>K. pneumoniae</i>	Recommended	Recommended	Recommended	Not recommended	Recommended
MDR/XDR non-fermentative Gram-negative bacilli	Recommended	Recommended <sup>a</sup>	Recommended prior to lung transplantation Not recommended for other SOT	Not recommended	Recommended

<sup>a</sup>Isolation room is not routinely recommended for patients infected or colonized with MDR/XDR *B. cepacia*.

is a promising alternative for refractory cases of MRSA bacteraemia and/or endocarditis [73]. For the treatment of non-bacteraemic MRSA infections, vancomycin is the drug of choice. It has been suggested that linezolid could improve the prognosis of MRSA pneumonia in comparison to vancomycin. However, a recently published meta-analysis found similar outcomes with the two drugs [74].

#### *Vancomycin-resistant enterococci.*

#### **Recommendations for the management of vancomycin-resistant enterococci in solid organ transplant patients**

- Routine screening for vancomycin-resistant enterococci (VRE) in areas of low or moderate prevalence of these strains is not recommended. However, during outbreaks or in areas with high prevalence of VRE, active surveillance for VRE colonization in SOT patients may be indicated (B-III).
- In patients known to be colonized with VRE, isolation in a single-bed room and implementation of contact precautions are indicated (B-II).
- Decolonization treatment for VRE-colonized patients is not recommended (D-II).
- The use of linezolid is recommended for the treatment of bloodstream infection with ampicillin-resistant VRE or with VRE in patients with allergy to penicillin (B-II).
- For monomicrobial non-bacteraemic VRE infections in SOT patients, the use of either linezolid or quinupristin-dalfopristin is recommended, or daptomycin when the infection does not involve the lung (B-III).

Enterococci are an emerging cause of infection in solid organ transplant recipients. Vancomycin resistance in

enterococci occurs more frequently due to the acquisition of either Van-A or Van-B genes/phenotype and it has been described for both *E. faecalis* and *E. faecium* [75]. The clinical relevance of vancomycin resistance to *E. faecium* is considerably greater, as most strains are resistant to the  $\beta$ -lactams that are active against *E. faecalis*. The Van-C phenotype is intrinsic for both *E. gallinarum* and *E. casseliflavus*, and Van-D and Van-E are highly infrequent in clinical practice [75].

While the overall prevalence of VRE in the United States reached 33% in 2006–2007 [76], in Europe there is a huge variation between countries in the prevalence of VRE. Countries such as Norway, Finland, Iceland, Sweden, Netherlands, Belgium, France and Spain reported an incidence lower than 5% in 2012, while in other countries such as Portugal and Ireland, the prevalence of vancomycin resistance among *E. faecium* isolates was higher than 20% ([http://www.ecdc.europa.eu/en/healthtopics/antimicrobial\\_resistance/database/Pages/graph\\_reports.aspx](http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/graph_reports.aspx), accessed April 27, 2004).

The clinical spectrum of VRE in organ transplant patients includes urinary tract infection, infected bilomas, intra-abdominal abscesses, surgical-site infection, bacteraemia and, rarely, endocarditis. Most infections by VRE occur in previously colonized patients. Liver transplant recipients with pre-transplant colonization of vancomycin-resistant enterococci have an almost four-fold increased risk of infection by these bacteria, and colonization doubles the risk of mortality [52]. VRE infection in liver transplant patients is associated with worse outcome and a higher risk of re-transplantation, hepatic artery thrombosis, biliary leak, haemodialysis and death [77,78].

Routine screening for VRE is not recommended in areas of low or moderate prevalence of VRE [77]. However, during outbreaks or in areas with high prevalence of VRE, active

surveillance for VRE colonization may be indicated, as the implementation of isolation and contact precautions has been shown to reduce the incidence of VRE bacteraemia [79]. Isolation of VRE-colonized patients and the implementation of contact policies have been shown to be effective for the control of nosocomial transmission of VRE [80,81]. As colonization with VRE can persist for weeks or months [82] and many patients who spontaneously decolonize reacquire VRE colonization [83,84], SOT patients previously colonized with VRE requiring hospital readmission should be considered colonized and isolated in a single-bed room (Table 2). Several antibiotic regimens have been tried for VRE decolonization, including bacitracin, gentamicin, tetracycline, doxycycline, novobiocin, rifampicin and ramoplanin, with different rates of efficacy [85]. The most promising option is ramoplanin, but in an experimental model of VRE colonization in mice its use increased the density of indigenous Enterobacteriaceae and overgrowth of an exogenously administered *Klebsiella pneumoniae* isolate [86], leading to concerns about the possibility of acquisition of MDR Enterobacteriaceae.

In contrast to vancomycin-resistant *E. faecalis*, which can be treated with ampicillin or the combination of ampicillin plus gentamicin, the treatment of vancomycin-resistant *E. faecium* is highly problematic. An *E. faecium* strain is defined as ampicillin-resistant if it is able to grow in 16 mg/L of ampicillin. However, strains with ampicillin MIC lower than 100 mg/L can be treated with high doses of the drug [87]. Other drugs available for the treatment of vancomycin-resistant *E. faecium* with high MIC for ampicillin are fluoroquinolones, daptomycin, linezolid, tigecycline, tetracycline and quinupristin-dalfopristin (Table 1), given that aminoglycosides are inactive against enterococci if no inhibitor of the cell wall is administered (due to the low permeability of the enterococcal wall). Teicoplanin may be used for the treatment of VanB-type enterococci. However, the description of a case in which teicoplanin resistance developed during treatment raises concerns about the use of this drug for VanB *E. faecium* [88]. Although only daptomycin is bactericidal against VRE, linezolid has also been widely used for the treatment of VRE bacteraemia. It should be noted that a recent report of a new mechanism of resistance to daptomycin in VRE, which appeared during the treatment of bloodstream infections, has raised concerns regarding the treatment of this microorganism [89]. A recent meta-analysis on the comparison of the outcomes of VRE bacteraemia treated with daptomycin or linezolid showed that patients treated with daptomycin had higher 30-day all-cause and overall mortality, infection-related mortality and relapse rates compared with those treated with linezolid [90].

For monomicrobial non-bacteraemic VRE infections in SOT patients, we recommend the use of linezolid, quinupristin-

dalfopristin or daptomycin. Daptomycin is inactivated by lung surfactant [91]. Clinical trials for the treatment of pneumonia showed that daptomycin failed to show non-inferiority against comparators [92], and breakthrough pneumonia due to daptomycin-susceptible strains may appear during treatment with daptomycin [93]. As several meta-analyses from clinical trials have reported an increased mortality for tigecycline vs. comparators [94–97], we do not recommend this drug for the treatment of monomicrobial infections with VRE. However, tigecycline could be a good choice for treating polymicrobial infections involving VRE with other MDR pathogens (i.e. carbapenemase-producing Enterobacteriaceae), a frequent situation in tertiary peritonitis with abdominal collections. Finally, a similar see-saw effect to that detected with the combination of oxacillin plus daptomycin in MRSA has been shown with the combined use of ampicillin plus daptomycin for VRE [98]. Therefore, in the case of persistent and refractory bacteraemia with vancomycin-resistant *E. faecium*, the combination of ampicillin plus daptomycin should be tried.

