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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-reistant (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])

S. aureus	*Enterococcus spp.*	*Enterobacteriaceae*	*P. aeruginosa*
Active agents: Antimicrobial category (agents) • Aminoglycosides (gentamicin) • Ansamycins (rifampin/rifampicin) • Cephalosporins (ceftaroline) • Anti-staphylococcal β-lactams (oxacillin) • Cephamycins (cefoxitin) • Fluorquinolones (cipro/moxifloxacin) • Folate pathway inhibitors (sulfamethoxazole-trimethoprim) • Fucidanes (fusidic acid) • Glycopeptides (vancomycin, teicoplanin, telavancin) • Glycylcyclines (tigecycline) • Lincosamides (clindamycin) • Lipopeptides (daptomycin) • Macrolides (erythromycin) • Oxazolidinones (linezolid) • Phenicols (chloramphenicol) • Phosphonic acids (fosfomycin) • Streptogramins (quinupristin-dalfopristin) • Tetracyclines (tetracycline, doxycycline, minocycline)	Active agents: Antimicrobial category (agents) • Aminoglycosides, except streptomycin (high-level resistance gentamicin) • Streptomycin (high-level resistance streptomycin) • Carbapenems (imipenem, meropenem, doripenem) • Fluorquinolones (ciprofloxacin, levofloxacin, moxifloxacin) • Glycopeptides (vancomycin, teicoplanin) • Glycylcyclines (tigecycline) • Lipopeptides (daptomycin) • Oxazolidinones (linezolid) • Penicillins (ampicillin) • Streptogramins (quinupristin-dalfopristin) • Tetracycline (doxycycline, minocycline)	Active agents: Antimicrobial category (agents) • Aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin) • Anti-MRSA cephalosporins (ceftaroline) • Anti-pseudomonal penicillins + β-lactamase inhibitors (ticarcillin-clavulanic acid, piperacillin-tazobactam) • Carbapenems (imipenem, meropenem, ertapenem, doripenem) • Non-extended spectrum cephalosporins; 1st and 2nd generation cephalosporins (cefazolin, cefuroxime) • Extended-spectrum cephalosporins; 3rd and 4th generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime) • Cephamycins (cefoxitin, cefotetan) • Fluorquinolones (ciprofloxacin) • Folate pathway inhibitors (sulfamethoxazole-trimethoprim) • Glycylcyclines (tigecycline) • Monobactams (aztreonam) • Penicillins (ampicillin) • Penicillins + β-lactamase inhibitors (amoxicillin-clavulanic acid, ampicillin-sulbactam) • Phenicols (chloramphenicol) • Phosphonic acids (fosfomycin) • Polymyxins (colistin) • Tetracyclines (tetracycline, doxycycline, minocycline)	Active agents: Antimicrobial category (agents) • Aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin) • Anti-pseudomonals carbapenems (imipenem, meropenem, doripenem) • Anti-pseudomonals cephalosporins (ceftazidime, cefepime) • Anti-pseudomonals fluorquinolones (ciprofloxacin, levofloxacin) • Anti-pseudomonal penicillins + β-lactamase inhibitors (ticarcillin-clavulanic acid, piperacillin-tazobactam) • Monobactams (aztreonam) • Phosphonic acids (fosfomycin) • Polymyxins (colistin polymyxin B)

Criteria for multidrug-resistant (MDR): non-susceptible to ≥1 agent in ≥3 antimicrobial categories or methicillin resistance in the case of *S. aureus*. Criteria for extensively drug-resistant (XDR): non-susceptible to ≥1 agent in all but ≤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 breakpoints 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 multidrug-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. baumanii* [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 recipients 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 ≥1 active agent in ≥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 β-lactams [71]. This synergistic effect seems to be achieved by a seesaw effect on daptomycin MIC induced by the use of antistaphylococcal β-lactams [72], increasing the incorporation of daptomycin in the *S. aureus* cellular wall [71]. Finally, the combination of daptomycin plus fosfomycin

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 *S. aureus*	Recommended	Recommended	Recommended prior to transplantation	Consider clorhexidin bathing in areas of high prevalence during ICU stay Consider nasal mupyrocin 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 *E. coli*	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 *E. coli*)	Recommended	Recommended	Not recommended	Not recommended	Recommended
KPC-producing *K. pneumoniae*	Recommended	Recommended	Recommended	Not recommended	Recommended
MDR/XDR non-fermentative Gram-negative bacilli	Recommended	Recommended[a]	Recommended prior to lung transplantation Not recommended for other SOT	Not recommended	Recommended

[a]Isolation room is not routinely recommended for patients infected or colonized with MDR/XDR *B. cepacea*.

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 β-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, 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 β-lactamases or carbapenemases require single-bed isolation and contact precautions (B-II).
- For the treatment of ESBL- or derepressed ampC β-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 β-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 carbapenamase-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 chromosomic 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, *Burkolderia* 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 (OFPBL 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-sphe-no-ethmoidectomy), 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. cepacea* 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 betalactam 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. xylosoxidans* 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 (betalactams, 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 betalactams, 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 glycylcycline 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 lipoglycopeptide 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 *E. faecalis*	No relevant interactions with immunosuppressants	Alterations of liver function test occurred in 2.5% of patients in phase 3 clinical trials	No	Seroconversion to positive direct Coombs' test in around 10% of patients	No published evidence
Tigecycline	MRSA Vancomycin-resistant enterococci MDR Enterobacteriaceae *Clostridium difficile*	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	No published evidence
Linezolid	MRSA Vancomycin-resistant enterococci *M. tuberculosis* Slow-growing mycobacteria Atypical pathogens: *Rhodococcus equi*, *Listeria monocytogenes*, *Nocardia* spp.	No relevant interactions with immunosuppressants	No	Not direct renal toxicity but some cases of acute interstitial nephritis have been reported	Thrombocytopenia Anaemia Lactic acidosis Peripheral polyneuropathy Serotoninergic 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	MRSA Vancomycin-resistant enterococci MDR Enterobacteriaceae MDR *P. aeruginosa*	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	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
Polymyxins/ Colistin	MDR Enterobacteriaceae MDR non-fermentative Gram-negative bacilli	No relevant interactions ith immunosuppressants	Slight increases of transaminases have been described.	Highly variable depending on the series (0–54.5%)	Peripheral and orofacial parestesias Ataxia Visual disturbances Vertigo Mental confusion Seizure Myasthenia-like syndrome	Renal toxicity has been reported to appear in nearly 1/3 of SOT patients

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 Enterobacteriaeae [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): • 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 • CLCR <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 • 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	According to creatinine clearance (CL_{CR}) and over 60 kg bodyweight: • CL_{CR} 20–50 mL/min, 1–2 million IU every 12 h • CL_{CR} 10–20 mL/min, 1 million IU every 12–18 h • CL_{CR} <10 mL/min, 1 million IU every 18–24 h	According to creatinine clearance (CL_{CR}) and over 60 kg bodyweight: • CL_{CR} 50–80 mL/min, 75–115 mg every 12 h • CL_{CR} 30–50 mL/min, 66–150 every 12–24 h • CL_{CR} 10–30 mL/min, 100–150 every 36 h
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 Intestinal/multivisceral transplantation
Mediastinitis	Heart transplantation Lung transplantation Combined heart-lung transplantation
Recurrent respiratory tract infection	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.

