Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations

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Review article

Title page

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Review article

Title page

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Abstract (199 words)

Solid organ transplant (SOT) recipients are especially at risk of developing infections by multidrug resistant (MDR) Gram-negative bacilli (GNB), as they are frequently exposed to antibiotics and the healthcare setting, and are regulary subject to invasive procedures. Nevertheless, no recommendations concerning prevention and treatment are available. A panel of experts revised the available evidence; this document summarizes their recommendations: (1) it is important to characterize the isolate´s phenotypic and genotypic resistance profile; (2) overall, donor colonization should not constitute a contraindication to transplantation, although active infected kidney and lung grafts should be avoided; (3) recipient colonization is associated with an increased risk of infection, but is not a contraindication to transplantation; (4) different surgical prophylaxis regimens are not recommended for patients colonized with carbapenem-resistant GNB; (5) timely detection of carriers, contact isolation precautions, hand hygiene compliance and antibiotic control policies are important preventive measures; (6) there is not sufficient data to recommend intestinal decolonization; (7) colonized lung transplant recipients could benefit from prophylactic inhaled antibiotics, specially for *Pseudomonas aeruginosa*; (8) colonized SOT recipients should receive an empirical treatment which includes active antibiotics, and directed therapy should be adjusted according to susceptibility study results and the severity of the infection.

Keywords:

Solid organ transplantation; multidrug resistant Gram-negative bacilli; extended-spectrum β-lactamases; carbapenem-resistant Gram-negative bacilli

List of abbreviations

BLBLI	β-lactam/β-lactamase inhibitor combination
BOS	Bronchiolitis obliterans syndrome
BSI	Bloodstream infection
CPE	Carbapenemase-producing *Enterobacteriaceae*
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRE	Carbapenem-resistant *Enterobacteriaceae*
CRKP	Carbapenem-resistant *Klebsiella pneumoniae*
CSKP	Carbapenem-susceptible *Klebsiella pneumoniae*
ESBL	Extended-spectrum β-lactamases
GNB	Gram-negative bacilli
HCAP	Healthcare-associated pneumonia
HCV	Hepatitis C virus
HT	Heart transplantation
ICU	Intensive care unit
KPC-Kp	KPC-producing *K. pneumoniae*
KT	Kidney transplantation
LT	Liver transplantation
LuT	Lung transplantation
MBL	Metallo-β-lactamase
MDR	Multidrug resistant
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
PDR	Pandrug-resistant
RCT	Randomized controlled trials
SOT	Solid organ transplantation
SSI	Surgical site infection
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia
VRE	Glycopeptide-resistant *Enterococcus* spp.
XDR	Extensive drug-resistant

1. Introduction

1.1. The need and justification for these recommendations

The expectancy and quality of life among patients undergoing solid organ transplantation (SOT) have significantly improved over the previous decades. These advances have stemmed from the development of more potent and safer immunosuppressive drugs and the implementation of clinical guidelines that have made possible to optimize prophylaxis strategies against the main opportunistic microorganisms. However, a major threat to this improvement has emerged from the progressive increase in the incidence of post-transplant infectious complications due to multidrug resistant (MDR) Gram-negative bacilli (GNB) [1]. These include non-fermenting GNB such as *Pseudomonas aeruginosa*, *Burkholderia* spp., *Stenotrophomonas* spp. or carbapenem-resistant *Acinetobacter baumannii* (CRAB), as well as extended-spectrum β-lactamases (ESBL) and carbapenem-resistant *Enterobacteriaceae* (CRE), with a special role played by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) [2, 3]. SOT recipients are particularly vulnerable to developing infections by MDR GNB as they usually face prolonged exposure to the healthcare environment, have frequent requirements for invasive diagnostic and therapeutic procedures, and are commonly exposed to broad-spectrum antibiotics [2, 4, 5]. Long-term post-transplant immunosuppression not only plays a relevant role in enhancing susceptibility to infection, but also in determining the prognosis of such complication through its deleterious effect on the host immune response. On the other hand, the limited therapeutic armamentarium available against these microorganisms often entail the use of potentially nephrotoxic agents, which represents an additional risk for kidney transplant (KT) recipients and other transplant populations with preexisting renal impairment or other concomitant nephrotoxic therapies (i.e., calcineurin inhibitors). Therefore, the therapeutic approach to infections due to MDR GNB in SOT recipients turns out to be particularly challenging as compared to other groups of patients.

1.2. Definition of the microorganisms constituting the focus of the present recommendation

In recent years there has been an increase in the simultaneous resistance to multiple antimicrobials in a number of Gram-positive and Gram-negative microorganisms, thus notably limiting the therapeutic alternatives for the infections produced by these pathogens. Although infections produced by Gram-positive microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and glycopeptide-resistant *Enterococcus* spp. (VRE) are frequent in some healthcare settings, newer anti-Gram-positive bacterial agents with excellent *in vitro* activity and favorable pharmacokinetics and safety profiles are becoming increasingly available [6-8]. However, the problem with MDR GNB is more worrisome, since some of them have developed mechanisms of resistance against most of, if not virtually all, available antimicrobials. Moreover, it is foreseeable a relative paucity of promising anti-Gram-negative bacterial agents in the pipeline over the next years. *Enterobacteriaceae, P. aeruginosa* and *A. baumannii* constitute the GNB in which such therapeutic challenges are more often observed in daily clinical practice and, therefore, the present recommendations will be exclusively focused on them.

Although the resistance of these microorganisms to different antimicrobials may be explained by the selection of chromosomal mutations, the most commonly involved mechanism is by far the acquisition of exogenous genes located in mobile genetic elements (plasmids, transposons). Among these genes, the pivotal role is played by those that code for the production of ESBL, AmpC β-lactamases and carbapenemases [9].

- **ESBL**. These enzymes can hydrolyze and, therefore, provide resistance to penicillins, aztreonam and all generations of cephalosporins, except for cephamycins (i.e, cefoxitin, cefotetan or cefmetazole). Besides cephamycins, ESBL do not hydrolyze carbapenems, and are inhibited by β-lactamase inhibitors such as clavulanic acid, tazobactam, sulbactam and avibactam. The ESBL-encoding genes can be located in plasmids, thus facilitating horizontal spread from one bacterium to another. There are multiple types of ESBL with agent-specific hydrolysis capacities. In addition

to *Enterobacteriaceae,* ESBL can also be produced by *P. aeruginosa* and *Acinetobacter* spp. [10].

- **AmpC-type β-lactamases**. These enzymes are cephalosporinases encoded on the chromosome of many *Enterobacteriaceae* and other GNB such as *P. aeruginosa* and *Acinetobacter* spp. which confer resistance to first- and second-generation cephalosporins and cefoxitin, as well as to most penicillins and β-lactam/β-lactamase inhibitor combinations (BLBLI). In many *Enterobacteriaceae* (including *Citrobacter freundii*, *Enterobacter cloacae* and *Serratia marcescens*) and *P. aeruginosa*, AmpC-type β-lactamases are constitutively expressed at low level, but may be induced under exposure to β-lactams through mutations in regulator genes. The resulting AmpC overproduction may confer additional resistance to third- and fifth-generation cephalosporins, while remaining susceptible to fourth-generation cephalosporins. Genes coding for these enzymes can be also located in mobile plasmids, with the potential for dissemination to other bacteria. Nevertheless, in overall terms AmpC-type β-lactamases are less frequently found in plasmids than ESBL [11].

- **Carbapenemases**. These enzymes constitute a diverse group characterized by their disparate ability to hydrolyze carbapenems (ertapenem, imipenem, meropenem, doripenem) and confer, in most cases, *in vitro* resistance to this class of antimicrobials. Carbapenemases fundamentally belong to three different classes according to Ambler´s molecular classification: i) class A, mainly KPC-type enzymes; ii) class B or metallo-β-lactamases (MBLs), mainly VIM-, IMP- and NDM-type enzymes; and iii) class D, mainly OXA-48 group. Although most of the carbapenemases also hydrolyze the remaining classes of β-lactams, some of them exerts no significant activity against broad-spectrum cephalosporins (such as cefotaxime and ceftazidime) and aztreonam (i.e., OXA-48-group carbapenemases) while others do not hydrolyze aztreonam (i.e., MBLs). Horizontal transfer via plasmids is the most common mode of dissemination. Carbapenemase producers are mainly identified among *K. pneumoniae* and *Escherichia coli* isolates, with a relatively lower

contribution to the resistance mechanisms in *P. aeruginosa* and *A. baumannii* [12].

1.3. How are MDR, XDR and PDR bacteria defined?

Although the term “MDR” literally stands for resistance to more than one antimicrobial, there are currently multiple well-established definitions for MDR, extensive drug-resistant (XDR) and pandrug-resistant (PDR) bacteria, which describe the different patterns of acquired resistance observed in drug-resistant bacteria involved in healthcare-related infections. The present recommendations will use the consensus definitions jointly proposed by the European Center for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC). This document establishes standardized international terminology to describe acquired resistance profiles in *Enterobacteriaceae* (excluding *Salmonella* and *Shigella*), *P. aeruginosa* and *Acinetobacter* spp. Of note, such epidemiologically significant antimicrobial categories do not take into account the intrinsic resistance patterns shown by the different microorganisms [13].