#### Gram-negative bacteria

##### *MDR-enterobacteriaceae.*

#### Recommendations for the management of ESBL-, ampC- or carbapenemase-producing Gram-negative bacilli in solid organ transplant patients

- Screening of bowel colonization with extended-spectrum betalactamases (ESBL)-, ampC- or carbapenemase-producing Gram-negative bacilli in patients awaiting solid organ transplantation is not recommended in a scenario of endemic infection. (B-III) However, in a situation of outbreak, active screening cultures and contact precautions in colonized patients are recommended (B-II).
- Intestinal decolonization of colonized patients with MDR Enterobacteriaceae prior to transplantation is not recommended because of its poor efficacy in the long term. (C-II) However, it may be evaluated during outbreaks (C-III).
- While in most cases ESBL-producing *E. coli* do not need single-bed isolation, ESBL-producing *K. pneumoniae* and Enterobacteriaceae producing derepressed ampC  $\beta$ -lactamases or carbapenemases require single-bed isolation and contact precautions (B-II).
- For the treatment of ESBL- or derepressed ampC  $\beta$ -lactamase-producing Enterobacteriaceae infections in hospitalized SOT patients, we recommend the use of ertapenem when the strain is susceptible, instead of imipenem, meropenem or doripenem, for ecological reasons (B-III).
- The cornerstone of the treatment of carbapenemase-producing Enterobacteriaceae is colistin or polymyxin B. In most cases, combination antibiotic therapy with tigecycline,



aminoglycosides, fosfomycin and/or carbapenems is desirable (B-III).

Cephalosporin-resistant Enterobacteriaceae due to the production of extended-spectrum beta-lactamases (ESBL) or inducible chromosomal beta-lactamases (ampC) are increasing worldwide as causes of infection in hospitalized and community patients. *E. coli* and *Klebsiella pneumoniae* are the most important pathogens producing extended-spectrum beta-lactamases (ESBL), and *Enterobacter* spp., *Citrobacter freundii* and *Morganella morganii* usually express inducible chromosomal beta-lactamases (ampC). The typical phenotype of these pathogens includes resistance to penicillins and cephalosporins and susceptibility to carbapenems. As MDR pathogens, these microorganisms typically carry additional mechanisms of resistance, such as DNA gyrase mutations conferring resistance to quinolones, deficient expression of porins, and so on. Other active antibiotics include tigecycline, aminoglycosides and colistin (Table 1). ESBL-producing *E. coli* are usually susceptible to nitrofurantoin; however, most strains of *Klebsiella* spp. are resistant to this antibiotic. In Europe, there is a high variability in the prevalence of MDR Enterobacteriaceae. Taking invasive infections with *E. coli* resistant to third-generation cephalosporins as the reference, we found a prevalence of 25–50% in Italy and Romania, 10–25% in Portugal, Spain, France, the United Kingdom and others, and prevalences of 1–5% in Sweden and Norway (<http://www.ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2012.pdf>; accessed 15 May 2014).

One of the most important risk factors for ESBL- or ampC-producing Enterobacteriaceae infection is prior bowel colonization. One study of an intensive care unit outbreak of ESBL-producing *K. pneumoniae* showed a 38% incidence of colonization, with the most important risk factors being clinical severity at admission, arterial catheterization, parenteral nutrition, urinary catheterization, mechanical ventilation and previous antibiotic treatment [99]. Bowel colonization with ESBL-producing Enterobacteriaceae in patients at risk increased from 1.5% in 2000 to 3.5% in 2005, a trend that is similar for SOT patients [100]. The incidence of ESBL-producing Enterobacteriaceae bloodstream infection increases proportionally with the prevalence of bowel colonization [100]. In one study the incidence of pre-transplant colonization with ESBL-producing Enterobacteriaceae in patients undergoing liver transplantation reached 16%, with previous ESBL infection, hospital admission or antibiotic treatment and more advanced liver disease being risk factors for colonization [101]. In addition, in a study of hospitalized patients, renal transplantation was an independent risk factor for developing bacteraemic infection with ESBL-producing *E. coli* or *Klebsiella*

spp [102]. Moreover, patients admitted to a renal transplant unit had a higher risk of infection by ESBL-producing enteric bacilli with quinolone-associated resistance [103].

In the paediatric renal transplantation population, ESBL-producing *E. coli* is the most frequent aetiological agent of infection, especially of the urinary tract [104]. Although data are scarce, renal transplant recipients seem to be at a higher risk of infection with these bacteria, with an incidence of 12%, especially in cases of simultaneous pancreas transplantation, previous use of antibiotics, post-transplant dialysis and post-transplant urinary obstruction [105]. Most ESBL- or ampC-producing Gram-negative rods in patients with renal transplantation are due to urinary tract infection (70%), although surgical-site infection is another possible source [105]. The frequency of urinary tract infections with ESBL-producing bacteria in non-renal transplant patients is lower, but one multicentre study reported a prevalence of 23% in liver, heart and lung transplant patients [106]. The overall incidence of ESBL-producing *K. pneumoniae* infection in the liver was lower than in renal transplant recipients (7% vs. 11%, respectively) [107]. In heart and lung transplant patients, the sources of ESBL infections include bacteraemia, urinary tract infections, pneumonia, central venous catheter-associated infection and wound infections, but the overall incidence was lower (2.2% and 5.5%, respectively) [108].

In recent years, infection with carbapenemase-producing Enterobacteriaceae, especially *K. pneumoniae* (KPC), has emerged as a global threat in SOT patients. Like ESBL or derepressed chromosomal  $\beta$ -lactamases, carbapenemase inactivates penicillins and cephalosporins, but also inactivates carbapenems. *In vitro* susceptibility data from numerous studies indicate that colistin, tigecycline and fosfomycin are the most effective antibacterial agents against KPC-producing Enterobacteriaceae [109]. A single-centre study including 17 SOT patients with KPC-producing Enterobacteriaceae infection (mainly liver and intestinal transplantation) showed that the main sources of the infection were intra-abdominal collections and the biliary tract [110]. Persistent bacteraemia was very frequent (one patient had persistent bacteraemia for more than 300 days) and more than 70% of patients had the same clone [110]. In contrast to liver and small-bowel transplantation, KPC-producing Enterobacteriaceae in renal transplant patients usually causes urinary tract infections [111,112]. Interestingly, the development of necrotizing soft tissue infections with KPC has been reported in liver transplant patients [113], as in the case of highly-virulent genotype K1 of *K. pneumoniae* in Asia [114]. KPC-producing *K. pneumoniae* can be also transmitted from donor to recipient, although an appropriate antimicrobial prophylaxis for the recipient can prevent the development of infection [115]. As described for

ESBL-producing Enterobacteriaceae, intestinal carriage of carbapenemase-producing *K. pneumoniae* (carbapenemase type 2, KPC-2-KP) was associated with a higher risk of infection, with a high percentage of patients suffering bloodstream infection, after liver transplantation [116].