References

1. Magiorakos AP, Srinivasan A, Carey RB *et al.* Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; 18: 268–281.

2. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis* 2008; 197: 1079–1081.
3. Rice LB. Progress and challenges in implementing the research on ESKAPE pathogens. *Infect Control Hosp Epidemiol* 2010; 31(suppl 1): S7–S10.
4. Daxboeck F, Budic T, Assadian O, Reich M, Koller W. Economic burden associated with multi-resistant Gram-negative organisms compared with that for methicillin-resistant *Staphylococcus aureus* in a university teaching hospital. *J Hosp Infect* 2006; 62: 214–218.
5. Linares L, Cofan F, Cervera C *et al.* Infection-related mortality in a large cohort of renal transplant recipients. *Transplant Proc* 2007; 39: 2225–2227.
6. Linares L, Cervera C, Cofan F *et al.* Epidemiology and outcomes of multiple antibiotic-resistant bacterial infection in renal transplantation. *Transplant Proc* 2007; 39: 2222–2224.
7. Kang CI, Kim SH, Park WB *et al.* Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrob Agents Chemother* 2005; 49: 760–766.
8. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007; 60: 913–920.
9. Hamandi B, Holbrook AM, Humar A *et al.* Delay of adequate empiric antibiotic therapy is associated with increased mortality among solid-organ transplant patients. *Am J Transplant* 2009; 9: 1657–1665.
10. Candel FJ, Grima E, Matesanz M *et al.* Bacteremia and septic shock after solid-organ transplantation. *Transplant Proc* 2005; 37: 4097–4099.
11. Edmond MB, Wenzel RP. Screening inpatients for MRSA–case closed. *N Engl J Med* 2013; 368: 2314–2315.
12. Wenzel RP, Edmond MB. Infection control: the case for horizontal rather than vertical interventional programs. *Int J Infect Dis* 2010; 14 (suppl 4): S3–S5.
13. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000; 132: 391–402.
14. Pronovost P, Needham D, Berenholtz S *et al.* An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006; 355: 2725–2732.
15. Derde LP, Cooper BS, Goossens H *et al.* Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *Lancet Infect Dis* 2014; 14: 31–39.
16. Bodro M, Sabe N, Tubau F *et al.* Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. *Transplantation* 2013; 96: 843–849.
17. Holmes NE, Johnson PD, Howden BP. Relationship between vancomycin-resistant *Staphylococcus aureus*, vancomycin-intermediate *S. aureus*, high vancomycin MIC, and outcome in serious *S. aureus* infections. *J Clin Microbiol* 2012; 50: 2548–2552.
18. Alam MR, Donabedian S, Brown W *et al.* Heteroresistance to vancomycin in *Enterococcus faecium*. *J Clin Microbiol* 2001; 39: 3379–3381.
19. Meletis G, Tzampaz E, Sianou E *et al.* Colistin heteroresistance in carbapenemase-producing *Klebsiella pneumoniae*. *J Antimicrob Chemother* 2011; 66: 946–947.
20. Pournaras S, Kristo I, Vrioni G *et al.* Characteristics of meropenem heteroresistance in *Klebsiella pneumoniae* carbapenemase (KPC)-producing clinical isolates of *K. pneumoniae*. *J Clin Microbiol* 2010; 48: 2601–2604.
21. Hermes DM, Pormann Pitt C, Lutz L *et al.* Evaluation of heteroresistance to polymyxin B among carbapenem-susceptible and -resistant *Pseudomonas aeruginosa*. *J Med Microbiol* 2013; 62 (Pt 8): 1184–1189.
22. Li J, Rayner CR, Nation RL *et al.* Heteroresistance to colistin in multidrug-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2006; 50: 2946–2950.
23. Maor Y, Hagin M, Belausov N *et al.* Clinical features of heteroresistant vancomycin-intermediate *Staphylococcus aureus* bacteremia versus those of methicillin-resistant *S. aureus* bacteremia. *J Infect Dis* 2009; 199: 619–624.
24. Satola SW, Farley MM, Anderson KF, Patel JB. Comparison of detection methods for heteroresistant vancomycin-intermediate *Staphylococcus aureus*, with the population analysis profile method as the reference method. *J Clin Microbiol* 2011; 49: 177–183.
25. Brook NR, White SA, Waller JR, Veitch PS, Nicholson ML. Non-heart beating donor kidneys with delayed graft function have superior graft survival compared with conventional heart-beating donor kidneys that develop delayed graft function. *Am J Transplant* 2003; 3: 614–618.
26. Dharnidharka VR, Agodoa LY, Abbott KC. Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients–an analysis of USRDS data. *Am J Transplant* 2007; 7: 653–661.
27. de Rave S, Hansen BE, Groenland TH *et al.* Heterotopic vs. orthotopic liver transplantation for chronic liver disease: a case-control comparison of short-term and long-term outcomes. *Liver Transpl* 2005; 11: 396–401.
28. Wang SF, Huang ZY, Chen XP. Biliary complications after living donor liver transplantation. *Liver Transpl* 2011; 17: 1127–1136.
29. DeOliveira ML, Jassem W, Valente R *et al.* Biliary complications after liver transplantation using grafts from donors after cardiac death: results from a matched control study in a single large volume center. *Ann Surg* 2011; 254: 716–722; discussion 22–3.
30. Arnow PM, Zachary KC, Thistlethwaite JR, Thompson KD, Bova JL, Newell KA. Pathogenesis of early operative site infections after orthotopic liver transplantation. *Transplantation* 1998; 65: 1500–1503.
31. Lo A, Stratta RJ, Hathaway DK *et al.* Long-term outcomes in simultaneous kidney-pancreas transplant recipients with portal-enteric versus systemic-bladder drainage. *Am J Kidney Dis* 2001; 38: 132–143.
32. Akhter K, Timpone J, Matsumoto C, Fishbein T, Kaufman S, Kumar P. Six-month incidence of bloodstream infections in intestinal transplant patients. *Transpl Infect Dis* 2012; 14: 242–247.
33. Guaraldi G, Cocchi S, Codeluppi M *et al.* Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. *Transplantation* 2005; 80: 1742–1748.
34. Middleton SJ, Jamieson NV. The current status of small bowel transplantation in the UK and internationally. *Gut* 2005; 54: 1650–1657.
35. Aguilar-Guisado M, Givalda J, Ussetti P *et al.* Pneumonia after lung transplantation in the RESITRA Cohort: a multicenter prospective study. *Am J Transplant* 2007; 7: 1989–1996.
36. Fluit AC, Jones ME, Schmitz FJ, Acar J, Gupta R, Verhoef J. Antimicrobial susceptibility and frequency of occurrence of clinical blood isolates in Europe from the SENTRY antimicrobial surveillance program, 1997 and 1998. *Clin Infect Dis* 2000; 30: 454–460.
37. Luzzaro F, Vigano EF, Fossati D *et al.* Prevalence and drug susceptibility of pathogens causing bloodstream infections in northern Italy: a two-year study in 16 hospitals. *Eur J Clin Microbiol Infect Dis* 2002; 21: 849–855.
38. Moreno A, Cervera C, Gavalda J *et al.* Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. *Am J Transplant* 2007; 7: 2579–2586.
39. de Kraker ME, Jarlier V, Monen JC, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. *Clin Microbiol Infect* 2013; 19: 860–868.
40. Kallen AJ, Mu Y, Bulens S *et al.* Health care-associated invasive MRSA infections, 2005-2008. *JAMA* 2010; 304: 641–648.