In these consensus definitions for MDR, XDR and PDR bacteria, the different antimicrobial classes are distributed into categories depending on whether they are prescribed against *Enterobacteriaceae, P. aeruginosa* or *Acinetobacter* spp. (**Table 2**) [13].

- **MDR**. Taking into account the antimicrobial categories specifically established for *Enterobacteriaceae, P. aeruginosa* and *Acinetobacter* spp., a microorganism is considered MDR when it shows acquired non-susceptibility (intermediate or resistant) to at least one agent in 3 or more antimicrobial categories (listed in **Table 2**).
- **XDR**. A microorganism is considered XDR when it shows acquired non-susceptibility to at least one agent in all but one or two antimicrobial categories (listed in **Table 2**) (i.e. bacterial isolate remains susceptible to only one or two of the indicated categories for each group of microorganisms).

- **PDR**. A microorganism is considered PDR when it shows acquired non-susceptibility to all agents in all antimicrobial categories (listed in **Table 2**).

To ensure that the above definitions are correctly applied, bacterial isolates should be tested against all or nearly all antimicrobial agents within each category. Although these definitions do not necessarily correlate with the presence of the most frequent resistance mechanisms found in *Enterobacteriaceae* (i.e., ESBL, AmpC-type β-lactamases or carbapenemases), according to these criteria, all isolates of this group harboring such mechanisms must be considered, at least, as MDR.

1.4. Particular clinical aspects of MDR GNB infection in different SOT populations (Table 3)

- **Liver transplantation (LT)**: Infectious complications due to MDR GNB are associated to significant morbidity and mortality among LT recipients [4, 14]. In this group of patients the rate of infection due to ESBL-producing *Enterobacteriaceae* ranges from 5.5% to 7%, with *K. pneumoniae* and *E. coli* as the most common species identified. The incidence of infections by CRE, particularly CRKP, ranges from 6% to 12.9% in some settings. Infection usually occurs at the early post-transplant period (mean of 12-24 days after the transplant procedure). More than half of the cases have an intra-abdominal origin, such as abscesses, infected bilomas, hematomas or biliary complications (i.e., cholangitis, recurrent cholangitis or biliary leakage). Healthcare-associated pneumonia (HCAP) or urinary tract infection (UTI) are other complications that may be caused by CRKP. Skin and soft tissue infections are less common, although cases of necrotizing infection (necrotizing fasciitis or myonecrosis) have been occasionally reported [15]. The mortality of LT recipients diagnosed with infection due to CRKP has been shown to be up to five times higher than that observed for carbapenem-susceptible isolates (CSKP) [16, 17].

  In certain series MDR microorganisms are involved in more than half of the cases of GNB bloodstream infection (BSI) in LT recipients (15). The prevalence of this antimicrobial phenotype, however, varies according to the

species involved (62.5% for *A. baumannii*, 54.8% for *Enterobacteriaceae,* 54.2% for *S. maltophilia* and 51.5% for *Pseudomonas* spp.) [18].

On the other hand HCAP, including ventilator-associated pneumonia (VAP), is the most common complication associated with CRAB and MDR *P. aeruginosa* in LT receptors [19-21].

Finally, superinfection by MDR GNB in cases of tertiary peritonitis after LT is not uncommon.

Risk factors include pre-transplant fecal carriage of ESBL-producing isolates, surgical reintervention, and a high MELD score (listed in **Table 4**). All-cause mortality is around 30% and reaches 41% in the presence of BSI [22, 23].

- **KT**: The urinary tract is the source for most of the post-transplant infections, including BSI, among KT recipients, frequently in form of uncomplicated cystitis (although acute graft pyelonephritis comprises up to one-tenth of the cases). Recurrent UTI represents a common problem that requires ruling out the presence of structural abnormalities such as vesicoureteral reflux, ureterovesical junction stenosis or neurogenic bladder. Infection of renal cysts in KT recipients with underlying renal polycystic disease may also explain UTI recurrence.

  In KT recipients, ESBL-producing *E. coli* accounts for up to 12% of infections, particularly in the presence of simultaneous pancreas transplantation, post-transplant requirement of renal replacement therapy, previous use of antibiotics, or urinary tract obstruction or instrumentation [21]. About 70% of the complications caused by ESBL-producing or AmpC-hyperproducing GNB are UTI, although other potential infection sources include the surgical site (SSI), the kidney cell or the presence of lymphocele or urinary fistulas [24].

  CRKP may be responsible for UTI after KT, associated or not with BSI and recurrent episodes [25, 26]. In addition, this microorganism is commonly involved in intra-abdominal infections related to the surgical procedure such as collections, abscesses or hematomas. Similarly to observe among LT recipients, attributable mortality is higher in infections caused by CRKP in comparison to susceptible counterparts.

With regards to MDR *P. aeruginosa*, the most common clinical manifestations in KT recipients are UTI and HCAP, often complicated by the development of associated BSI [21, 27].

Similarly, CRAB constitutes a not uncommon cause of HCAP, particularly in form of VAP, and is responsible for up to 3% of all the episodes of BSI after KT [19, 20].

Risk factors generally associated with MDR GNB infection in KT recipients include age older than 50 years, hepatitis C virus (HCV) infection, renal replacement therapy after transplantation and surgical reintervention, kidney-pancreas transplantation and post-transplant nephrostomy [14, 15, 18, 21, 24] (listed in **Table 4**).

- **Heart transplantation (HT)**: HCAP and UTI are the main forms of bacterial infection after HT. The incidence of pneumonia is highest in the first months after transplantation. The most common causative agents are MDR *P. aeruginosa*, CRAB and MDR *S. maltophilia*, and associate BSI is also frequent [28].

  The incidence of mediastinitis and sternal surgical wound infection after HT is close to 2.5%. Although most episodes are due to *Staphylococcus* spp., an increasing number of cases of mediastinitis caused by ESBL-producing *E. coli* [29] or non-fermenting GNB has been reported in recent years [30].

- **Lung Transplantation (LuT)**: Colonization of the respiratory tract by MDR *P. aeruginosa* during pre-transplant period is especially common in LuT recipients with cystic fibrosis, with a prevalence greater than 50% that may increase up to 75% after transplantation [5]. On the other hand, *P. aeruginosa* is the leading cause of HCAP after LuT, accounting for up to 25% of cases [31]. It has been suggested that *P. aeruginosa* colonization and infection may play a role in the pathogenesis of bronchiolitis obliterans syndrome (BOS) and in the risk of developing bronchovascular fistula, complications that negatively impact medium- and long-term prognosis [32, 33].

  Most infections due to CRAB are associated to epidemic outbreaks. HCAP is the most common complication, but UTI, catheter-related BSI and SSI

have been also reported [31]. Infectious complications caused by this pathogen frequently entail a high mortality rate among LuT recipients [34].

Burkholderia spp. has been associated with various complications after LuT, such as chronic lung infections, mediastinal abscesses, pleural effusion or chest wall infection [35]. In this group of patients, mediastinitis is also a common complication.

More than 50% of all episodes of GNB BSI in LuT are produced by strains with a MDR phenotype, which may account for up to 100% of *B. cepacia* isolates in this setting [36].

1.5. Attributable mortality to MDR GNB infections in SOT recipients

Overall, infections caused by MDR GNB result in a significantly higher attributable mortality than those due to susceptible microorganisms. One study identified the inadequacy of empirical antibiotic treatment and the inability to identify the primary source of infection as risk factors for mortality associated with BSI due to ESBL-producing *E. coli* in non-transplanted patients [37]. Other authors have reported a higher risk of death associated with CRKP infection among LT and LuT recipients [16, 38]. It has also been shown that patients with CRAB infection after SOT had a longer hospital stay and an increased risk of graft loss and death compared to patients without any infection or those with infection due to carbapenem-susceptible *A. baumannii* [19, 20, 39]. Infection due to MDR *P. aeruginosa* was associated with higher mortality in LT recipients, reaching 38% in case of BSI [21, 40]. Such poorer outcomes are mainly driven by an increased odds for inappropriateness of empirical antimicrobial therapy and clinical failure of targeted therapy, even when antimicrobial agents with *in vitro* activity are used [4].

2. Infections produced by ESBL-producing *Enterobacteriaceae*

2.1. What are the risk factors for developing ESBL-producing Enterobacteriaceae infections after SOT?

Studies performed in Spain have estimated that approximately 20% of infections in SOT recipients are caused by MDR bacteria, from which 75% are due to ESBL-producing *Enterobacteriaceae* [41]. More than 20% of all *E. coli* isolated in urine cultures of SOT recipients with a diagnosis of UTI are ESBL-producing *Enterobacteriaceae* [42]. KT recipients are significantly at risk [42]. Different period comparison has confirmed that the incidence of the infections produced by these microorganisms is increasing [43].

SOT has been identified as a classical risk factor for ESBL-producing *Enterobacteriaceae* infection, together with prior hospital admittance, use of antibiotics in last 3 months, cancer and admittance in long-term care facilities [23]. Other known risk factors are advanced age, intensive care unit (ICU) requirement, use of intravascular catheters or other intravascular devices, mechanical ventilation, renal replacement therapy and parenteral nutrition [44] (listed in **Table 4**).