The best prevention strategy 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, and so many centres do not apply isolation measures in the case of patients infected with ESBL-producing *E. coli* [117,118]. Patients infected with ESBL-*K. pneumoniae* and carbapenemase-producing Enterobacteriaceae must always be admitted under contact isolation (Table 2). We do not recommend active surveillance to detect colonization with ESBL or ampC-producing Enterobacteriaceae. However, active surveillance, when accompanied by implementation of contact precautions for colonized patients, daily decontamination of environmental surfaces and cohorting of patient care staff, has led to major reductions in the carbapenem-resistant infection rate not only for outbreaks but also in the endemic setting [119–121]. Little information is available about the usefulness of intestinal decolonization in organ transplant patients. In a multicentre observational study, the use of fluoroquinolones did not protect liver transplant patients from developing early bacterial infections [122]. In another study, the use of oral gentamicin and oral polymyxin E was able to reduce colonization with carbapenemase-producing *K. pneumoniae* [123]. However, no study has proved that a strategy of intestinal decolonization reduces the incidence of infection with ESBL-, ampC- or carbapenemase-producing Gram-negative bacilli. Therefore, in scenarios with endemic infections with ESBL-producing Enterobacteriaceae, active screening cultures to detect colonized patients are not recommended. During outbreaks of infections caused by ESBL-producing Enterobacteriaceae or in any situation (endemic or outbreaks) of infections with carbapenemase-producing Enterobacteriaceae, active surveillance cultures and contact precautions are strongly recommended [118].

Carbapenems are the cornerstone of treatment for ESBL or derepressed chromosomal betalactamase-producing Enterobacteriaceae. ESBL-producing strains of *E. coli* and *Klebsiella* spp. are often resistant to quinolones and cotrimoxazole [124,125] and usually no oral active antibiotic is available to complete the treatment after hospital discharge. When choosing a carbapenem for the treatment of these infections it should be borne in mind that the use of ertapenem may allow downscaling of the use of imipenem and ciprofloxacin and that this can improve the local susceptibility of non-fermentative Gram-negative bacilli [126]. However, in recent years, an increase in the incidence of

ertapenem-resistant *K. pneumoniae* strains due to porin deficiency has been detected [127,128], which may produce outbreaks in intensive care units [129]. Although prolonged *in vitro* exposure to ertapenem may lead to the development of porin-deficient subpopulations of *E. coli* [130], this has not yet been associated with clinical consequences [131]. There is no evidence in favour of combination antibiotic therapy for the treatment of ESBL or chromosomal betalactamase-producing Enterobacteriaceae, although adding an aminoglycoside to carbapenem in haemodynamically unstable or critically ill patients seems a reasonable strategy. For the treatment of cystitis caused by ESBL-producing *E. coli*, amoxicillin-clavulanate and fosfomycin had a clinical efficacy of 84% and 93%, respectively, when the isolate showed susceptibility to those drugs [132]. Other options for the treatment of these MDR pathogens include tigecycline, cotrimoxazole, quinolones and nitrofurantoin in the case of proven susceptibility.

In contrast to ESBL- or ampC-producing Enterobacteriaceae, most physicians use combination antibiotic therapy against carbapenemase-producing Enterobacteriaceae [110,112]. Colistin is the most active agent against these strains and should be considered the basis of treatment in most patients [133]. Tigecycline could represent an optimal choice for patients with co-infection with additional MDR pathogens (e.g. VRE or MRSA). Aminoglycosides, fosfomycin and even high-dose carbapenems [110,112,134] should be evaluated for the use of combination antibiotic therapy.

#### *Non-fermentative Gram-negative bacilli.*

#### **Recommendations for the management of non-fermentative Gram-negative bacilli infection in SOT patients**

- Pre-transplantation lung colonization by MDR/XDR *P. aeruginosa* (B-II) or *B. cenocepacia* (B-III) is not an absolute contraindication for lung transplantation. If present, this colonization should be evaluated together with other co-morbidities to assess whether their combination might lead to unacceptably high post-transplant mortality.
- To avoid colonization by non-fermenters, antibiotic therapies should be used with parsimony, and contact between patients both pre- and post-transplantation should be avoided (B-II).
- Treatment of MDR/XDR non-fermenters should include combination therapies using two to three classes of antibiotics based on resistance phenotypes (B-II).
- Time-dependent antibiotics (beta-lactam) should be given as prolonged or continuous infusion, whereas concentration-dependent antibiotics (aminoglycosides and fluoroquinolones) should be given in high once-daily doses (B-II).

*Pseudomonas aeruginosa* is a significant nosocomial pathogen in all types of SOT recipients, being responsible for early post-transplant pneumonia and bacteraemia. Significantly, the frequency of MDR, XDR or PR isolates is higher in SOT recipients than in the non-transplant population, and accounts for 50% of the *P. aeruginosa* bloodstream isolates [135,136]. The risk of infection is highest in lung transplant recipients, because more than half of cystic-fibrosis lung transplant candidates are colonized before transplantation by MDR or XDR *P. aeruginosa*, and up to 75% are colonized thereafter [137]. Importantly, however, pre-transplant colonization of lung transplant candidates by MDR/XDR *P. aeruginosa* does not impact overall survival and should not contraindicate lung transplantation [138,139]; it should be included together with other co-morbidities in a comprehensive evaluation. Colonization and infections by other non-fermenters such as *Burkholderia*, *Stenotrophomonas* and *Achromobacter* species remain less frequent. While the data on *Stenotrophomonas* and *Achromobacter* from SOT recipients are too scarce to determine their particular pathogenicity in this population, *Burkholderia* species and especially *B. cenocepacia* (genomovar III) are clearly associated with reduced survival rates in lung transplant recipients [140,141]. Reports of unacceptably high fatality rates of lung transplant recipients colonized by XDR *B. cenocepacia* have accumulated, leading to recommendations of extreme caution and adequate patient information before accepting these patients for lung transplantation. As adequate identification and resistance profile determination may be challenging, these strains should be evaluated by laboratories using both conventional (OFBBL agar, PC agar, BCSA) and molecular identification techniques.

Similarly to MDR Enterobacteriaceae, there is a high variability in the prevalence of MDR *P. aeruginosa* in Europe. Taking invasive infections with carbapenem-resistant *P. aeruginosa* as the reference, we found a prevalence of more than 50% in Romania, 25–50% in Italy, Greece, Bulgaria and Hungary, and 5–10% in the United Kingdom, Sweden, Norway and Finland (<http://www.ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2012.pdf>; accessed 15 May 2014).