41. Torre-Cisneros J, Herrero C, Canas E, Reguera JM, De La Mata M, Gomez-Bravo MA. High mortality related with Staphylococcus aureus bacteremia after liver transplantation. *Eur J Clin Microbiol Infect Dis* 2002; 21: 385–388.
42. Wertheim HF, Melles DC, Vos MC *et al.* The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infect Dis* 2005; 5: 751–762.
43. Abudu L, Blair I, Fraise A, Cheng KK. Methicillin-resistant *Staphylococcus aureus* (MRSA): a community-based prevalence survey. *Epidemiol Infect* 2001; 126: 351–356.
44. Charlebois ED, Bangsberg DR, Moss NJ *et al.* Population-based community prevalence of methicillin-resistant *Staphylococcus aureus* in the urban poor of San Francisco. *Clin Infect Dis* 2002; 34: 425–433.
45. Jernigan JA, Pullen AL, Partin C, Jarvis WR. Prevalence of and risk factors for colonization with methicillin-resistant *Staphylococcus aureus* in an outpatient clinic population. *Infect Control Hosp Epidemiol* 2003; 24: 445–450.
46. Paterson DL, Rihs JD, Squier C, Gayowski T, Sagnimeni A, Singh N. Lack of efficacy of mupirocin in the prevention of infections with *Staphylococcus aureus* in liver transplant recipients and candidates. *Transplantation* 2003; 75: 194–198.
47. Santoro-Lopes G, de Gouvea EF, Monteiro RC *et al.* Colonization with methicillin-resistant *Staphylococcus aureus* after liver transplantation. *Liver Transpl* 2005; 11: 203–209.
48. Acton DS, Plat-Sinnige MJ, van Wamel W, de Groot N, van Belkum A. Intestinal carriage of *Staphylococcus aureus*: how does its frequency compare with that of nasal carriage and what is its clinical impact? *Eur J Clin Microbiol Infect Dis* 2009; 28: 115–127.
49. Squier C, Rihs JD, Risa KJ *et al. Staphylococcus aureus* rectal carriage and its association with infections in patients in a surgical intensive care unit and a liver transplant unit. *Infect Control Hosp Epidemiol* 2002; 23: 495–501.
50. Hashimoto M, Sugawara Y, Tamura S *et al.* Methicillin-resistant *Staphylococcus aureus* infection after living-donor liver transplantation in adults. *Transpl Infect Dis* 2008; 10: 110–116.
51. Bert F, Bellier C, Lassel L *et al.* Risk factors for *Staphylococcus aureus* infection in liver transplant recipients. *Liver Transpl* 2005; 11: 1093–1099.
52. Russell DL, Flood A, Zaroda TE *et al.* Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. *Am J Transplant* 2008; 8: 1737–1743.
53. Singh N, Squier C, Wannstedt C, Keyes L, Wagener MM, Cacciarelli TV. Impact of an aggressive infection control strategy on endemic *Staphylococcus aureus* infection in liver transplant recipients. *Infect Control Hosp Epidemiol* 2006; 27: 122–126.
54. Ramos A, Asensio A, Munez E *et al.* Incisional surgical infection in heart transplantation. *Transpl Infect Dis* 2008; 10: 298–302.
55. Ramos A, Asensio A, Munez E *et al.* Incisional surgical site infection in kidney transplantation. *Urology* 2008; 72: 119–123.
56. Asensio A, Ramos A, Cuervas-Mons V *et al.* Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. *Liver Transpl* 2008; 14: 799–805.
57. Bonatti H, Pruett TL, Brandacher G *et al.* Pneumonia in solid organ recipients: spectrum of pathogens in 217 episodes. *Transplant Proc* 2009; 41: 371–374.
58. Manuel O, Lien D, Weinkauf J, Humar A, Cobos I, Kumar D. Methicillin-resistant *Staphylococcus aureus* infection after lung transplantation: 5-year review of clinical and molecular epidemiology. *J Heart Lung Transplant* 2009; 28: 1231–1236.
59. Raboud J, Saskin R, Simor A *et al.* Modeling transmission of methicillin-resistant *Staphylococcus aureus* among patients admitted to a hospital. *Infect Control Hosp Epidemiol* 2005; 26: 607–615.
60. McBryde ES, Pettitt AN, McElwain DL. A stochastic mathematical model of methicillin resistant *Staphylococcus aureus* transmission in an intensive care unit: predicting the impact of interventions. *J Theor Biol* 2007; 245: 470–481.
61. Sadsad R, Sintchenko V, McDonnell GD, Gilbert GL. Effectiveness of Hospital-Wide Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection control policies differs by Ward Specialty. *PLoS ONE* 2013; 8: e83099.
62. Bootsma MC, Diekmann O, Bonten MJ. Controlling methicillin-resistant *Staphylococcus aureus*: quantifying the effects of interventions and rapid diagnostic testing. *Proc Natl Acad Sci USA* 2006; 103: 5620–5625.
63. Robotham JV, Jenkins DR, Medley GF. Screening strategies in surveillance and control of methicillin-resistant *Staphylococcus aureus* (MRSA). *Epidemiol Infect* 2007; 135: 328–342.
64. Huang SS, Septimus E, Kleinman K *et al.* Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013; 368: 2255–2265.
65. Liu C, Bayer A, Cosgrove SE *et al.* Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011; 52: 285–292.
66. Baddour LM, Wilson WR, Bayer AS *et al.* Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 111: e394–e434.
67. Fowler VG Jr, Boucher HW, Corey GR *et al.* Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006; 355: 653–665.
68. Soriano A, Marco F, Martinez JA *et al.* Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008; 46: 193–200.
69. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis* 2012; 54: 755–771.
70. Murray KP, Zhao JJ, Davis SL *et al.* Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. *Clin Infect Dis* 2013; 56: 1562–1569.
71. Dhand A, Bayer AS, Pogliano J *et al.* Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: role of enhanced daptomycin binding. *Clin Infect Dis* 2011; 53: 158–163.
72. Yang SJ, Xiong YQ, Boyle-Vavra S, Daum R, Jones T, Bayer AS. Daptomycin-oxacillin combinations in treatment of experimental endocarditis caused by daptomycin-nonsusceptible strains of methicillin-resistant *Staphylococcus aureus* with evolving oxacillin susceptibility (the "seesaw effect"). *Antimicrob Agents Chemother* 2010; 54: 3161–3169.
73. Miro JM, Entenza JM, Del Rio A *et al.* High-dose daptomycin plus fosfomycin is safe and effective in treating methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother* 2012; 56: 4511–4515.
74. Kalil AC, Klompas M, Haynatzki G, Rupp ME. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. *BMJ Open* 2013; 3: e003912.
75. Gold HS. Vancomycin-resistant enterococci: mechanisms and clinical observations. *Clin Infect Dis* 2001; 33: 210–219.
76. Hidron AI, Edwards JR, Patel J *et al.* NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the national healthcare safety