ESBL-producing *Enterobacteriaceae* infections are more frequent in KT and kidney-pancreas transplant recipients than in other SOT because these patients have a higher incidence of UTI. Recurrence of UTI in KT is associated with ESBL-producing *Enterobacteriaceae*: half of recurrent UTI are caused by these microorganisms in some studies [41]. A Spanish study that enrolled more than 4.000 SOT recipients, including 249 episodes (4.4%) of bacterial UTI, reported that *E. coli* was the microorganism most frequently isolated (57.8%) and 25% were ESBL-producing bacteria [42]. Specific risk factors for ESBL-producing *Enterobacteriaceae* infection in KT include kidney-pancreas transplantation, prior use of antibiotics, renal replacement therapy after transplantation and post-transplant urinary obstruction [24]. The association between rectal ESBL-producing *Enterobacteriaceae* colonization and the risk of UTI by these microorganisms in KT has also been previously reported: 55% of patients with UTI by ESBL-producing *Enterobacteriaceae* had a previous history of rectal colonization; these studies have also confirmed that UTI relapse by ESBL-

producing *Enterobacteriaceae* is frequent (40%) and is associated with older age and persistent bacteriuria after appropriate treatment [45].

The epidemiology and risk factors vary according to the different ESBL-producing *Enterobacteriaceae.* Although the rate of horizontal transmission of ESBL-producing *K. pneumoniae* is high, it is lower in the case of ESBL-producing *E. coli* [46]. A Spanish study that analyzed 116 episodes of *K. pneumoniae* infection in SOT recipients reported that more than half of the isolates were ESBL-producers (53%); approximately half of them were diagnosed in the first month after transplantation and UTI were more frequently recorded (72%), especially in KT (11%), followed by LT (7%), HT (5%) and kidney-pancreas or liver-kidney (6%).

Prolonged use of broad-spectrum antibiotics during the pre-transplant period and long-term tracheal intubation (>72 h) have been reported as risk factors for ESBL-producing *Enterobacteriaceae* infections after LT [47]. LT recipients are considered specifically at risk since liver failure has been identified as an independent risk factor for ESBL-producing *Enterobacteriaceae* colonization [48].

Other risk factors in SOT recipients are prolonged hospitalization [49], urologic manipulation, use of ureteral stents and urethral catheterization, which is common in KT [5, 50], duration of antibiotic treatment and perioperative prophylaxis, specifically in KT [51].

Outbreaks of ESBL-producing *K. pneumoniae* in pediatric intestinal transplantation have been associated with prior exposure to piperacillin-tazobactam, especially in children under 5 years of age and in patients who had had more than three central venous catheters before the infection [52].

2.1.1. Consensus recommendations

- SOT is a specific risk factor for developing ESBL-producing *Enterobacteriaceae* infections (AII).

- KT recipients and LT recipients are especially at risk for developing infections by these microorganisms. Previous antibiotic exposure, pre-transplant colonization, perioperative prophylaxis, prolonged tracheal intubation, long-term hospitalization, urologic manipulation, kidney-pancreas

transplantation, renal replacement therapy after transplantation, post-transplant urinary obstruction and recurrent UTI are some of the identified risk factors (BII).

2.2. How can ESBL-producing Enterobacteriaceae be identified through an antibiogram?

Recognition of ESBL-producing *Enterobacteriaceae* is relatively easy as long as there are no other mechanisms of resistance that may mask their presence, such as other enzymes with an overlapped hydrolytic spectrum (plasmid-mediated AmpC, AmpC overexpression or carbapenemases) or permeability resistance mechanisms (porins and efflux pumps) [53].

There are different types of ESBL, which share a similar phenotypic profile. Cefotaxime, ceftriaxone, ceftazidime and cefepime are similarly hydrolyzed by TEM, SHV and OXA variants. This determines the increase of the minimum inhibitory concentration (MIC) values compared to the bacteria that lack these enzymes [53]. With a few exceptions (e.g. CTX-M-15), the majority of CTX-M type enzymes hydrolyze more efficiently cefotaxime, ceftriaxone and cefepime than ceftazidime. Generally, they are inactivated by the combination of penicillins or cephalosporins with a β-lactamase inhibitor (amoxicillin-clavulanic acid, piperacillin-tazobactam, ceftazidime-avibactam or ceftolozane-tazobactam) although this depends on the coexistence of other resistance mechanisms. Moreover, ESBL-producing *Enterobacteriaceae* are usually less susceptible to non-β-lactam antibiotics (aminoglycosides, quinolones or cotrimoxazole) than other bacteria [54].

The phenotypic profile and the type of enzymes in ESBL-producing *Enterobacteriaceae* isolated from clinical and/or surveillance samples of SOT recipients do not differ from other patients. Notwithstanding, some variations can be observed, depending on the geographical area and epidemiological setting, such as those associated with outbreaks. CTX-M type, followed by SHV, is the most prevalent, while TEM-type is the less common [22, 49, 55, 56]. Currently, it is not uncommon to also find ESBL in carbapenemase-producing *Enterobacteriaceae* (CPE) [57].

2.2.1. Consensus recommendations

It is important to recognize ESBL-producing *Enterobacteriaceae* isolated from clinical and/or surveillance samples of SOT recipients, as they increase the risk of inappropriate use of antibiotics and death (AIII).

2.3. Can a colonized or infected patient with ESBL-producing Enterobacteriaceae be accepted as an organ donor?

As mentioned, SOT recipients have a higher risk for developing infections by MDR microorganisms, including ESBL-producing *Enterobacteriaceae* [3]. Although donor-derived infections caused by MDR bacteria have been previously reported [58-63], there is no evidence to contraindicate transplantation from donors colonized with ESBL-producing *Enterobacteriaceae.*

2.3.1. Consensus recommendations

- Donor colonization with ESBL-producing *Enterobacteriaceae* does not constitute a contraindication to transplantation (AIII).

2.4. Can a patient colonized with ESBL-producing Enterobacteriaceae be accepted for transplantation?

ESBL-producing *Enterobacteriaceae* adversely affects the outcome, due to the higher risk of inappropriate use of antibiotics and higher mortality rate [64, 65]. A case-control study with 55 ICU patients diagnosed with BSI confirmed a significant higher mortality rate in patients with ESBL-producing *Enterobacteriaceae* (68.8% *vs*. 35.9%) [66]. This trend in the mortality rate has also been confirmed in studies with neutropenic patients [67]. Despite the risk of inadequate treatment and increased morbidity and mortality in colonized patients, this should not contraindicate transplantation; nevertheless, measures should be taken to improve the prognosis of these patients.

2.4.1. Consensus recommendations

- Recipient colonization with ESBL-producing *Enterobacteriaceae* is associated with worse outcome, but it is not a contraindication for transplantation (BII).

2.5. Should a different surgical prophylaxis regimen be prescribed when a donor or a recipient is colonized with ESBL-producing Enterobacteriaceae?

There are no prospective studies evaluating the efficacy of a directed prophylaxis regimen against ESBL-producing *Enterobacteriaceae* in SOT recipients. However, indirect data can be obtained from the impact of colonization on these patients. According to the ENTHERE study, which is currently ongoing in seven Spanish centers, 20 of the first 112 enrolled SOT recipients (17.8%) proved to be colonized with MDR bacteria at the moment of transplantation: 45.5% with ESLB-producing *E. coli*, 24.9% with ESBL-producing *K. pneumoniae* and 9.5% were colonized with CPE (Fariñas C, personal communication). In this study, 5.15% of the colonized recipients developed an infection by ESBL-producing *Enterobacteriaceae* versus 2.4% of the non-colonized.

A French study with 710 LT recipients, and a pre-transplant colonization incidence with ESBL-producing *Enterobacteriaceae* of 5.5%, reported that 44.8% of the colonized recipients developed an infection by these microorganisms in the following four months. This incidence was significantly higher than in the non-colonized recipients (3.8%). Median time to infection was also shorter in the colonized recipients (9 *vs*. 25 days) [22]. This study also described a gradual increase in the rates of ESBL-producing *Enterobacteriaceae* colonization, from 0% in 2001-2003 to 10.6% in 2009-2010. Finally, another study reported that 47% of KT recipients with asymptomatic bacteriuria caused by ESBL-producing *Enterobacteriaceae* eventually developed an UTI by the same microorganism [45].

Colonized patients should receive specific prophylactic regimens and, in the case of bacterial infection, an empirical treatment with active antibiotics against ESBL-producing *Enterobacteriaceae* [22]. There are too heterogeneous data to make a strong recommendation of the alternative use of β-lactamase inhibitors,

quinolones, or aminoglycosides in these patients [65]. The use of ertapenem, cefoxitin, or fosfomycin-trometamol reduced the incidence of BSI after prostatic biopsy in patients colonized with ESBL-producing *Enterobacteriaceae* and/or resistant to quinolones, and it could be an acceptable alternative in some patients [68-70].