To avoid colonization by these isolates, particular care should be taken both pre- and post-transplantation to reduce exposure to antibiotic therapies. If these therapies are required, their duration should be kept as short as possible. To avoid transmission of epidemic strains such as the *P. aeruginosa* Liverpool strain, contact between patients should be restricted [142]. Contact isolation is indicated for transplant recipients harbouring MDR/XDR *P. aeruginosa* and *B. cepacia*. As nebulizers can potentially transmit *B. cepacia*, the use of these devices should include strict

hygiene measures. Sinus surgery (endoscopic fronto-sphenoidectomy), potentially combined with sinonasal and bronchial colistin inhalation, has been suggested as a way to prevent post-lung transplant recolonization by *P. aeruginosa* from a sinus reservoir [143,144]. However, the experience with such aggressive management remains controversial, and for the moment it cannot be routinely recommended [145].

Infection control policies do not differ from those recommended for the general population (Table 2). SOT patients infected or colonized with MDR/XDR non-fermentative bacilli other than *B. cepacia* should be isolated. In all cases, hand hygiene measures and other contact precautions, and environment cleaning, are recommended.

Treatment data specific to transplant recipients are lacking. In all situations time-dependent beta-lactam antibiotics (piperacillin tazobactam, ceftazidime, meropenem and doripenem) should be given, using prolonged or continuous infusion in order to optimize pharmacokinetic parameters [146,147]. In contrast, concentration-dependent antibiotics (aminoglycosides and fluoroquinolones) should be given in high once-daily doses. For MDR/XDR *P. aeruginosa* infections, combination therapies including two to three different antibiotic classes (beta-lactam + aminoglycoside ± fluoroquinolone) are recommended for 10–14 days [139,148]. Clinical experience with novel combinations including systemic colistin, fosfomycin and rifampicin is scarce. Colistin or beta-lactams given as adjunctive aerosolized therapies have shown promising results and can be used in difficult cases [149,150]. For MDR/XDR *B. cepacia* infections, triple combinations including meropenem, aminoglycosides and either ceftazidime or trimethoprim sulfamethoxazole are recommended. The clinical significance of MDR/XDR *A. xylooxidans* is questionable. Treatment should therefore be restricted to chronically colonized/infected patients with clear clinical decline, using combination therapies including piperacillin-tazobactam, carbapenems and/or trimethoprim sulfamethoxazole. MDR/XDR *Stenotrophomonas* infections require high-dose trimethoprim sulfamethoxazole combined with ceftazidime, and levofloxacin. Depending on the resistance profile, alternative combinations might also include bacteriostatic compounds such as doxycycline and tigecycline.

### Antimicrobial Spectrum, Interactions and Adverse Effects of Less Frequently Used Antibiotics for Treatment of MDR Pathogens in SOT Patients

A great deal of information is available on the toxicity, drug interactions and adverse effects in SOT patients of the most

common antibiotics (beta-lactams, aminoglycosides, cotrimoxazole, etc.). However, there is a subgroup of antibiotics – both new and old – in which the experience in SOT patients is very limited, but which are being increasingly used for the treatment of MDR infections. These antibiotics include ceftaroline, tigecycline, daptomycin, linezolid, fosfomycin and colistin (Table 3).

Ceftaroline-fosamil is a new cephalosporin approved in the United States and in Europe for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Ceftaroline-fosamil is a prodrug of the active metabolite, ceftaroline. Its mechanism of action is by binding bacterial penicillin-binding proteins (PBPs), but, in contrast to the rest of the beta-lactams, ceftaroline has high affinity for binding PBP 2A [151]. Its microbiological spectra include Gram-positive (including MRSA, MDR *S. pneumoniae* and vancomycin-resistant *E. faecalis*) and Gram-negative bacteria. Ceftaroline does not possess activity against *E. faecium*. The incidence of adverse effects for ceftaroline in clinical trials has been low and no relevant drug interactions have been described. Alterations in liver function tests occurred in 2.5% of patients who received ceftaroline in phase 3 clinical trials [152]. Around 10% of patients treated with ceftaroline-fosamil may experience seroconversion from a negative to a positive direct Coombs' test [153]. In SOT patients with MDR infections, ceftaroline may represent a good option for the treatment of invasive infections with MRSA, although no published evidence is available at present.

Tigecycline belongs to the new glycycline family and it is structurally similar to the tetracyclines. This antibiotic possesses an extended antimicrobial spectrum which includes most MDR pathogens: MRSA, VRE, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and MDR Enterobacteriaceae (including ESBL-, derepressed AmpC- and carbapenemase-producing strains) [154]. Tigecycline lacks activity against *Pseudomonas aeruginosa*. Its volume of distribution is very high, with good concentrations in tissue and low concentrations in serum, and only 15% of the drug is excreted unaltered in the urine. These two pharmacokinetic properties have triggered a debate on the appropriateness of tigecycline for the treatment of urinary tract infections and bacteraemic patients [155]. As commented above (treatment of VRE infections), several meta-analyses of clinical trials have reported increased mortality in tigecycline vs. comparators for the treatment of diverse sources of infection. For this reason, tigecycline should be reserved for the treatment of MDR pathogens, especially in the case of polymicrobial infections. Most of the published experience of its use in SOT patients comes from the description of cases with carbapenemase-producing Enterobacteriaceae [110–113,115,134]. No serious adverse effects in

SOT patients have been described with the use of tigecycline. Increased bioavailability of cyclosporine has been reported upon concomitant treatment with tigecycline [156].

Daptomycin is a cyclic lipopeptide with rapid bactericidal effect against Gram-positive bacteria, causing depolarization of the cytoplasmic membrane after irreversible binding in a calcium-dependent manner. In SOT patients, the most frequent bacterial targets for the use of daptomycin are *S. aureus* and VRE. The information available regarding the safety and efficacy of daptomycin in SOT patients is limited to case reports [157–160]. In the major clinical trials with daptomycin, the drug was well tolerated and its profile of adverse effects was similar to that of the comparator drugs [67,161]. In general, daptomycin does not alter liver function tests, but cases of liver toxicity related to its use have been reported [162,163]. In a randomized clinical trial, daptomycin was less nephrotoxic than the comparator [67]. Its most characteristic adverse effect is skeletal muscle toxicity. In most patients, muscle toxicity consists of asymptomatic increases in the creatine kinase serum levels, which return to normal after discontinuation of the treatment. Consequently, monitoring creatine kinase serum levels during treatment with daptomycin is recommended. Discontinuation of treatment with statins is mandatory prior to the use of daptomycin, because the concomitant use of the two drugs can increase the incidence of muscle toxicity. As noted above, daptomycin is inactivated by the lung surfactant, and does not have a therapeutic effect on low-tract respiratory infections. No significant interactions with immunosuppressants have been reported.