network at the centers for disease control and prevention, 2006-2007. *Infect Control Hosp Epidemiol* 2008; 29: 996–1011.
77. Gearhart M, Martin J, Rudich S *et al.* Consequences of vancomycin-resistant enterococcus in liver transplant recipients: a matched control study. *Clin Transplant* 2005; 19: 711–716.
78. Papanicolaou GA, Meyers BR, Meyers J *et al.* Nosocomial infections with vancomycin-resistant *Enterococcus faecium* in liver transplant recipients: risk factors for acquisition and mortality. *Clin Infect Dis* 1996; 23: 760–766.
79. Weber SG, Huang SS, Oriola S *et al.* Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: position statement from the Joint SHEA and APIC Task Force. *Am J Infect Control* 2007; 35: 73–85.
80. Price CS, Paule S, Noskin GA, Peterson LR. Active surveillance reduces the incidence of vancomycin-resistant enterococcal bacteremia. *Clin Infect Dis* 2003; 37: 921–928.
81. Wang JT, Chen YC, Chang SC *et al.* Control of vancomycin-resistant enterococci in a hospital: a five-year experience in a Taiwanese teaching hospital. *J Hosp Infect* 2004; 58: 97–103.
82. Yoonchang SW, Peck KR, Kim OS *et al.* Efficacy of infection control strategies to reduce transmission of vancomycin-resistant enterococci in a tertiary care hospital in Korea: a 4-year follow-up study. *Infect Control Hosp Epidemiol* 2007; 28: 493–495.
83. Montecalvo MA, de Lencastre H, Carraher M *et al.* Natural history of colonization with vancomycin-resistant *Enterococcus faecium*. *Infect Control Hosp Epidemiol* 1995; 16: 680–685.
84. Donskey CJ, Hoyen CK, Das SM, Helfand MS, Hecker MT. Recurrence of vancomycin-resistant Enterococcus stool colonization during antibiotic therapy. *Infect Control Hosp Epidemiol* 2002; 23: 436–440.
85. Lee WG, Park IJ, Jin HY, Park MH. Relapse and reacquisition of rectal colonization by vancomycin-resistant *Enterococcus faecium* after decolonization. *Epidemiol Infect* 2010; 138: 1449–1453.
86. Kauffman CA. Therapeutic and preventative options for the management of vancomycin-resistant enterococcal infections. *J Antimicrob Chemother* 2003; 51 (suppl 3): iii23–30.
87. Stiefel U, Pultz NJ, Helfand MS, Donskey CJ. Efficacy of oral ramoplanin for inhibition of intestinal colonization by vancomycin-resistant enterococci in mice. *Antimicrob Agents Chemother* 2004; 48: 2144–2148.
88. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. *Clin Microbiol Rev* 2000; 13: 686–707.
89. Arias CA, Panesso D, McGrath DM *et al.* Genetic basis for in vivo daptomycin resistance in enterococci. *N Engl J Med* 2011; 365: 892–900.
90. Balli EP, Venetis CA, Miyakis S. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. *Antimicrob Agents Chemother* 2014; 58: 734–739.
91. Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis* 2005; 191: 2149–2152.
92. Pertel PE, Bernardo P, Fogarty C *et al.* Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. *Clin Infect Dis* 2008; 46: 1142–1151.
93. Koplowicz YB, Schwartz BS, Guglielmo BJ. Development of daptomycin-susceptible, methicillin-resistant *Staphylococcus aureus* pneumonia during high-dose daptomycin therapy. *Clin Infect Dis* 2009; 49: 1286–1287.
94. Cai Y, Wang R, Liang B, Bai N, Liu Y. Systematic review and meta-analysis of the effectiveness and safety of tigecycline for treatment of infectious disease. *Antimicrob Agents Chemother* 2011; 55: 1162–1172.
95. Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. *Clin Infect Dis* 2012; 54: 1699–1709.
96. Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. *Lancet Infect Dis* 2011; 11: 834–844.
97. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother* 2011; 66: 1963–1971.
98. Sakoulas G, Bayer AS, Pogliano J *et al.* Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother* 2012; 56: 838–844.
99. Pena C, Pujol M, Ricart A *et al.* Risk factors for faecal carriage of *Klebsiella pneumoniae* producing extended spectrum beta-lactamase (ESBL-KP) in the intensive care unit. *J Hosp Infect* 1997; 35: 9–16.
100. Reddy P, Malczynski M, Obias A *et al.* Screening for extended-spectrum beta-lactamase-producing Enterobacteriaceae among high-risk patients and rates of subsequent bacteremia. *Clin Infect Dis* 2007; 45: 846–852.
101. Bert F, Larroque B, Dondero F *et al.* Risk factors associated with preoperative fecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in liver transplant recipients. *Transpl Infect Dis* 2014; 16: 84–89.
102. Martinez JA, Aguilar J, Almela M *et al.* Prior use of carbapenems may be a significant risk factor for extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella* spp. in patients with bacteraemia. *J Antimicrob Chemother* 2006; 58: 1082–1085.
103. Katsandri A, Avlamis A, Vasilakopoulou A *et al.* Risk factors for coexistence of fluoroquinolone resistance and ESBL production among Enterobacteriaceae in a Greek university hospital. *J Chemother* 2008; 20: 452–457.
104. Martin-Pena A, Cordero E, Fijo J *et al.* Prospective study of infectious complications in a cohort of pediatric renal transplant recipients. *Pediatr Transplant* 2009; 13: 457–463.
105. Linares L, Cervera C, Cofan F *et al.* Risk factors for infection with extended-spectrum and AmpC beta-lactamase-producing gram-negative rods in renal transplantation. *Am J Transplant* 2008; 8: 1000–1005.
106. Vidal E, Torre-Cisneros J, Blanes M *et al.* Bacterial urinary tract infection after solid organ transplantation in the RESITRA cohort. *Transpl Infect Dis* 2012; 14: 595–603.
107. Linares L, Cervera C, Hoyo I *et al. Klebsiella pneumoniae* infection in solid organ transplant recipients: epidemiology and antibiotic resistance. *Transplant Proc* 2010; 42: 2941–2943.
108. Bui KT, Mehta S, Khuu TH *et al.* Extended spectrum beta-lactamase-producing Enterobacteriaceae infection in heart and lung transplant recipients and in mechanical circulatory support recipients. *Transplantation* 2014; 97: 590–594.
109. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev* 2012; 25: 682–707.
110. Clancy CJ, Chen L, Shields RK *et al.* Epidemiology and molecular characterization of bacteremia due to carbapenem-resistant *Klebsiella pneumoniae* in transplant recipients. *Am J Transplant* 2013; 13: 2619–2633.
111. Cicora F, Mos F, Paz M, Allende NG, Roberti J. Infections with blaKPC-2-producing *Klebsiella pneumoniae* in renal transplant patients: a retrospective study. *Transplant Proc* 2013; 45: 3389–3393.
112. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D *et al.* Infection with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in solid organ transplantation. *Transpl Infect Dis* 2012; 14: 198–205.