Since the use of carbapenems has been associated with an increased risk of carbapenemases [16], their use in prophylaxis regimens must be avoided whenever possible. As for the use of carbapenems in empirical treatment regimens, it must be reserved for restricted patients that are colonized or at risk of infections with ESBL-producing *Enterobacteriaceae* [22, 71]. It is always important to balance the risk of infection against the risk of developing adverse effects to the antibiotics and/or carbapenem-resistance.

2.5.1. Consensus recommendations

- Patients colonized with ESBL-producing *Enterobacteriaceae* should receive a specific prophylaxis regimen and, in the case of infection, an empirical treatment which includes active antibiotics against these microorganisms. However, the use of carbapenems should be avoided whenever possible (BIII).

2.6. Should intestinal colonization by ESBL-producing Enterobacteriaceae be monitored in SOT recipients?

As mentioned, the risk of ESBL-producing *Enterobacteriaceae* infections is higher in colonized than in non-colonized recipients [22, 72]. Besides, screening for colonized patients could help increase infection control [73].

In a German prospective study, all colonized patients with ESBL-producing *Enterobacteriaceae* who developed infection during follow-up received an adequate empirical treatment. On the contrary, adequate antibiotic treatment was only prescribed in two of the four non-colonized patients, and both died of severe sepsis [74].

Colonization and infection with ESBL-producing *K. pneumoniae* is more frequently healthcare-acquired, whereas colonization with ESBL-producing *E. coli* is usually community-acquired [44]. Moreover, environmental contamination

is more frequent with ESBL-producing *K. pneumoniae* than with ESBL-producing *E. coli* [75].

All these data, based on retrospective studies, suggest the potential benefit of performing surveillance cultures in high-risk patients, including transplant recipients, although the real impact of this strategy should be confirmed in prospective, multicenter studies.

2.6.1. Consensus recommendations

- Data analysis of retrospective studies favors the screening of patients with high risk for ESBL-producing *Enterobacteriaceae* colonization, including SOT recipients (BII). Prospective studies are warrant for supporting this approach.

2.7. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with ESBL-producing Enterobacteriaceae?

The human digestive tract is the main reservoir of ESBL-producing *Enterobacteriaceae* [76, 77]. Preventive strategies against transmission of ESBL-producing *Enterobacteriaceae* in healthcare facilities include basic measures such as timely detection of carriers, contact isolation precautions, hand and body hygiene (chlorhexidine washing) and the implementation of an antibiotic control policy [76, 78, 79]. However, not all these measures have proven to be equally effective. In fact, in most cases they have been implemented as part of a bundle of measures for infection control, making it difficult to estimate their importance separately.

Although a few studies have evaluated the direct impact of hand hygiene on the transmission of MDR GNB, this measure is a fundamental intervention for control of healthcare-associated outbreaks by these microorganisms [80]. Most clinical guidelines advocate the implementation of educational programs to improve and control hand hygiene [79-82] and this measure is especially critical in SOT wards. It is recommended to use alcohol-based products before and after touching the colonized patients and/or furniture in their potentially contaminated room [81].

In addition to other contact isolation measures, clinical guidelines now recommend single-room isolation for colonized or infected patients as a way of reducing the horizontal transmission. Several studies have shown that this measure is effective during ESBL-producing *K. pneumoniae* outbreaks [80, 81, 83]. However, in the case of patients colonized by ESBL-producing *E. coli*, isolation precautions are not as strongly recommended [76]. This has two explanations; the first is that in many hospitals it is an endemic problem and isolation is not feasible; the second is that the epidemiological pattern reported in ESBL-producing *Enterobacteriaceae* outbreaks is dependent of plasmid dissemination between different clones influenced by the selective pressure of antibiotics (more relevant in *K. pneumoniae* than *E. coli*). Avoiding the spread of ESBL, especially in the case of *E. coli*, is a major challenge and recommended measures should go beyond the hospital setting and into the community, where the number of carriers is bigger and the reservoirs and mechanisms of transmission are more difficult to identify and control [84].

It is important to improve the terminal cleansing of the rooms in which these patients are admitted. Most clinical guidelines do not recommend disinfection with hypochlorite, but hydrogen peroxide vapor is advisable [80].

A combined effort between clinical microbiology, preventive medicine, nursing staff, healthcare assistants and cleaning personnel is essential for handling the problem. The measures contemplated in the setting of an outbreak are the relocation of patients in special sectors or assigning exclusive clinical staff to these patients [80, 81]. Finally, there is no consensus in performing surveillance cultures to detect healthcare personnel colonized by MDR GNB [80, 81].

2.7.1. Consensus recommendations

- Hand washing and disinfection with alcohol-based gels are recommended before and after touching the patients (AIII).
- In the case of patients colonized by ESBL-producing *K. pneumoniae*, contact isolation precautions are also recommended, including single-room isolation (AIII). For patients colonized with ESBL-producing *E. coli* this recommendation is not so strong (BII).

2.8. Is intestinal decolonization recommended?

Intestinal decolonization was first evaluated in 1983 [85]. Since then several controlled clinical trials and meta-analysis have been published [86]. The goal is to minimize or prevent endogenous and exogenous infections, by reducing the bacterial overgrowth of the aerobic flora, while preserving the anaerobic flora. Most published studies enrolled patients admitted to the ICU. These studies have shown that intestinal decolonization significantly reduces rectal colonization by GNB [87]. However, the long-term benefit of these measures is doubtful. A controlled, double blind, placebo-group clinical trial demonstrated a transient effect on intestinal decolonization with ESBL-producing *Enterobacteriaceae* using colistin and neomycin [88].

Evidence in SOT is scarce. A prospective study that analyzed SOT recipients from 12 Spanish hospitals, showed no advantage in administering fluoroquinolones as an independent protective factor for the development of early bacterial infections due to *Enterobacteriaceae* [89].

A multicenter study conducted in the Netherlands, including 5,939 patients admitted into the ICU, showed a difference in the incidence of ICU-acquired BSI when selective intestinal decolonization and oral decolonization were performed and a decrease of up to 3.5% in the mortality rate at day 28 in the intestinal decolonization group [90]. Other studies also demonstrated that intestinal decolonization had a positive impact on mortality reduction in ICU patients in whom eradication of the carrier state was achieved [91]. However, a meta-analysis with 32 intestinal decolonization studies performed in critically ill patients concluded that these studies overestimated the effect of intestinal decolonization on the mortality rate [92].

One of the main concerns over the use of intestinal decolonization is the risk of MDR bacteria selection. Brink et al. reported the emergence of colistin-resistant OXA-181-producing *K. pneumoniae* during the use of oral decolonization with colistin [93]. Other authors also reported an increase in the prevalence of ESBL-producing *K. pneumoniae* strains resistant to tobramycin and colistin, and an increase in BSI caused by these agents after the use of intestinal decolonization [94], including neonates [95].

Currently, a cohort study and a randomized, open-label, multicenter clinical trial study are being carried out (ENTHERE Study, EudraCT: 2013-004838-15). The aim of this study is to analyze the clinical relevance of intestinal colonization by MDR *Enterobacteriaceae* in LT and KT recipients, and evaluate whether treatment with colistin (50 mg 4 times / day) and neomycin (250 mg 4 times / day) orally for 14 days reduce the risk of infection by MDR bacteria.

2.8.1. Consensus recommendations

- There is no evidence so far to support decolonization of SOT recipients colonized by ESBL-producing *Enterobacteriaceae.* Retrospective studies performed in other types of patients have confirmed a transient effect but a potential risk of selecting resistant strains. Further studies are needed to clarify its benefits in SOT recipients (CIII).

2.9. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with ESLB-producing Enterobacteriaceae?

Inhaled antibiotics are an attractive option for the treatment of respiratory tract infections by MDR microorganisms. They allow for a maximum drug delivery to the target site of infection, as well as limited systemic exposure and toxic effects [96-98].

Most data on the use of inhaled antibiotics derive from patients with VAP or cystic fibrosis. Nevertheless, even in these groups of patients, the number of well-designed studies on the efficacy and tolerance of the treatment is very low. Although there is no available evidence on the use of inhaled antibiotics in SOT recipients with respiratory colonization by ESBL-producing *Enterobacteriaceae,* nebulized antibiotics are often used in specific situations, such as LuT [3, 31].

There are several commercialized antibiotics prepared specifically for nebulization, but most data derive from the use of aminoglycosides and colistin. In a single-center, randomized, double-blind trial with critically ill patients, administration of inhaled gentamicin or amikacin every 8 hours for 2 weeks was associated with a greater eradication of MDR microorganisms compared to placebo [99]. In another small sample size study, inhaled tobramycin-solution

was effective and had less adverse effects than intravenous tobramycin for the treatment of VAP caused by *P. aeruginosa* or *Acinetobacter* spp. [100].

Recently, it was reported that the combination of inhaled amikacin and fosfomycin in patients with Gram-negative VAP was not associated with clinical improvement when compared to the placebo [101]. Some studies have shown that nebulized colistin can be effective and safe in the treatment of pneumonia caused by MDR GNB [102, 103]. However, other studies have not confirmed these results [104, 105].