Linezolid belongs to the new family of oxazolidinones and is an active agent against Gram-positive pathogens. As a result, it can represent an alternative for the treatment of MRSA and vancomycin-resistant enterococci. Linezolid does not cause direct nephrotoxicity, but several cases of acute interstitial nephritis have been described [164,165], one of them in a renal transplant patient [166]. A study performed in 46 liver transplant patients with Gram-positive bacterial infections treated with linezolid during a mean of 11 days showed neither significant haematological abnormalities nor any other relevant side-effects [167]. A subgroup analysis of patients who received treatment for 15 or more days did not show any relevant side-effects [167]. One multicentre trial of compassionate use of linezolid for the treatment of VRE included 85 SOT patients with demonstrated VRE infection (liver, kidney, heart, lung and multivisceral), of whom 43 were bacteraemic, and reported an incidence of thrombocytopenia of 4.7% and decreased leukocyte count in 3.5% of patients [168]. No relevant interactions with immunosuppressants have been reported with linezolid.

**TABLE 3. Main characteristics of antibiotics with less experience of use for the treatment of MDR bacteria in SOT patients**

	Target bacteria	Relevant drug interactions in the transplant setting	Liver toxicity	Renal toxicity	Other adverse effects	Specific information for solid organ transplant patients
Ceftaroline- fosamil	MRSA Vancomycin-resistant <i>E. faecalis</i>	No relevant interactions with immunosuppressants	Alterations of liver function test occurred in 2.5% of patients in phase 3 clinical trials Rarely reported	No	Seroconversion to positive direct Coombs' test in around 10% of patients	No published evidence
Tigecycline	MRSA Vancomycin-resistant enterococci MDR Enterobacteriaceae <i>Clostridium difficile</i>	Tigecycline can increase the oral bioavailability of cyclosporin	Rarely reported	No	Nausea (26%) and vomiting (18%) Pancreatitis Rash (Stevens-Johnson-type reactions) 1% higher mortality than comparators	Most of the published experience comes from the description of the efficacy of tigecycline for the treatment of carbapenemase-producing Enterobacteriaceae
Daptomycin	MRSA Vancomycin-resistant enterococci	No relevant interactions with immunosuppressants	Rarely reported	No	Skeletal muscle toxicity around 7–10% of patients at a dose of 6–8 mg/kg/day Thrombocytopenia	No published evidence
Linezolid	MRSA Vancomycin-resistant enterococci <i>M. tuberculosis</i> Slow-growing mycobacteria Atypical pathogens: <i>Rhodococcus equi</i> , <i>Listeria monocytogenes</i> , <i>Nocardia</i> spp.	No relevant interactions with immunosuppressants	No	Not direct renal toxicity but some cases of acute interstitial nephritis have been reported	Lactic acidosis Anaemia Peripheral polyneuropathy Serotonergic syndrome	Linezolid was safe in liver transplant recipients receiving a mean of 11 days of treatment in 85 SOT patients treated with linezolid; thrombocytopenia occurred in 4.7% and decreased leukocyte count in 3.5% of patients Fosfomycin for the treatment of urinary tract infections in renal transplant patients resulted in a low bacterial clearance rate (31%) and high incidence of recurrence (54%) in one study Renal toxicity has been reported to appear in nearly 1/3 of SOT patients
Fosfomycin	MRSA Vancomycin-resistant enterococci MDR Enterobacteriaceae MDR <i>P. aeruginosa</i>	No relevant interactions with immunosuppressants	No	No	High sodium intake that can result in fluid retention, oedemas, ascites and heart failure in susceptible patients after i.v. fosfomycin Oral fosfomycin is associated with diarrhoea in near 10% of patients	
Polymyxins/ Colistin	MDR Enterobacteriaceae MDR non-fermentative Gram-negative bacilli	No relevant interactions with immunosuppressants	Slight increases of transaminases have been described.	Highly variable depending on the series (0–54.5%)	Peripheral and orofacial paresthesias Ataxia Visual disturbances Vertigo Mental confusion Seizure Myasthenia-like syndrome	

Fosfomycin may be an alternative for the treatment of MRSA, vancomycin-resistant enterococci, ESBL-producing enterobacteriaceae and MDR *P. aeruginosa* infections in organ transplant patients. Fosfomycin can also act synergistically with amoxicillin, daptomycin and linezolid against vancomycin-resistant *E. faecium* [169]. Adverse effects related to intravenous fosfomycin-disodium are rare. The most common and the most relevant is a high-sodium intake, resulting in water retention, oedema, ascites and heart failure in susceptible patients [170]. Oral fosfomycin may be a good option for the treatment of MDR bacteria causing urinary tract infection; it is generally well tolerated, although nearly 10% of patients may develop diarrhoea. One retrospective study of 14 episodes of urinary infections in nine renal transplant patients treated with fosfomycin (3 g per day for 1–7 days) showed that the drug was well tolerated, although the overall bacterial clearance rate at 3 months was low (31%) and the incidence of recurrence was high (54%) [171]. No relevant interactions with immunosuppressants have been described.

The two main adverse effects of intravenous administration of colistin are renal and neurological toxicity. The mechanism of renal toxicity of colistin is not fully understood but *in vitro* electrophysiological studies demonstrate that the drug is directly toxic to urothelium by increasing transepithelial conduction, especially during long-term use [172]. The incidence of colistin-related nephrotoxicity varies widely depending on the series (0–54.5%) [173], but several studies have shown that it mainly depends on the basal renal function, and is higher in patients with altered renal function [174–176]. In the transplant setting, in a recently published study of 92 transplant patients treated with polymyxin, renal toxicity appeared in nearly a third of the sample, and was correlated with the duration of therapy [177]. Special attention must be paid to the association of polymyxin B or colistin with aminoglycosides, which may result in a higher risk of renal toxicity [178]. Colistin-related neurological adverse effects probably occur because of a similar renal toxicity mechanism. Colistin can modify conduction of neurons, which are rich in lipids, resulting in visual disturbances, confusion, peripheral paresthesias and seizures [179]. The most life-threatening neurological adverse effect related to the use of colistin is neuromuscular blockade, which resembles myasthenia gravis and may cause respiratory muscle paralysis and apnoea [180,181]. No specific or relevant interactions of colistin with immunosuppressants have been described. In one prospective study of colistin-treated patients, slight increases in aspartate amino-transferase were observed after prolonged treatments [182]. Another important point is that there are no clinical breakpoints for polymyxins or colistin against Enterobacteriaceae, and the pharmacokinetics of the drug has not been fully

established. Thus, it is very important to know the appropriate dosage of these drugs in order to maintain the balance between efficacy and adverse side-effects. Table 4 shows the recommended dosage of polymyxin and the two main presentations of colistimethate sodium.