113. Rana MM, Sturdevant M, Patel G, Huprikar S. Klebsiella necrotizing soft tissue infections in liver transplant recipients: a case series. *Transpl Infect Dis* 2013; 15: E157–E163.
114. Cheng NC, Yu YC, Tai HC *et al.* Recent trend of necrotizing fasciitis in Taiwan: focus on monomicrobial *Klebsiella pneumoniae* necrotizing fasciitis. *Clin Infect Dis* 2012; 55: 930–939.
115. Ariza-Heredia EJ, Patel R, Blumberg EA *et al.* Outcomes of transplantation using organs from a donor infected with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*. *Transpl Infect Dis* 2012; 14: 229–236.
116. Lubbert C, Becker-Rux D, Rodloff AC *et al.* Colonization of liver transplant recipients with KPC-producing *Klebsiella pneumoniae* is associated with high infection rates and excess mortality: a case-control analysis. *Infection* 2014; 42: 309–316.
117. Rodriguez-Bano J, Navarro MD, Romero L *et al.* Clinical and molecular epidemiology of extended-spectrum beta-lactamase-producing *Escherichia coli* as a cause of nosocomial infection or colonization: implications for control. *Clin Infect Dis* 2006; 42: 37–45.
118. Tacconelli E, Cataldo MA, Dancer SJ *et al.* ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect* 2014; 20(suppl 1): 1–55.
119. Munoz-Price LS, Hayden MK, Lolans K *et al.* Successful control of an outbreak of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* at a long-term acute care hospital. *Infect Control Hosp Epidemiol* 2010; 31: 341–347.
120. Kochar S, Sheard T, Sharma R *et al.* Success of an infection control program to reduce the spread of carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2009; 30: 447–452.
121. Schwaber MJ, Lev B, Israeli A *et al.* Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in israeli hospitals via a nationally implemented intervention. *Clin Infect Dis* 2011; 52: 848–855.
122. San-Juan R, Aguado JM, Lumbreras C *et al.* Selective intestinal decontamination with fluoroquinolones for the prevention of early bacterial infections after liver transplantation. *Liver Transpl* 2011; 17: 896–904.
123. Saidel-Odes L, Polachek H, Peled N *et al.* A randomized, double-blind, placebo-controlled trial of selective digestive decontamination using oral gentamicin and oral polymyxin E for eradication of carbapenem-resistant *Klebsiella pneumoniae* carriage. *Infect Control Hosp Epidemiol* 2012; 33: 14–19.
124. Machado E, Coque TM, Canton R, Baquero F, Sousa JC, Peixe L. Dissemination in Portugal of CTX-M-15-, OXA-1-, and TEM-1-producing Enterobacteriaceae strains containing the aac(6')-Ib-cr gene, which encodes an aminoglycoside- and fluoroquinolone-modifying enzyme. *Antimicrob Agents Chemother* 2006; 50: 3220–3221.
125. Puerto AS, Fernandez JG, del Castillo Jde D, Pino MJ, Angulo GP. In vitro activity of beta-lactam and non-beta-lactam antibiotics in extended-spectrum beta-lactamase-producing clinical isolates of *Escherichia coli*. *Diagn Microbiol Infect Dis* 2006; 54: 135–139.
126. Sousa D, Castelo-Corral L, Gutierrez-Urbon JM *et al.* Impact of ertapenem use on *Pseudomonas aeruginosa* and *Acinetobacter baumannii* imipenem susceptibility rates: collateral damage or positive effect on hospital ecology? *J Antimicrob Chemother* 2013; 68: 1917–1925.
127. Elliott E, Brink AJ, van Greune J *et al.* In vivo development of ertapenem resistance in a patient with pneumonia caused by *Klebsiella pneumoniae* with an extended-spectrum beta-lactamase. *Clin Infect Dis* 2006; 42: e95–e98.
128. Hawser SP, Bouchillon SK, Lascols C *et al.* Susceptibility of *Klebsiella pneumoniae* isolates from intra-abdominal infections and molecular characterization of ertapenem-resistant isolates. *Antimicrob Agents Chemother* 2011; 55: 3917–3921.
129. Poulou A, Voulgari E, Vrioni G *et al.* Outbreak caused by an ertapenem-resistant, CTX-M-15-producing *Klebsiella pneumoniae* sequence type 101 clone carrying an OmpK36 porin variant. *J Clin Microbiol* 2013; 51: 3176–3182.
130. Tangden T, Adler M, Cars O, Sandegren L, Lowdin E. Frequent emergence of porin-deficient subpopulations with reduced carbapenem susceptibility in ESBL-producing *Escherichia coli* during exposure to ertapenem in an in vitro pharmacokinetic model. *J Antimicrob Chemother* 2013; 68: 1319–1326.
131. Hawser SP, Bouchillon SK, Lascols C *et al.* Susceptibility of European *Escherichia coli* clinical isolates from intra-abdominal infections, extended-spectrum beta-lactamase occurrence, resistance distribution, and molecular characterization of ertapenem-resistant isolates (SMART 2008-2009). *Clin Microbiol Infect* 2012; 18: 253–259.
132. Rodriguez-Bano J, Alcala JC, Cisneros JM *et al.* Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008; 168: 1897–1902.
133. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006-09). *J Antimicrob Chemother* 2011; 66: 2070–2074.
134. Taglietti F, Di Bella S, Galati V, Topino S, Iappelli M, Petrosillo N. Carbapenemase-producing *Klebsiella pneumoniae*-related mortality among solid organ-transplanted patients: do we know enough? *Transpl Infect Dis* 2013; 15: E164–E165.
135. Shi SH, Kong HS, Xu J *et al.* Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. *Transpl Infect Dis* 2009; 11: 405–412.
136. Johnson LE, D'Agata EM, Paterson DL *et al. Pseudomonas aeruginosa* bacteremia over a 10-year period: multidrug resistance and outcomes in transplant recipients. *Transpl Infect Dis* 2009; 11: 227–234.
137. Botha P, Archer L, Anderson RL *et al. Pseudomonas aeruginosa* colonization of the allograft after lung transplantation and the risk of bronchiolitis obliterans syndrome. *Transplantation* 2008; 85: 771–774.
138. Hadjiliadis D, Steele MP, Chaparro C *et al.* Survival of lung transplant patients with cystic fibrosis harboring panresistant bacteria other than *Burkholderia cepacia*, compared with patients harboring sensitive bacteria. *J Heart Lung Transplant* 2007; 26: 834–838.
139. Meachery G, De Soyza A, Nicholson A *et al.* Outcomes of lung transplantation for cystic fibrosis in a large UK cohort. *Thorax* 2008; 63: 725–731.
140. Alexander BD, Petzold EW, Reller LB *et al.* Survival after lung transplantation of cystic fibrosis patients infected with *Burkholderia cepacia* complex. *Am J Transplant* 2008; 8: 1025–1030.
141. De Soyza A, Meachery G, Hester KL *et al.* Lung transplantation for patients with cystic fibrosis and *Burkholderia cepacia* complex infection: a single-center experience. *J Heart Lung Transplant* 2010; 29: 1395–1404.
142. Saiman L. Infection prevention and control in cystic fibrosis. *Curr Opin Infect Dis* 2011; 24: 390–395.
143. Vital D, Hofer M, Benden C, Holzmann D, Boehler A. Impact of sinus surgery on pseudomonal airway colonization, bronchiolitis obliterans syndrome and survival in cystic fibrosis lung transplant recipients. *Respiration* 2013; 86: 25–31.
144. Suhling H, Rademacher J, Greer M *et al.* Inhaled colistin following lung transplantation in colonised cystic fibrosis patients. *Eur Respir J* 2013; 42: 542–544.
145. Leung MK, Rachakonda L, Weill D, Hwang PH. Effects of sinus surgery on lung transplantation outcomes in cystic fibrosis. *Am J Rhinol* 2008; 22: 192–196.
146. Apisarnthanarak A, Mundy LM. Carbapenem-resistant *Pseudomonas aeruginosa* pneumonia with intermediate minimum inhibitory concen-