Choosing the nebulized antibiotic treatment depends both on the antibiotic and the nebulization device. The antibiotic should be selected based on the susceptibility profile, taking into account that cut-off values used for systemic treatment are not applicable for nebulized therapy. Moreover, if an antibiotic without a specific commercialized preparation is prescribed, bronchodilator drugs should be previously administered to reduce the risk of associated bronchospasm. On the other hand, to improve the effectiveness of this type of treatment, appropriate nebulization devices are essential. Vibrating mesh nebulizers, which are smaller and faster than jet nebulizers, are recommended [106].

One concern about nebulized therapy is the possibility of inducing antibiotic resistance. However, studies with both cystic fibrosis and critically ill patients did not report a resistance increase when compared to conventional therapy or placebo [99, 107, 108].

2.9.1. Consensus recommendations

- The use of inhaled antibiotics may be considered for LuT recipients with respiratory tract colonization with ESBL-producing *Enterobacteriaceae* or that have received a colonized graft. Appropriate nebulization devices (electronic or vibrating mesh nebulizers) are recommended (BIII).

2.10. What treatment should be prescribed? Can BLBLI be used for the treatment of ESBL-producing Enterobacteriaceae infections in SOT recipients?

While ESBL are capable to hydrolyze β-lactam antibiotics and non-cephamycin-type cephalosporins, they do not hydrolyze carbapenems. As such,

carbapenems are usually considered as first-line treatment. There are no comparative studies between the different carbapenems for the treatment of ESBL-producing *Enterobacteriaceae* infections. However, in the case of ESBL-producing *E. coli* strains exposed to carbapenems, a greater selection of strains resistant to ertapenem and meropenem, but almost none to imipenem, has been described [109].

β-lactamase inhibitors are capable of inactivating ESBL, which is not the case with chromosomal-mediated AmpC β-lactamases. Several retrospective observational studies have been conducted to assess the efficacy of BLBLI compared to carbapenems for the treatment of ESBL-producing *Enterobacteriaceae* infections. Second-generation BLBLI, such as ceftolozane-tazobactam and ceftazidime-avibactam have acceptable activity against ESBL-producing *Enterobacteriaceae* and appear to be reasonable alternatives to carbapenems.

Amoxicillin-clavulanic acid has shown efficacy in the treatment of UTI caused by ESBL-producing *E. coli*, with a 93% cure rate with susceptible strains and 56% with intermediate or resistant strains [110]. Piperacillin-tazobactam cured 10/11 patients with ESBL-producing *E. coli* or *Klebsiella* spp. infections from sites other than the urinary tract when the MIC was ≤16/4 µg/mL, but only 1/5 patients when the MIC was >16/4 µg/mL [111]. Resistance during treatment with piperacillin-tazobactam was reported in a case of ESBL-producing *Klebsiella* endocarditis [112], which leads to the question of the efficacy of BLBLI in infections with high bacterial load. Mortality rates are higher when BSI caused by ESBL-producing *Enterobacteriaceae* is treated empirically with BLBLI than with a carbapenem: 38% (10/16) vs 16% (10/63) for ESBL-producing *E. coli* or *K. pneumoniae* [113] and 25% (2/8) versus 14% (8/57) for ESBL-producing *E. coli*, *K. pneumoniae and Proteus mirabilis,* respectively [114]. A recent study that included 331 patients with ESBL-producing *Enterobacteriaceae* BSI, 103 (48%) treated with piperacillin-tazobactam and 110 (52%) treated with carbapenem, showed that the risk of death was 1.92 times higher in the group treated empirically with piperacillin-tazobactam [115]. However, two other recent published articles showed similar mortality rates in the treatment of BSI caused by ESBL: the first included 151 patients treated empirically with either piperacillin-tazobactam (94) or carbapenem (57), with

similar mortality rates (30.9% and 29.8%, respectively), and risk-adjusted mortality rate (OR 1.0, 95% CI; 0.45-2.17) [116]; the second study differentiated between empirical treatment (365 patients), directed treatment (601 patients) and overall cohort (627 patients), finding no differences in cure/improvement or 30-day mortality rate between carbapenem and BLBLI [117].

Second-generation BLBLI, ceftolozane-tazobactam and ceftazidime-avibactam, have a better activity profile against ESBL-producing *Enterobacteriaceae.* Data extracted from two pivotal clinical trials of ceftolozane-tazobactam for the treatment of UTI [118] and intra-abdominal infections [119] included 150/1346 patients with ESBL-producing *Enterobacteriaceae* infections [120]. Clinical cure rates were 97.4% (76/78) for ceftolozane-tazobactam, 82.6% (38/46) for levofloxacin (prescribed for UTI) and 88.5% (23/26) for meropenem (prescribed for intra-abdominal infections) [120]. The *in vitro* activity profile of ceftazidime-avibactam against ESBL-producing *Enterobacteriaceae* and plasmid-determined AmpC is excellent, reaching almost 100% of all susceptible strains [121].

Cephamycins, such as cefoxitin, cefotetan or cefmetazole have shown *in vitro* activity against ESBL-producing *Enterobacteriaceae.* Although the number and quality of the clinical studies is very limited, cefoxitin has shown efficacy for the treatment of UTI caused by ESBL-producing strains [122]. A recent retrospective study with 69 patients with ESBL-producing BSI, in which 26 were treated with cefmetazole and 43 with carbapenems, showed an adequate efficacy of the cephamycin (1 death in the cefmetazole group and 5 deaths in the carbapenem group) [123].

Other active antibiotics against ESBL-producing *Enterobacteriaceae* are aminoglycosides, colistin, fosfomycin, and tigecycline. All of them should be considered second-line antibiotics due their adverse effects and the increased mortality rate when compared to β-lactams.

2.10.1. Consensus recommendations

- Carbapenems are recommended as empirical and targeted treatment of moderate or severe infections caused by ESBL-producing *Enterobacteriaceae* in SOT recipients (BII).

- The use of BLBLI seems reasonable in recipients with non-bacteremic ESBL-producing *Enterobacteriaceae* infections (especially UTI) (BII).

3. Infections produced by CPE

3.1. What are the risk factors for developing CPE infections after SOT?

Approximately 3 to 10% of all SOT recipients in areas where CPE are endemic develop an infection by these microorganisms. The infection site frequently correlates with the type of transplant performed. Mortality rates associated with CPE infections in SOT recipients are close to 40% [124]. Therefore, it is very important to know the risk factors for developing infections by these microorganisms (listed in **Table 4**).

Several studies have evaluated the risk factors for developing a CPE infection. Renal replacement therapy (especially more than 3 sessions after transplantation) has been identified as the major risk factor for developing CPE infections in LT recipients that were already colonized before transplantation (up to 82% of carriers) [125]. Kidney-pancreas transplantation and ureteral stent placement have also been identified as risk factors for CPE infections in KT. In these cases, patient's outcome is poor due to the higher incidence of recurrence and greater 30-day mortality rate (42% in KT) [126].

Other studies, showed in the univariate analysis that LT due to HCV infection and/or hepatoma were risk factors for BSI caused by CRKP, whereas SOFA and APACHE II were risk factors for mortality [127]. Previous exposure to broad-spectrum antibiotic therapy was also reported as a risk factor for CRKP infection in LT. Age, gender, diabetes and other comorbidities did not entail a greater risk. The mortality rate in patients with CRKP infections was 46% (far superior to the mortality rate in patients with CSKP infections) [25].

In the non-transplanted population, risk factors for CPE include previous antibiotic selective pressure (glycopeptides, cefoperazone/sulbactam, fluoroquinolones and cephalosporins) [128], advanced age, mechanical ventilation [129], prolonged central venous catheterization [130] and

tracheostomy [131]. Likewise, studies carried out during healthcare-associated outbreaks have identified age, severity of the infection, ICU admittance, previous use of antibiotics (mainly carbapenems, fluoroquinolones and cephalosporins), invasive procedures (principally mechanical ventilation) and previous colonization by these agents as risk factors for CPE [132].

In a study involving 94 patients, prolonged hospital stay, mechanical ventilation, use of catheters and previous surgery were associated with a higher rate of infection by CRKP [133]. CRKP colonized patients develop more infections and, usually, more severe. In a study that enrolled non-transplanted diabetic patients diagnosed with diabetic foot, the mortality rate was much higher in the colonized group than in the control group (47% *vs*. 4%). Overall, 28% of the colonized patients developed a foot ulcer infection [134].

ICU admission, use of central venous catheters, antibiotic exposure, and diabetes mellitus have been identified as risk factors for colonization with CPE. Exposure to fluoroquinolones and metronidazole has been associated with subsequent infection by these microorganisms. In conclusion, antibiotic therapy, and specifically fluoroquinolones and metronidazole, should be cautiously used in CPE carriers [135].

3.1.1. Consensus recommendations

- Post-transplant renal replacement therapy, HCV infection, hepatoma and previous antibiotic exposure have been identified as risk factors for CPE in LT. Kidney-pancreas transplantation and ureteral stent placement have been reported as risk factors in KT (AII).