Pivmecillinam is a pro-drug of mecillinam, a betalactam with specific activity against Gram-negative bacteria. Given orally, it achieves bacteriological cure rates higher than 90% in patients with low-tract urinary tract infections [183]. Although pivmecillinam has poor activity against Gram-positive bacteria, it has good activity against ESBL-producing *E. coli* [184] and can represent an alternative to carbapenems for the treatment of recurrent cystitis due by this bacterium in kidney transplant recipients. Another option for the treatment of MDR Gram-negative bacteria is temocillin, a derivate of ticarcillin. Developed during the 1980s, temocillin was abandoned because of its lack of activity against Gram-positive bacteria, anaerobes and *P. aeruginosa* [185]. However, this drug is active against most ESBL, AmpC and KPC-producing Enterobacteriaceae [186]. Temocillin is, however, inactivated by other carbapenemases.

## Common Difficult-to-Treat Bacterial Infections Associated With MDR After SOT

### Recommendations for the management of difficult-to-treat infections in SOT patients

- Antibiotic therapy for complex or recurrent infections in SOT patients should be used with caution, especially when used as prophylaxis. Care should be taken to avoid treating asymptomatic patients, in order to reduce the possibility of infection with MDR pathogens (B-III).
- When treating patients with suppurating collections (abdominal abscesses, infected bilomas), surgical management or drainage of the collections is desirable when possible, as the likelihood of curing these infections conservatively is very low (B-III).
- Recurrent cholangitis in liver transplant patients is usually associated with biliary strictures. Most cases benefit from surgical or percutaneous treatment to restore the biliary tree (B-III).
- Recurrent urinary tract infection is a common problem in renal transplant patients and, although many patients do not have structural lesions, a morphological and/or dynamic study of the urinary tract should be performed in all patients (B-III). The use of antibiotic prophylaxis for recurrent urinary tract infection (UTI) after renal transplantation is not supported by published evidence so the decision to give it or not depends on the experience of the treating physician (C-III).

**TABLE 4. Recommended dosage of polymyxin B and colistimethate sodium, either for intravenous or inhalation therapy**

	Polymyxin B	Colistimethate sodium (CMS) Colomycin® injection	Colistimethate sodium (CMS) Coly-Mycin® M Parenteral
Composition of vials	500 000 units (c. 50 mg)	500 000 IU (40 mg) 1 000 000 IU (80 mg) 2 000 000 IU (120 mg)	150 mg colistin base activity (400 mg CMS)
Recommended dose for patients with normal renal function	15 000–25 000 IU/kg/day in one daily or two divided doses (equivalent to 1.5–2.5 g)	≤60 kg, 50 000–75 000 IU/kg/day in three divided doses (equivalent to 4–6 mg/kg/day CMS) 60 kg, 1–2 million IU three times a day (equivalent to 80–160 mg CMS three times per day) Maximum dose of 6 million IU in 24 h	2.5–5.0 mg/kg/day colistin base activity in 2–4 doses (equivalent to c. 6.67–13.3 mg/kg/day CMS)
Recommended dose adjustment in patients with renal impairment	According to creatinine clearance (CLCR): <ul style="list-style-type: none"> <li>• CLCR of 30–80 mL/min, loading dose of 2.5 mg/kg/day on the first day and then 1.0–1.5 mg/kg/day</li> <li>• CLCR &lt;30 mL/min, loading dose of 2.5 mg/kg/day on the first day and then 1.0–1.5 mg/kg/day every 2–3 days</li> <li>• Anuric patients, loading dose of 2.5 mg/kg/day on the first day and then 1.0–1.5 mg/kg/day every 5–7 days</li> </ul>	According to creatinine clearance (CLCR) and over 60 kg bodyweight: <ul style="list-style-type: none"> <li>• CLCR 20–50 mL/min, 1–2 million IU every 12 h</li> <li>• CLCR 10–20 mL/min, 1 million IU every 12–18 h</li> <li>• CLCR &lt;10 mL/min, 1 million IU every 18–24 h</li> </ul>	According to creatinine clearance (CLCR) and over 60 kg bodyweight: <ul style="list-style-type: none"> <li>• CLCR 50–80 mL/min, 75–115 mg every 12 h</li> <li>• CLCR 30–50 mL/min, 66–150 every 12–24 h</li> <li>• CLCR 10–30 mL/min, 100–150 every 36 h</li> </ul>
Recommended dose for inhalation therapy	2.5 mg/kg daily in divided doses every 6 h (respiratory infections) to 500 000 IU twice a day (pneumonia)	1–2 million units twice daily, dissolved in 2–4 mL of water for injections or 0.9% sodium chloride intravenous infusion for use in a nebuliser	1–2 million IU, 2 or 3 times daily, diluting the appropriate dose in 2–4 mL of preservative-free 0.9% sodium chloride injection, sterile water, or a mixture of 0.9% sodium chloride injection and sterile water for use in a nebuliser

- Initial management of mediastinitis after heart transplantation includes aggressive surgical debridement and antibiotic treatment should be active against Gram-positive pathogens, including MDR strains, depending on the local epidemiology (B-III).
- Recurrent tracheobronchial infections after lung transplantation are usually associated with strictures of the bronchial anastomosis. Little evidence is available regarding the management of this situation, but many centres use aerosolized antibiotics to treat infections with low risk of invasion and reserve systemic therapies for more severe infections (C-III).

Some patients with SOT will develop difficult-to-treat infections, which in most cases are directly related to the surgical procedure. In many cases, these infections tend to reoccur and, consequently, the patients are exposed to repeated courses of antibiotics. This can lead to the development of recurrent MDR bacterial infections. Thus, antibiotic therapy for complex or recurrent infections in SOT patients should be used with caution. This is especially relevant when we give prophylactic antibiotics or when we treat asymptomatic patients. Table 5 summarizes the most frequent conditions associated with recurrent infections after SOT.

**Infected bilomas**

Infected bilomas can occur in around 10% of patients with orthotopic liver transplantation [187], causing high morbidity and resource consumption due to frequent hospital readmissions, need for re-transplantation and mortality [187,188]. When infected biloma coexists with hepatic artery thrombosis, the best therapeutic approach for its management in many

**TABLE 5. Common difficult-to-treat syndromes associated with recurrent infection leading to a higher risk of selection or superinfection with MDR pathogens in SOT patients**