trations to doripenem: combination therapy with high-dose, 4-h infusion of doripenem plus fosfomycin versus intravenous colistin plus fosfomycin. *Int J Antimicrob Agents* 2012; 39: 271–272.
147. Prescott WA Jr, Gentile AE, Nagel JL, Pettit RS. Continuous-infusion antipseudomonal Beta-lactam therapy in patients with cystic fibrosis. *P T* 2011; 36: 723–763.
148. Lim TP, Lee W, Tan TY *et al.* Effective antibiotics in combination against extreme drug-resistant *Pseudomonas aeruginosa* with decreased susceptibility to polymyxin B. *PLoS ONE* 2011; 6: e28177.
149. Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* ventilator-associated pneumonia. *Respir Care* 2012; 57: 1226–1233.
150. Naesens R, Vlieghe E, Verbrugghe W, Jorens P, Ieven M. A retrospective observational study on the efficacy of colistin by inhalation as compared to parenteral administration for the treatment of nosocomial pneumonia associated with multidrug-resistant *Pseudomonas aeruginosa*. *BMC Infect Dis* 2011; 11: 317.
151. Laudano JB. Ceftaroline fosamil: a new broad-spectrum cephalosporin. *J Antimicrob Chemother* 2011; 66 (suppl 3): iii11–18.
152. File TM Jr, Wilcox MH, Stein GE. Summary of ceftaroline fosamil clinical trial studies and clinical safety. *Clin Infect Dis* 2012; 55(suppl 3): S173–S180.
153. Corrado ML. Integrated safety summary of CANVAS 1 and 2 trials: phase III, randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 2010; 65 (suppl 4): iv67–iv71.
154. Noskin GA. Tigecycline: a new glycylcycline for treatment of serious infections. *Clin Infect Dis* 2005; 41(suppl 5): S303–S314.
155. Stein GE, Babinchak T. Tigecycline: an update. *Diagn Microbiol Infect Dis* 2013; 75: 331–336.
156. Stumpf AN, Schmidt C, Hiddemann W, Gerbitz A. High serum concentrations of cyclosporin related to administration of tigecycline. *Eur J Clin Pharmacol* 2009; 65: 101–103.
157. Polilli E, Ursini T, Mazzotta E *et al.* Successful salvage therapy with Daptomycin for osteomyelitis caused by methicillin-resistant *Staphylococcus aureus* in a renal transplant recipient with Fabry-Anderson disease. *Ann Clin Microbiol Antimicrob* 2012; 11: 6.
158. Iwen PC, Mindru C, Kalil AC, Florescu DF. *Pediococcus acidilactici* endocarditis successfully treated with daptomycin. *J Clin Microbiol* 2012; 50: 1106–1108.
159. Vernadakis S, Saner FH, Rath PM *et al.* Successful salvage therapy with daptomycin after linezolid and vancomycin failure in a liver transplant recipient with methicillin-resistant *Staphylococcus aureus* endocarditis. *Transpl Infect Dis* 2009; 11: 346–348.
160. Jacobs JV, Hodges TN, Bremner RM, Walia R, Huang J, Smith MA. Hardware preservation after sternal wound infection in a lung transplant recipient. *Ann Thorac Surg* 2011; 92: 718–720.
161. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 2004; 38: 1673–1681.
162. Abraham G, Finkelberg D, Spooner LM. Daptomycin-induced acute renal and hepatic toxicity without rhabdomyolysis. *Ann Pharmacother* 2008; 42: 719–721.
163. Echevarria K, Datta P, Cadena J, Lewis JS 2nd. Severe myopathy and possible hepatotoxicity related to daptomycin. *J Antimicrob Chemother* 2005; 55: 599–600.
164. Marino EA, Blanchard E, Samuel R, Gallagher J. Acute interstitial nephritis associated with linezolid. *Ann Pharmacother* 2009; 43: 1728.
165. Savard S, Desmeules S, Riopel J, Agharazii M. Linezolid-associated acute interstitial nephritis and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. *Am J Kidney Dis* 2009; 54: e17–e20.
166. Esposito L, Kamar N, Guilbeau-Frugier C, Mehrenberger M, Modesto A, Rostaing L. Linezolid-induced interstitial nephritis in a kidney-transplant patient. *Clin Nephrol* 2007; 68: 327–329.
167. Radunz S, Juntermanns B, Kaiser GM *et al.* Efficacy and safety of linezolid in liver transplant patients. *Transpl Infect Dis* 2011; 13: 353–358.
168. El-Khoury J, Fishman JA. Linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* in solid organ transplant recipients: report of a multicenter compassionate-use trial. *Transpl Infect Dis* 2003; 5: 121–125.
169. Descourouez JL, Jorgenson MR, Wergin JE, Rose WE. Fosfomycin synergy in vitro with amoxicillin, daptomycin, and linezolid against vancomycin-resistant *Enterococcus faecium* from renal transplant patients with infected urinary stents. *Antimicrob Agents Chemother* 2013; 57: 1518–1520.
170. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. *Int J Infect Dis* 2011; 15: e732–e739.
171. Reid GE, Grim SA, Layden JE *et al.* The use of fosfomycin to treat urinary tract infections in kidney transplant recipients. *Transplantation* 2013; 96: e12–e14.
172. Lewis JR, Lewis SA. Colistin interactions with the mammalian urothelium. *Am J Physiol Cell Physiol* 2004; 286: C913–C922.
173. Spapen H, Jacobs R, Van Gorp V, Troubleyn J, Honore PM. Renal and neurological side effects of colistin in critically ill patients. *Ann Intensive Care* 2011; 1: 14.
174. Kasiakou SK, Michalopoulos A, Soteriades ES, Samonis G, Sermaides GJ, Falagas ME. Combination therapy with intravenous colistin for management of infections due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Antimicrob Agents Chemother* 2005; 49: 3136–3146.
175. Levin AS, Barone AA, Penco J *et al.* Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin Infect Dis* 1999; 28: 1008–1011.
176. Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic. *Clin Microbiol Infect* 2005; 11: 115–121.
177. Mostardeiro MM, Pereira CA, Marra AR, Pestana JO, Camargo LF. Nephrotoxicity and efficacy assessment of polymyxin use in 92 transplant patients. *Antimicrob Agents Chemother* 2013; 57: 1442–1446.
178. Pintado V, San Miguel LG, Grill F *et al.* Intravenous colistin sulphomethate sodium for therapy of infections due to multidrug-resistant gram-negative bacteria. *J Infect* 2008; 56: 185–190.
179. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. *Ann Intern Med* 1970; 72: 857–868.
180. Parisi AF, Kaplan MH. Apnea during treatment with sodium colistimethate. *JAMA* 1965; 194: 298–299.
181. McQuillen MP, Cantor HA, O'Rourke JR. Myasthenic syndrome associated with antibiotics. *Trans Am Neurol Assoc* 1967; 92: 163–167.
182. Falagas ME, Rizos M, Bliziotis IA, Rellos K, Kasiakou SK, Michalopoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. *BMC Infect Dis* 2005; 5: 1.
183. Graninger W. Pivmecillinam–therapy of choice for lower urinary tract infection. *Int J Antimicrob Agents* 2003; 22(suppl 2): 73–78.
184. Jansaker F, Frimodt-Moller N, Sjogren I, Dahl Knudsen J. Clinical and bacteriological effects of pivmecillinam for ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* in urinary tract infections. *J Antimicrob Chemother* 2014; 69: 769–772.
185. Livermore DM, Tulkens PM. Temocillin revived. *J Antimicrob Chemother* 2009; 63: 243–245.