3.2. What microbial mechanisms cause resistance to carbapenems? How can CPE be identified through an antibiogram?

In addition to carbapenemase production, carbapenem resistance can also occur by the combination of class C enzymes expression (encoded by chromosomal or plasmid genes) or some ESBL and the loss or structural modification of porins [136, 137], and, less frequently, due to changes in penicillin-binding proteins [138].

Detection of carbapenem resistance is based on EUCAST (http://www.eucast.org/clinical_breakpoints/) or CLSI breakpoints [139], and in analyzing the overall susceptibility of each microorganism, as CPE frequently contain genes that cause resistance to many other antimicrobial families [140]. Some carbapenemase-producing strains have a MIC value below the susceptible clinical breakpoint or have an inhibition halo diameter, measured by disc diffusion method, greater than the one defined as susceptible. Therefore, EUCAST recommends suspecting the presence of these enzymes considering screening cut-off values. Phenotypic methods (available at each Microbiology Unit or Department) and genotypic methods (available at each center or microbiology reference laboratories) allow for microbiologists to confirm carbapenemase production and for the enzyme characterization. EUCAST has a guide for the detection of CPE.
(http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_v1.0_20131211.pdf)

3.2.1. Consensus recommendations

- Standard EUCAST clinical breakpoints should be used for detection of carbapenem resistance in *Enterobacteriaceae* (AIII).
- Carbapenemase production should be suspected when EUCAST screening cut-off values are exceeded (AII).
- Clinical Microbiology Units or Departments must have the means for the phenotypic detection of carbapenemase and for their genotypic classification or have access to reference laboratories for enzyme characterization (AIII).

3.3. Can a colonized or infected patient with CPE be accepted as an organ donor?

When assessing the risk of transmitting a CPE infection from a colonized and/or infected donor, we can only rely on the limited experience from specific

centers with an endemic outbreak, mainly from colonization/infection with KPC-producing *K. pneumoniae* (KPC-Kp). The only study that systematically analyzed donor-transmission of these microorganisms included only 5 colonized or infected donors with KPC-Kp. Donor-derived infection occurred in four of eleven recipients (36%). Three of the recipients (two kidney and one liver) developed a severe SSI, with a death-related case [61]. Failure in communicating the microbiological data and, therefore, a delay of more than 7 days in beginning the specific antibiotic regimen were identified as risk factors for both transmission and severe infection development [61]. Case records of KPC-Kp donor-derived infections make up for the rest of the limited published data [59, 60, 62]. The only relevant conclusion that can be drawn out of these limited data is that grafts with high potential colonization by CPE should be avoided (KT from donors with UTI, LuT from donors with respiratory tract infections). If the donor has an undiagnosed BSI before transplantation, recipients should receive, at least, 7-days of adequate treatment.

3.3.1. Consensus recommendations

- Donation from patients with non-bacteremic, non-graft-related CPE infections is not contraindicated. Nevertheless, recipients should receive, as soon as possible, a minimum of 7-days effective antibiotic treatment after transplantation (BIII).

- Donation should be avoided if the donor has a CPE bacteremic infection. If transplantation was performed before microbiological data was available, a minimum 7-days effective antibiotic treatment should be prescribed as soon as possible (BIII).

- It is recommended to avoid kidney grafts from donors with CPE-related UTI (BIII) and lung grafts from patients with lung CPE-related infection (BIII).

3.4. Can a patient colonized with CPE be accepted for transplantation?

There are only a few studies that have focused on determining if the presence of a previous colonization in a recipient could determine the risk of developing a severe infection by CPE after transplantation. Most of the scarce available data derives from LT. A LT center with an endemic setting of KPC-Kp infection reported that 5 of the 6 previously colonized recipients subsequently developed an infection. In most cases it was a recurrence of a previous infection [17]. Although this study reported a 35% overall mortality rate associated with the KPC-Kp infection, the specific outcome of these infections was not detailed.

A different study that compared the clinical outcomes of 9 LT recipients colonized with KPC-Kp with 18 LT recipients in whom carbapenem-resistant pathogens were not detected, reported that 8 of the 9 patients developed an infection, 5 of them with BSI, with an overall mortality rate of 78%. The authors concluded that pre-transplant KPC-Kp colonization could constitute a relative contraindication to transplantation [141]. Other studies coincided in the increase of the mortality rate related to KPC-Kp infections in LT recipients [16, 142, 143]. In KT, the impact of the recipient previous colonization with CEP was not clearly evaluated. Nevertheless, an increase in the morbidity, mortality and risk of recurrences associated with these microorganisms has been reported [126, 144]. KPC-Kp infection was also related to a higher mortality rate in LuT [38].

With the available data, it can only be concluded that CEP infected/colonized SOT recipients have a higher risk of recurrence and/or *de novo* infection by these microorganisms. Associated morbidity and mortality is also high. There are no studies that specifically measure whether this risk is outweighed by the negative impact of excluding these patients from transplantation. In any case, transplantation should depend on our ability to control the infection, similar to potential recipients infected/colonized by other microorganisms.

3.4.1. Consensus recommendations

- There are no data to contraindicate the transplantation of patients colonized with CPE. Nonetheless, these recipients have an increased risk of graft infection and, probably, of death (CIII).

3.5. Should a different surgical prophylaxis regimen be prescribed when a donor or a recipient is colonized with CPE?

There are no studies that have specifically addressed the surgical prophylaxis regimens in patients colonized with CPE. As we mentioned, SOT recipients previously colonized by CPE have a higher risk of developing infections by these microorganisms [125]. However, the incidence of SSI in SOT is very variable and is directly related to the epidemiological situation of the center. A RESITRA study that included 1400 KT recipients, reported a high incidence of SSI due to GNB. Prophylaxis with cefazolin was not associated with an increased risk of infection by these microorganisms [145]. A different RESITRA study with 1222 LT recipients, observed that SSI caused by GNB was also more frequent and prophylaxis with cefazolin, in the univariate analysis, was identified as a risk factor. Nonetheless, this association was lost in the multivariate analysis, when variables, such as center or Child-Pugh score, were involved [146]. On the other hand, a Chinese study has shown that ertapenem is as effective as ceftriaxone / metronidazole for the prophylaxis of SSI in patients undergoing elective colorectal surgery [147]. In a different study, patients who underwent colorectal surgery and received ertapenem had a lower rate of SSI (4% patients with ertapenem vs. 13% with other antibiotic, P = 0.01) [148].

With the available data, it is not possible to issue recommendations concerning the surgical prophylaxis in patients colonized by CPE. Nevertheless, centers with a high rate of SSI caused by these bacteria, should adjust their prophylaxis regimen according to their antibiotic susceptibility patterns.

3.5.1. Consensus recommendations

- It is not recommended to use of a different surgical prophylaxis regimen in patients colonized with CPE. Nevertheless, centers that have a high incidence of SSI caused by CPE should change their prophylaxis regimen according to the microorganisms' susceptibility results (BIII).

3.6. When and how should CPE colonization screening studies be performed in SOT recipients?

Surveillance cultures for detection of colonized patients with CPE and implementation of contact precautions, among other measures, have allowed a reduction of the infection rate, both in outbreak and in endemic settings [149-151]. However, none of the studies specifically addressed the SOT population. A recent systematic review which included ten studies and a total of 1806 patients described a 16.5% risk of CEP infection in colonized patients (intestinal colonization was detected by rectal swab screening in most studies) [152]. One of the studies specifically included LT recipients [141].

Infections caused by carbapenemase-producing *K. pneumoniae* have been associated with an increase of the morbidity and the mortality rates [17, 153]. In endemic areas, the incidence of CRKP after LT is approximately 5%, with a crude mortality rate between 25 and 71% [16, 57, 141, 154]. A prospective Italian study which included LT recipients, screened for intestinal colonization with CRKP by obtaining rectal swab samples before and after transplantation. Of the 237 transplanted patients, 41 were colonized (11 at the moment of transplantation and 30 after transplantation). Twenty developed a CRKP-associated infection (BSI in 18 and pneumonia in 2 patients), mean of 41.5 days after transplantation. The incidence of infection among non-colonized patients, colonized at the moment of transplantation and colonized after transplantation was 2%, 18.2% and 46.7% (P <0.001), respectively [155]. In a German case-control study, intestinal colonization with KPC-Kp (carbapenemase type 2, KPC-2-Kp) was associated with an increased risk of infection after a LT (relative risk of 7, 95 % CI; 1.8-27.1). The mortality rate was also higher (78% vs. 11% in non-colonized patients, P = 0.001) [141]. In another study with KT recipients, CRKP bacteriuria after transplantation was associated with pre-transplant CRKP infection or colonization (OR 18.3, 95% CI; 2.0-170.5). An increase in the mortality rate was also observed when compared to recipients with CSKP bacteriuria (30% *vs*. 10%, P = 0.03) [156].

According to these data, it seems advisable to recommend obtaining rectal swabs from SOT recipients at the moment of transplantation in order to assess intestinal colonization by CPE (especially in LT recipients). Subsequently

surveillance cultures could be recommended depending on the local epidemiological pattern and the individual risk factors of each patient.