Syndrome	Type of transplantation
Recurrent urinary tract infections	Renal transplantation Simultaneous kidney-pancreas transplantation
Cyst infections	Renal transplantation for polycystic renal disease and/or coexisting liver cysts
Infected biloma	Liver transplantation Multivisceral transplantation
Recurrent cholangitis	Liver transplantation Multivisceral transplantation
Tertiary peritonitis and abdominal abscesses	Pancreas transplantation Liver transplantation
Mediastinitis	Intestinal/multivisceral transplantation Heart transplantation Lung transplantation
Recurrent respiratory tract infection	Combined heart-lung transplantation Lung transplantation Combined heart-lung transplantation

cases is liver re-transplantation, as the likelihood of cure by applying conservative treatments is very low [187]. Gram-positive bacteria are the main causes of infected bilomas (including coagulase-negative staphylococci and enterococci), followed by *Candida* spp., enterobacteriaceae and *Pseudomonas aeruginosa* [187]. Conservative treatment includes percutaneous catheter drainage and single aspiration (for extrahepatic bilomas) as well as appropriate antimicrobial treatment. The duration of antibiotic treatment in conservative management of infected bilomas has not been established, but it should be probably prolonged for 4–6 weeks, taking into account the improvement of patient's clinical symptoms, radiological studies and inflammatory markers in blood analysis. However, prolonged or cyclic broad-spectrum antibiotics for infected bilomas may produce superinfection or selection of MDR bacteria. Therefore, antimicrobial treatment for infected bilomas needs to be used with caution. In the case of methicillin-resistant coagulase-negative staphylococci or vancomycin-resistant enterococci infection, linezolid and daptomycin may be a good treatment option as both drugs achieve excellent biliary pharmacodynamic exposure [189,190]. For the treatment of Gram-negative infected bilomas, imipenem [191], meropenem [192] and ertapenem [193] achieve optimal concentrations in bile after systemic administration. No information is available on the bile concentrations of colistin after intravenous treatment. Tigecycline achieves high concentrations in bile [194] and can be used for the treatment of infected bilomas with carbapenemase-producing Enterobacteriaceae. For the treatment of infected bilomas with *Candida* spp., fluconazole is the drug of choice because of its good concentration in bile [195] and good safety profile. Voriconazole probably also achieves good concentrations in bile, as it was demonstrated to have optimal concentrations in the liver of eight deceased patients on autopsy [196].

#### **Recurrent cholangitis**

Chronic recurrent bacterial cholangitis may appear in liver transplant patients with structural lesions of the biliary tree. The most frequent structural biliary lesions include bile leak, anastomotic and non-anastomotic strictures and ampullary dysfunction [197]. Some patients, especially recipients of a liver from a cardiac-death donor, may develop ischaemic cholangiopathy leading to non-anastomotic strictures [29]. Other less frequent complications such as recurrence of a primary sclerosing cholangitis in the liver graft and secondary sclerosing cholangitis can produce structural lesions in the biliary tree. Living donor liver transplantation also has a high incidence of biliary complications (for example, leaks and stenosis) because of certain features of the surgical technique. This complication may increase both morbidity and resource consumption in some

patients. However, few recommendations or case descriptions are currently available. The case reports that have been published describe patients with multiple episodes of bacterial cholangitis requiring readmission and the use of broad-spectrum antibiotics [198], which may increase bile and bowel colonization with MDR pathogens. When a liver transplant patient develops recurrent cholangitis, we must always search for a biliary stenosis and try to resolve it surgically or by percutaneous dilatation. Little information is available regarding the management of recurrent cholangitis in the setting of liver transplantation, although this clinical situation may be more frequent in daily clinical practice than the literature suggests.

#### **Recurrent urinary tract infection**

Recurrent urinary tract infection (UTI), defined as three or more episodes of symptomatic urinary tract infection over a 12-month period or two episodes in the previous 6 months [199], is a common problem in renal transplant patients. Febrile recurrent UTI in patients with no abnormalities in bladder voiding such as neurogenic bladder or diabetic cystopathy may be secondary to post-transplant vesicoureteral reflux; in most of these patients, surgical correction leads to resolution of the episodes of UTI and prolongs the life of the graft [200]. However, most recurrent cystitis and some recurrent febrile UTIs have no underlying anatomical alterations and, consequently, should be managed medically. In addition, recurrent UTI in renal transplantation without vesicoureteral reflux may cause allograft scarring, although no impairment of long-term graft functioning has been shown [201]. The first diagnostic approach in renal transplant patients with recurrent UTI should include static or dynamic imaging studies of the genitourinary tract in order to rule out anatomical defects. Surgical correction of the urinary obstruction or vesico-ureteric reflux may cure recurrent infections in the majority of patients. However, in many cases no underlying anatomical or functional reason for recurrent UTI will be identified and the dilemma of giving long-term antibiotic prophylaxis may arise. In addition to increasing the risk of acquiring MDR pathogens, few data regarding the efficacy of antibiotic prophylaxis in renal transplant patients with recurrent UTI are available. There is also a lack of information about non-pharmacological measures, such as cranberry extract, to prevent UTI in this population of patients.

Finally, many kidney transplant recipients have recurrent UTI with MDR pathogens, narrowing the options for prophylaxis with orally available antibiotics. A recently published systematic review of the literature regarding five strategies to control recurrent UTI in women concluded that daily low-dose nitrofurantoin prophylaxis was the most efficacious strategy [202]. However, in patients with low glomerular filtration rate



(<60 mL/min) nitrofurantoin serum levels may increase, leading to toxicity, and urinary concentrations decrease, leading to treatment failures. Thus, daily low-dose nitrofurantoin prophylaxis should be evaluated with caution for renal transplant patients and it should be contraindicated in most patients due to the little information about its safety. Currently, the available evidence does not allow making a final recommendation on this issue and management should be individualized.

#### Cyst infection

Cyst infection of the native kidney can occur in patients with renal transplantation due to polycystic renal disease. Many patients with polycystic disease also have liver cysts, which may also suffer infectious complications. Around 75% of the episodes are caused by *E. coli* and around 70% can be cured with antibiotics [203]. However, some cases require surgical drainage, especially larger infected cysts [203]. The success of medical treatment of this complication depends mainly on the penetration of antibiotics into the infected cysts. While fluoroquinolones, sulfamethoxazole-trimethoprim, metronidazole and clindamycin reach optimal concentrations inside the cysts, betalactams and aminoglycosides have poor penetration [204–209]. This may lead to subtherapeutic antibiotic concentrations in the cyst, increasing the rate of drug resistance. No studies are available about the management of infected cysts with MDR pathogens in renal transplant patients. However, infected cysts with aggressive multidrug-resistant pathogens (such as *P. aeruginosa*) may require surgical treatment, including drainage or native kidney nephrectomy.

#### Mediastinitis

Bacterial mediastinitis is a possible complication of heart, lung and combined heart-lung transplantation. While the incidence of mediastinitis after cardiac surgery is estimated to be below 2% of patients, its mortality remains high (around 35%) [210]. In heart transplant patients, mediastinitis is often associated with the use of left-ventricular assist devices [211,212]. The majority of the cases are caused by Gram-positive bacteria (including *S. aureus* and coagulase-negative staphylococci), although around a third are caused by Gram-negative bacilli [212]. The incidence of MDR bacteria in surgical site infections after heart transplantation was high in one study (including coagulase-negative staphylococci, MRSA and ESBL-producing *E. coli*) [54], so we must bear in mind a possible high incidence of MDR pathogens causing mediastinitis in heart transplant patients. Cases of MRSA [213], vancomycin-intermediate *S. aureus* [214], VRE [215] and non-fermentative bacilli [216] have been described in *Mediastinitis* after heart transplantation. The first approach for the treatment of bacterial mediastinitis in lung or heart transplantation is early and aggressive surgical

debridement [217]. Vacuum-assisted closure therapy combined with appropriate antibiotic treatment may be useful after surgery [218]. Choice of antibiotic therapy should be guided by bacterial isolation and antibiogram.