186. Woodford N, Pike R, Meunier D, Loy R, Hill R, Hopkins KL. In vitro activity of temocillin against multidrug-resistant clinical isolates of *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp., and evaluation of high-level temocillin resistance as a diagnostic marker for OXA-48 carbapenemase. *J Antimicrob Chemother* 2014; 69: 564–567.
187. Safdar N, Said A, Lucey MR *et al.* Infected bilomas in liver transplant recipients: clinical features, optimal management, and risk factors for mortality. *Clin Infect Dis* 2004; 39: 517–525.
188. Tzakis AG, Gordon RD, Shaw BW Jr, Iwatsuki S, Starzl TE. Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. *Transplantation* 1985; 40: 667–671.
189. Cremaschi E, Maggiore U, Maccari C, Cademartiri C, Andreoli R, Fiaccadori E. Linezolid levels in a patient with biliary tract sepsis, severe hepatic failure and acute kidney injury on sustained low-efficiency dialysis (SLED). *Minerva Anestesiol* 2010; 76: 961–964.
190. Tascini C, Di Paolo A, Polillo M *et al.* Case report of a successful treatment of methicillin-resistant Staphylococcus aureus (MRSA) bacteremia and MRSA/vancomycin-resistant Enterococcus faecium cholecystitis by daptomycin. *Antimicrob Agents Chemother* 2011; 55: 2458–2459.
191. Mayer M, Tophof C, Opferkuch W. Bile levels of imipenem in patients with T-drain following the administration of imipenem/cilastatin. *Infection* 1988; 16: 225–228.
192. Granai F, Smart HL, Triger DR. A study of the penetration of meropenem into bile using endoscopic retrograde cholangiography. *J Antimicrob Chemother* 1992; 29: 711–718.
193. Sharara AI, El H II, Mroueh M *et al.* Prophylaxis with ertapenem in patients with obstructive jaundice undergoing endoscopic retrograde cholangiopancreatography: safety, efficacy, and biliary penetration. *South Med J* 2011; 104: 189–194.
194. Rodvold KA, Gotfried MH, Cwik M, Korth-Bradley JM, Dukart G, Ellis-Grosse EJ. Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. *J Antimicrob Chemother* 2006; 58: 1221–1229.
195. Lee CH, Yeh PH, Tsai TH. Hepatobiliary excretion of fluconazole and its interaction with cyclosporin A in rat blood and bile using microdialysis. *Int J Pharm* 2002; 241: 367–373.
196. Weiler S, Fiegl D, MacFarland R *et al.* Human tissue distribution of voriconazole. *Antimicrob Agents Chemother* 2011; 55: 925–928.
197. Seehofer D, Eurich D, Veltzke-Schlieker W, Neuhaus P. Biliary complications after liver transplantation: old problems and new challenges. *Am J Transplant* 2013; 13: 253–265.
198. Vrochides D, Fischer SA, Soares G, Morrissey PE. Successful treatment of recurrent cholangitis complicating liver transplantation by Roux-en-Y limb lengthening. *Transpl Infect Dis* 2007; 9: 327–331.
199. Albert X, Huertas I, Pereiro II, Sanfelix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev* 2004: CD001209.
200. Dinckan A, Aliosmanoglu I, Kocak H *et al.* Surgical correction of vesico-ureteric reflux for recurrent febrile urinary tract infections after kidney transplantation. *BJU Int* 2013; 112: E366–E371.
201. Dupont PJ, Psimenou E, Lord R, Buscombe JR, Hilson AJ, Sweny P. Late recurrent urinary tract infections may produce renal allograft scarring even in the absence of symptoms or vesicoureteric reflux. *Transplantation* 2007; 84: 351–355.
202. Eells SJ, Bharadwa K, McKinnell JA, Miller LG. Recurrent urinary tract infections among women: comparative effectiveness of 5 prevention and management strategies using a Markov chain Monte Carlo model. *Clin Infect Dis* 2014; 58: 147–160.
203. Sallee M, Rafat C, Zahar JR *et al.* Cyst infections in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1183–1189.
204. Bennett WM, Elzinga L, Pulliam JP, Rashad AL, Barry JM. Cyst fluid antibiotic concentrations in autosomal-dominant polycystic kidney disease. *Am J Kidney Dis* 1985; 6: 400–404.
205. Elzinga LW, Golper TA, Rashad AL, Carr ME, Bennett WM. Trimethoprim-sulfamethoxazole in cyst fluid from autosomal dominant polycystic kidneys. *Kidney Int* 1987; 32: 884–888.
206. Telenti A, Torres VE, Gross JB Jr, Van Scoy RE, Brown ML, Hattery RR. Hepatic cyst infection in autosomal dominant polycystic kidney disease. *Mayo Clin Proc* 1990; 65: 933–942.
207. Hiyama L, Tang A, Miller LG. Levofloxacin penetration into a renal cyst in a patient with autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2006; 47: e9–e13.
208. Elzinga LW, Golper TA, Rashad AL, Carr ME, Bennett WM. Ciprofloxacin activity in cyst fluid from polycystic kidneys. *Antimicrob Agents Chemother* 1988; 32: 844–847.
209. Schwab SJ, Weaver ME. Penetration of trimethoprim and sulfamethoxazole into cysts in a patient with autosomal-dominant polycystic kidney disease. *Am J Kidney Dis* 1986; 7: 434–438.
210. Zuckermann A, Barten MJ. Surgical wound complications after heart transplantation. *Transpl Int* 2011; 24: 627–636.
211. Senechal M, LePrince P, Tezenas du Montcel S *et al.* Bacterial mediastinitis after heart transplantation: clinical presentation, risk factors and treatment. *J Heart Lung Transplant* 2004; 23: 165–170.
212. Monkowski DH, Axelrod P, Fekete T, Hollander T, Furukawa S, Samuel R. Infections associated with ventricular assist devices: epidemiology and effect on prognosis after transplantation. *Transpl Infect Dis* 2007; 9: 114–120.
213. Pasic M, Schaffarczyk R, Hetzer R. Successful treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) mediastinitis in a heart transplant recipient. *Eur J Cardiothorac Surg* 2004; 25: 1127–1128.
214. Swartz TH, Huprikar S, Labombardi V *et al.* Heart transplantation in a patient with heteroresistant vancomycin-intermediate *Staphylococcus aureus* ventricular assist device mediastinitis and bacteremia. *Transpl Infect Dis* 2013; 15: E177–E181.
215. Malani PN, Dyke DB, Pagani FD, Armstrong WS, Chenoweth CE. Successful treatment of vancomycin resistant *Enterococcus faecium* mediastinitis associated with left ventricular assist devices. *Ann Thorac Surg* 2003; 76: 1719–1720.
216. George RS, Birks EJ, Haj-Yahia S *et al.* Acinetobacter mediastinitis in a heart transplant patient. *Ann Thorac Surg* 2006; 82: 715–716.
217. Abid Q, Nkere UU, Hasan A *et al.* Mediastinitis in heart and lung transplantation: 15 years experience. *Ann Thorac Surg* 2003; 75: 1565–1571.
218. Sjogren J, Gustafsson R, Dobre M, Koul B, Ingemansson R, Algotsson L. Vacuum-assisted closure therapy in mediastinitis after heart transplantation. *J Heart Lung Transplant* 2004; 23: 506–507.
219. Verleden GM, Vos R, van Raemdonck D, Vanaudenaerde B. Pulmonary infection defense after lung transplantation: does airway ischemia play a role? *Curr Opin Organ Transplant* 2010; 15: 568–571.
220. Sole A, Morant P, Salavert M, Peman J, Morales P. Aspergillus infections in lung transplant recipients: risk factors and outcome. *Clin Microbiol Infect* 2005; 11: 359–365.
221. Hadjiliadis D, Howell DN, Davis RD *et al.* Anastomotic infections in lung transplant recipients. *Ann Transplant* 2000; 5: 13–19.
222. Burguete SR, Maselli DJ, Fernandez JF, Levine SM. Lung transplant infection. *Respirology* 2013; 18: 22–38.
223. Kroegel C, Hekmat K, Moser A, Happe J, Walther R, Reissig A. Airway complications following lung transplantation - clinic, diagnosis, and interventional management. *Pneumologie* 2011; 65: 293–307.
224. Berger N, Guggenbichler S, Steurer W *et al.* Bloodstream infection following 217 consecutive systemic-enteric drained pancreas transplants. *BMC Infect Dis* 2006; 6: 127.