3.6.1 Consensus recommendations

- Rectal swab samples should be obtained at transplantation as a screening measure for CPE intestinal colonization, especially in LT (CII). It is recommended that subsequent surveillance cultures be obtained based on the local epidemiological setting and the individual risk factors of each recipient (CIII).

3.7. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with CPE? Is intestinal decolonization recommended?

According to international guidelines, besides standard precautions that include good hand hygiene compliance policies as the main measure to avoid dissemination, contact precautions should be established for all infected/colonized patients with CPE [157][158]. These include disposable gloves and gowns whenever entering the patient´s single isolation room and if physical contact with the patient or the patient´s surrounding is assumed.

A thorough hygiene and environmental cleaning interventions are essential. Numerous studies have highlighted the important role played by the environmental reservoir, surfaces and medical equipment in the dissemination of these microorganisms [159]. Isolation rooms should be cleansed twice a day. If located in high risk departments, this procedure should be even more frequent [160].

Intestinal decolonization therapies are applied as an infection prevention strategy by using different oral antibiotic regimens, usually aminoglycosides, colistin or the combination of both. A recent meta-analysis showed good tolerance and significant reduction of colonization rates: from 37.1% (CI 95%; 27.5%-47.7%) to 57.9% (CI 95%; 43.1%-71.4%) at the end of treatment [161]. However, 4 of the 13 analyzed studies described the emergence of resistance to the antibiotics administered. A randomized, double-blind, placebo-controlled study, reported the efficacy of selective intestinal decolonization with oral

gentamicin and polymyxin E for 7 days in 40 patients colonized with CRKP. At week 2, 16.1% of rectal swab cultures in the placebo group and 61.1% in the treatment group were negative (OR 0.13, 95% CI; 0.02-0.74, P <0.0016). A similar difference was also reported at week 6 (33.3% vs 58.5%) [162]. In another study, 44 of 77 (57.1%) patients colonized with colistin-resistant CRKP were decolonized with oral aminoglycosides (gentamicin or neomycin/streptomycin). Patients who received aminoglycosides had a lower mortality rate. Those who received gentamicin also had fewer invasive CRKP infections and a better microbiological response at the 180-day follow-up [163].

Long-term effects and clinical impact of these decolonization therapies are unclear. More studies are necessary, since available data is still insufficient to resolve the doubts concerning the effectiveness of intestinal decolonization among carriers.

3.7.1 Consensus recommendations

- Educational programs on hand hygiene compliance reduce transmission of CPE (AII).
- Contact precaution measures are recommended for patients infected and/or colonized with CPE (AII).
- There is not sufficient data to recommend intestinal decolonization among carriers of CPE (CIII).

3.8. How is a healthcare-associated outbreak caused by CPE in a SOT ward diagnosed and controlled?

A structure that allows rapid detection of carriers and fast implementation of measures against outbreaks caused by CPE is fundamental for minimizing their dissemination. These measures are usually implemented as a bundle, and it is difficult to point out their isolated efficacy. Early detection of carriers at admission, good hand hygiene, contact precautions, assigning qualified healthcare personnel and cleaning staff to attend that specific area and group of patients, educational programs and good antibiotic stewardship programs are the measures usually included in most studies [149, 164-167]. An exhaustive

systematic review of the literature, with the purpose of better defining the effectiveness of these different infection control and preventing measures, in order to reduce the incidence of colonization/infection, concluded that the most successful measures were systematic screening of carriers, contact precautions, and cohort nursing by a separate team [168].

3.8.1. Consensus recommendations

- Assigning healthcare personnel to specific areas and group of patients reduces the risk of acquiring CPE, as well as the possibility of transmission and dissemination (AII).
- Systematic screening for carriers at admission, followed by correct contact precaution measures reduces dissemination of CPE (AIII).
- Antimicrobial stewardship programs and interventional measures in the management and treatment of infections caused by CPE reduce dissemination of these bacteria (AIII).

3.9. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with CPE?

There are no data on SOT recipients with respiratory tract colonization by CPE. A pilot study that included patients with VAP caused by *P. aeruginosa* or *Acinetobacter* spp. reported that the administration of inhaled tobramycin was safe and effective when compared to intravenous tobramycin [100]. Some studies have shown that inhaled colistin may be effective and safe in patients diagnosed with HCAP due to MDR GNB [102, 169]. However, these data have not been confirmed in other studies [104, 170]. A recent retrospective study showed an acceptable efficacy of nebulized colistin in patients with extremely resistant *A. baumanii* pneumonia but was not effective in patients with respiratory tract colonization [171].

In conclusion, the administration of inhaled antibiotics to LuT recipients with respiratory tract colonization by CPE could be useful. The decision on whether to prescribe aminoglycosides or colistin should be made according to the susceptibility test results of the microbiological isolates.

3.9.1. Consensus recommendations

- Inhaled antibiotics could be prescribed to LuT recipients with respiratory tract colonization with CPE (CII).

3.10. What is the first-line therapy for a patient with an infection caused by CPE? Is monotherapy or combination therapy recommended?

CPE infections are an important and worrying threat to SOT recipients [57, 124, 154, 172]. Carbapenem monotherapy regimens could be considered in the case of mild infections, if the site of the infection is adequately controlled and the isolate is susceptible, while combination therapy is the best treatment regimen for critically ill patients [124, 173-176]. Combination therapy with at least two active drugs was associated with lower mortality rate in an Italian study (OR 0.52, 95% CI; 0.35-0.77). Moreover, regimens that have included meropenem were associated with significantly higher rates of survival whenever the KPC-Kp had a MIC value ≤8 mg/L [176]. In a different study, which also included KPC-Kp strains, patients treated with a monotherapy regimen of colistin/polymyxin B or tigecycline had a significantly higher mortality rate (66.7%) than those treated with a therapy regimen that combined a carbapenem antibiotic with the previous antibiotics (12.5%) [177]. Daikos et al. have also described a lower mortality rate in treatment regimens that included carbapenems (19.3% vs 30.6%); carbapenem treated episodes with a MIC value ≤8 mg/L had a lower mortality rate than those with a MIC value >8 mg/L (19.3% vs 35.5%) [178]. There is not enough data to support the use of carbapenems in a combination therapy regimen if the MIC value is >8 mg/L. In this case, carbapenems are probably ineffective, especially if the MIC value is >16 mg/L.

Ceftazidime-avibactam is active against KPC-producing carbapenemase-resistant *Enterobacteriaceae,* and has been recently approved by the FDA for the treatment of complicated intra-abdominal infections and complicated UTI. Studies on pneumonia have not yet been published [179-182]. Treatment with ceftazidime-avibactam could be considered whenever the strains show *in vitro* susceptibility (**Table 5**).

3.10.1. Consensus recommendations

- Combination therapy is recommended as first-line treatment for patients diagnosed with a severe infection caused by CPE (BII).

- Monotherapy is recommended for non-severe infections, whenever a fully active antimicrobial, with an adequate infection site penetration, can be prescribed, particularly, for non-severe UTI (in this case, fosfomycin-trometamol or aminoglycosides could be considered) (CIII).

- Carbapenem monotherapy (administered by extended-infusion) may be considered for mild infections if the isolate is susceptible and the site of the infection is adequately controlled, e.g., urinary sepsis without urinary tract obstruction, or symptoms or signs of severe sepsis or septic shock (CIII).

- Patients for whom combination therapy is recommended, a carbapenem with a MIC value ≤8 mg/L, administered by extended-infusion, plus one or two fully active antimicrobials (including colistin, tigecycline, an aminoglycoside or fosfomycin) could be considered. Fosfomycin is preferably used in three-drug combination treatments. The mean serum concentrations and the urinary concentrations of tigecycline are low. Therefore, tigecycline is unsuitable for the treatment of BSI and UTI. These treatment regimens are mainly recommended for patients with severe infections due to KPC-Kp (BII).

- There are not enough data to recommend the use of a carbapenem antibiotic in a combination therapy regimen if the MIC value is >8 mg/L. In this case, carbapenems are probably ineffective, especially if the MIC value is >16 mg/L. We recommend a combination therapy regimen that includes at least two completely active antimicrobials, according to the susceptibility study and the site of the infection (colistin, aminoglycosides, fosfomycin and tigecycline) (CIII).

- Ceftazidime-avibactam may be considered if the strain shows *in vitro* susceptibility (CIII).

- Patients with less severe invasive infections and complicated UTI could benefit of a carbapenem-free treatment regimen (colistin, aminoglycosides, fosfomycin and tigecycline –the latter not for UTI). Both monotherapy and combination treatment regimens could be considered, as previously mentioned (CIII).

4. Infections produced by MDR *P. aeruginosa*

4.1. What are the risk factors for developing MDR P. aeruginosa infections after SOT?

The incidence of infections produced by MDR *P. aeruginosa* strains is higher in SOT recipients than in the general population. Almost 50% of all *P. aeruginosa* BSI in SOT recipients are caused by MDR strains [18, 27]. The risk of infection is higher in LuT, since more than half of the cystic fibrosis patients that are candidates for LuT are colonized by MDR strains, and up to 75% will subsequently be colonized after transplantation [32].