#### Tracheobronchial bacterial infections in lung transplant patients

The surgical procedure of lung transplantation implies the interruption of the bronchial artery circulation. As a consequence of ischaemia, the epithelium integrity is destroyed and the mucociliary clearance impaired, leading to epithelial sloughing, which together with bronchial hyperresponsiveness, increased mucus production and post-surgical altered cough reflexes, impairs the airway defences against pathogens [219]. Obviously, as a consequence of a limited exposure to immune defence mechanisms and poor concentrations of a systemically-administered antibiotic in the necrotic tissues, bacterial colonization and infection at the bronchial anastomosis is very frequent in lung transplant patients. This unfavourable situation is transient. Patients are at risk until collateral circulation develops from the pulmonary artery circulation, reaching a stable situation between 4–6 weeks post-transplantation. During the period of high risk, most centres perform routine bronchoscopic examinations to evaluate necrosis, purulence, ulcerations, dehiscence and strictures, and to obtain samples for microbiological identification of potential pathogens at the anastomotic site. Whereas little information on bacterial pathogens is available in the literature, fungal bronchial anastomotic infections leading to life-threatening bronchovascular fistulas have been reported [220,221]. Bacterial pathogens include *P. aeruginosa* and staphylococci [222]. Although no published data are available, most centres use aerosolized antibiotics (colistin and/or tobramycin) to treat these infections and reserve systemic therapies for situations where there is risk of local invasion.

Some patients develop late sequelae that include anastomotic strictures and bronchial stenosis that lead to long-term impairment of mucus clearance and recurrent post-obstructive lung infection. These situations frequently require balloon dilation, laser photoresection and/or endobronchial stent placement [223]. Moreover, whereas the highest incidence of pneumonia after lung transplantation is during the first month [35], at later stages of the post-transplant period many lung recipients develop bronchiectasis that increases the risk of recurrent infections. In both situations, because of the frequent exposure to antibiotics, lung transplant patients have a high risk of colonization and subsequent infection with MDR/XDR pathogens (mainly *P. aeruginosa* and *S. aureus*) that become progressively more difficult to treat. Therefore, whereas no literature is available to directly support this view, a judicious use of

antibiotics is recommended, trying to treat only proven acute infections. Combination therapies including both systemic and aerosolized antibiotics might reduce the risk of rapid selection of resistant isolates. The use of antibiotics at high doses and the optimization of pharmacokinetics by using continuous/prolonged infusion of beta-lactams might further be helpful. Other strategies are based on the hypothesis that repeated and regular antibiotic therapies could reduce the bacterial burden leading to infection. In order to minimize the risk of selecting resistant isolates, such therapies have been given twice weekly and always include a full day of combination therapy with a continuous/prolonged infusion of a betalactam and a once daily high dose of fluoroquinolone, as well as aerosolized colistin/tobramycin. This strategy followed for up to 12 months has so far been successful in a limited number of patients, avoiding pneumonia recurrence without selection of resistant isolates (C. van Delden, unpublished data). However in the absence of a clinical trial, this strategy can so far not be recommended routinely.

#### **Intra-abdominal infection and abscesses**

Intra-abdominal infection is a common complication after liver, pancreas, intestinal or multivisceral transplantation, because all those surgeries involve manipulation of the abdominal viscera. This complication affected 22% of patients in a study of 217 pancreas transplant recipients at a single institution and was frequently accompanied by bloodstream infection [224]. In pancreas transplant patients, secondary peritonitis is usually associated with anastomotic leaks or pancreas fistulae. Infection with bacteria in general and specifically surgical-site bacterial infection occurs mainly within the first month of transplantation [225] but bacterial peritonitis after pancreas transplantation may occur later, due to the development of late anastomotic leaks [226]. Usually, secondary peritonitis after pancreas, liver or intestinal transplantation is cured after surgical repair of the anatomical site of the infection and with appropriate antimicrobial therapy. However, if infection persists, a shift from a pro-inflammatory cytokine to an anti-inflammatory pattern may occur, reducing the percentage of HLA-DR (CD 14) expressing monocytes, which culminates in a situation of immune palsy [227]. Clinically, tertiary peritonitis leads to an impairment of the wound healing capacity. As many of these patients receive broad-spectrum antibiotics, peritoneal super-infection with MDR pathogens occurs frequently, leading finally to tertiary peritonitis. In these patients, the risk of infection with MDR Gram-positive and Gram-negative bacteria increases considerably [228], and *Candida* spp. appear frequently as a co-pathogen.

The first approach to the treatment of secondary and tertiary peritonitis in SOT patients includes the identification and surgical repair of the leak responsible for this situation.

Antimicrobial therapy for tertiary peritonitis should be guided by local antimicrobial resistance data and by antibiogram of the strains isolated after surgical procedure or drainage of the collections. Little information is available about the pharmacokinetics of antimicrobials in the peritoneal fluid after systemic administration, and much of it comes from case reports or short case series. Imipenem [229], meropenem [230], daptomycin [231], linezolid [214,232] and colistin [233] probably reach optimal concentrations in peritoneal fluid after systemic treatments and are good options for the treatment of peritonitis due to MDR bacteria. Other antimicrobials such as ertapenem [234] and tigecycline [235] reach inappropriate concentrations in peritoneal fluid, and so dose increases must be considered for the treatment of tertiary peritonitis. Although vancomycin may reach concentrations above the MIC in peritoneal fluid after systemic administration in patients with peritonitis [236], its pharmacokinetics in peritoneal fluid during prolonged treatments has not been established. Fluconazole is the treatment of choice for *Candida* spp. peritonitis [237]. Although no information about the distribution of echinocandins in peritoneal fluid is available, some clinical trials and case series suggest that these drugs may be an optimal treatment for non-albicans *Candida* peritonitis [238,239].

#### **Transparency Declaration**

CC reports receiving speaker honoraria, grant support or consultancy fees from Astellas, Pfizer, Novartis, Roche, Gilead, Genzyme and Merck. CVD reports speaker honoraria, grant support, travel support and consultancy fees from Astellas, Gilead, Pfizer, MSD, Basilea and Sanofi. JG has received grant support from Gilead, Pfizer and Instituto de Salud Carlos III. TW is a member of the Advisory Board of AstraZeneca, Basilea, Bayer Pharma, Novartis and Pfizer Pharma, and has received fees for lectures from Astellas, AstraZeneca, Bayer Pharma, GSK, Infectopharm, Novartis and Pfizer. MA reports receiving grant support from Gilead and Merck, and speaker honoraria from Pfizer, Gilead, Merck and Sanofi. JC reports grants from Instituto Carlos III, payment for lectures from Novartis, Merck, Pfizer and Roche and payment for development of educational presentations from Astellas.

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