225. Herrero-Martinez JM, Lumbreras C, Manrique A *et al.* Epidemiology, risk factors and impact on long-term pancreatic function of infection following pancreas-kidney transplantation. *Clin Microbiol Infect* 2013; 19: 1132–1139.
226. Nath DS, Gruessner A, Kandaswamy R, Gruessner RW, Sutherland DE, Humar A. Late anastomotic leaks in pancreas transplant recipients - clinical characteristics and predisposing factors. *Clin Transplant* 2005; 19: 220–224.
227. Buijk SE, Bruining HA. Future directions in the management of tertiary peritonitis. *Intensive Care Med* 2002; 28: 1024–1029.
228. Martin-Lopez A, Castano-Avila S, Maynar-Moliner FJ, Urturi-Matos JA, Manzano-Ramirez A, Martin-Lopez HP. Tertiary peritonitis: as difficult to define as it is to treat. *Cir Esp* 2012; 90: 11–16.
229. Dahyot-Fizelier C, Lefeuvre S, Laksiri L *et al.* Kinetics of imipenem distribution into the peritoneal fluid of patients with severe peritonitis studied by microdialysis. *Clin Pharmacokinet* 2010; 49: 323–334.
230. Karjagin J, Lefeuvre S, Oselin K *et al.* Pharmacokinetics of meropenem determined by microdialysis in the peritoneal fluid of patients with severe peritonitis associated with septic shock. *Clin Pharmacol Ther* 2008; 83: 452–459.
231. Goedecke VA, Clajus C, Burkhardt O *et al.* Pharmacokinetics and dialysate levels of daptomycin given intravenously in a peritoneal dialysis patient. *Scand J Infect Dis* 2009; 41: 155–157.
232. Allcock NM, Krueger TS, Manley HJ, Kumar VK, Abdallah J. Linezolid disposition during peritonitis: a case report. *Perit Dial Int* 2004; 24: 68–70.
233. Mimoz O, Petitpas F, Gregoire N, Gobin P, Marchand S, Couet W. Colistin distribution in the peritoneal fluid of a patient with severe peritonitis. *Antimicrob Agents Chemother* 2012; 56: 4035–4036.
234. Verdier MC, Seguin P, Le Touvet B, Cady A, Malledant Y, Tribut O. Ertapenem in plasma and peritoneal fluid from patients with severe intra-abdominal infections. *J Antimicrob Chemother* 2011; 66: 1934–1936.
235. Scheetz MH, Reddy P, Nicolau DP *et al.* Peritoneal fluid penetration of tigecycline. *Ann Pharmacother* 2006; 40: 2064–2067.
236. Whitby M, Edwards R, Aston E, Finch RG. Pharmacokinetics of single dose intravenous vancomycin in CAPD peritonitis. *J Antimicrob Chemother* 1987; 19: 351–357.
237. Solomkin JS, Mazuski JE, Bradley JS *et al.* Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50: 133–164.
238. Bassetti M, Marchetti M, Chakrabarti A *et al.* A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. *Intensive Care Med* 2013; 39: 2092–2106.
239. Bartoletti M, Cervera C, Hoyo I *et al.* Incidence and outcome of early *Candida peritonitis* after liver and pancreas transplantation. *Mycoses* 2013; 56: 162–167.