The risk of developing MDR *P. aeruginosa* infections depends on several factors, such as previous antibiotic therapy, renal replacement therapy, surgical reoperation, prolonged ICU stay, prolonged tracheal intubation and tracheostomy [18, 41, 183-186]. Most of these risk factors have been identified in critically ill or ICU patients [187-190]. Of note, in SOT, most of the studies are focused on the risk factors for developing infections due to MDR GNB and not specifically due to MDR. *P. aeruginosa*.

Only two studies have analyzed the risk factors for developing infections caused by MDR *P. aeruginosa* in SOT recipients. A prospective study that included 318 LT, KT and HT recipients diagnosed with BSI identified that the risk factors for XDR *P. aeruginosa* BSI were previous transplantation, nosocomial acquisition and septic shock [21]. A different retrospective study that included 207 episodes of *P. aeruginosa* BSI in SOT and hematopoietic stem cell transplant recipients identified that previous transplantation, nosocomial acquisition and ICU admission in the previous year were risk factors

for BSI caused by MDR *P. aeruginosa* [27]. Nosocomial acquisition and previous transplantation were risk factors identified in both studies (listed in **Table 4**).

4.1.1. Consensus recommendations

- The risk factors for developing MDR *P. aeruginosa* BSI in SOT recipients include previous transplantation, hospital-acquired infection, previous admission to ICU, and septic shock (BIII).

4.2. What are the most important mechanisms of antimicrobial resistance in MDR/XDR P. aeruginosa? How can MDR/XDR P. aeruginosa be identified through an antibiogram?

The prevalence of infections caused by MDR *P. aeruginosa* varies accordingly to the geographical area, the type of transplant performed and the definition used [3, 5].

Worldwide, the prevalence of MDR *P. aeruginosa* strains already exceeds 30%. This includes Spanish hospitals; approximately half of the MDR isolates would also be XDR in this country [191]. The increasing prevalence is due to the extraordinary ability of *P. aeruginosa* to develop resistance by chromosomal mutations and the increasing production of exogenous resistance determinants [192]. The main mutational mechanisms of antibiotic resistance include constitutive hyperproduction of inducible chromosomal cephalosporinase AmpC (derepression), responsible for resistance to penicillins and antipseudomonal cephalosporins, inactivation of the OprD porin, which confers resistance to carbapenems or hyperexpression of some of the multiple efflux pumps. MDR/XDR phenotypes result from the combination of several of these mutations. Nevertheless, these strains frequently remain susceptible to the new BLBLI (ceftolozane-tazobactam and ceftazidime-avibactam). On the other hand, though proportionally lesser common, the detection of mobile genetic elements carrying carbapenemase or ESBL genes is increasingly frequent. Recent studies show that most carbapenemase-producing or ESBL-producing strains belong to the so-called high-risk clones, mainly ST235, ST111 or ST175 [193].

High risk clone ST175, whose antibiotic resistance is mainly due to mutational mechanisms, remains susceptible to ceftolozane-tazobactam and ceftazidime-avibactam [194, 195]

Class B or MBL carbapenemases are particularly concerning. When compared to the strains with a mutational resistance mechanism, class B or MBL carbapenemases have a bigger ability to disseminate and are resistant to the new BLBLI.

Specific selective media, such as MacConkey agar supplemented with meropenem, are recommended for screening of colonization with MDR/XDR *P. aeruginosa* [196]. Study of LuT isolates may be hampered by the typical cystic fibrosis phenotype (eg, mucoid, slow-growing, or hypermutator strains) [197]. The definition of MDR/XDR strain is exclusively based on the resistance profile reported by the antibiogram. Nevertheless, due to its particular epidemiological relevance and resistance to new β-lactams, it is recommended to perform phenotypic, biochemical and genetic tests for detection of MBL-producing strains [196].

4.2.1. Consensus recommendations

- In order to recognize the resistance profile of the *P. aeruginosa* isolate (MDR or XDR), it is necessary to create an antibiogram that contains the appropriate antibiotics in accordance with the existing recommendations. Phenotypic, biochemical and genetic test for the detection of MBL-producing strains are recommended due to their particular epidemiological relevance and resistance to the new β-lactams (AIII).

4.3. Can a colonized or infected patient with MDR P. aeruginosa be accepted as an organ donor?

Data are very limited. LuT and KT are generally not recommended if the donor has respiratory or urinary tract colonization with MDR bacteria, respectively. If this is not the case, then donation is accepted. Nevertheless, all recipients should be closely monitored after transplantation, since MDR *P. aeruginosa* transmission from donors diagnosed with pneumonia to KT recipients has been described, with fatal outcomes due to the lack of an

effective antibiotic prophylactic or directed treatment in some cases [63, 198]. A case of MDR *P. aeruginosa* transmission from a donor with an infected peritoneal fluid to HT, LT and KT recipients has also been reported. All received directed antibiotic treatment from the first day after transplantation, and although 2 recipients died, mortality did not appear to be clearly associated with a donor-derived infection [199]. If we refer strictly to colonized, uninfected donors, there are no data regarding MDR *P. aeruginosa*. Nevertheless, it seems recommendable to change the surgical prophylaxis regimen according to the donor´s colonization isolates. The larger experience dates from 2015; 30 recipients received an organ from 18 donors that were infected or colonized with a carbapenem-resistant GNB, and which was not known at the moment of transplantation. Donor transmission was detected in 4 cases. No donor-derived infections were diagnosed in patients who received an effective antibiotic treatment, in whom the graft was not colonized or in cases where no BSI was detected [61]. In any case, the decision to accept the organ from a colonized donor must be individualized.

4.3.1. Consensus recommendations

- In exceptional cases, organs from donors colonized with MDR *P. aeruginosa* can be accepted for transplantation, as long as the strain remains susceptible to some antibiotics (BIII).

4.4. Can a patient colonized with MDR P. aeruginosa be accepted for transplantation?

Up to 50% of LuT recipients diagnosed with cystic fibrosis have their respiratory tract colonized with MDR/XDR *P. aeruginosa*. It can reach up to 75% after transplantation [200]. Despite this, survival is similar regardless of colonization [201]. For this reason, it does not constitute an absolute contraindication for LuT. Notwithstanding, the development of bronchiolitis obliterans (the principal limitation for long-term survival after LuT) has been associated to this infection, and, as such, candidates should be individually evaluated [202].

As for the rest of SOT, not enough data are available for issuing strong recommendations. Prior rectal colonization with CRKP has been identified as a risk factor for developing an infection after LT transplantation [155]. It has even been associated with higher post-transplant mortality rate in the setting of an epidemic outbreak [141]. This was not confirmed in KT [126]. Therefore, at the moment and due to the absence of further data, transplantation should not be contraindicated. No specific preventive measures are recommended for SOT candidates, apart from LuT candidates colonized with MDR *P. aeruginosa*.

4.4.1. Consensus recommendations

- Previous colonization with MDR *P. aeruginosa* does not constitute a contraindication for LuT (AII) or any other type of SOT (AIII).

4.5. Should a different surgical prophylaxis regimen be prescribed when a donor or a recipient is colonized with MDR P. aeruginosa?

4.5.1 Consensus recommendations

- Surgical prophylaxis should be the same for all non-LuT recipients colonized with *P. aeruginosa* (CIII).
- Recipients with a septic lung disease (with cystic fibrosis or bronchiectasis) should receive antibiotics accordingly to their preoperative culture results (CIII).
- The duration of prophylactic antibiotic therapy in LuT will depend on the donor´s and the recipient´s bronchial aspirate (BAS) or bronchoalveolar lavage (BAL) culture results, obtained at the moment of transplantation. If cultures are informed as sterile, antimicrobials will be stopped within 3-5 days. If they are informed as positive or the receptor has a septic lung disease, then they are adjusted accordingly and maintained for 10-15 days (CIII).

4.6. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with MDR P. aeruginosa?

Most of the data concerning this problem does not come from studies that have specifically focused the transplanted population. However, there is sufficient data concerning MDR *P. aeruginosa* in other group of patients to issue recommendations for the SOT population.

Patients can acquire MDR *P. aeruginosa* through contact with a contaminated environment or through the hands of healthcare workers [203-205]. Patient-to-patient transmission of MDR *P. aeruginosa* epidemic clones has also been reported in patients with cystic fibrosis [206].

Hand hygiene with soap and water or alcohol based solutions significantly reduces colonization by GN bacteria [207]. The implementation of contact isolation measures as a bundle of care has shown to significantly reduce the dissemination of these agents within the hospital setting: hand washing, surveillance cultures, single room isolation, use of gowns and gloves, together with educational courses and meetings [208]. There is no consensus concerning its duration. It is recommended to maintain contact isolation measures until two or three weekly separated sterile cultures have been obtained, and antibiotic treatment must have been stopped at least one week before [81].

Active screening through rectal, urinary, respiratory and wound swab sampling can identify colonized patients earlier. However, the false-negative rate is high [209]. Moreover, there is still a debate concerning frequency and timing, as well as the type of samples used. The existence of risk factors for colonization with MDR *P. aeruginosa* could help discriminate the population that would benefit from these measures. However, a single retrospective study failed to demonstrate differences of infection/colonization rate with carbapenem-resistant *P. aeruginosa* before and after the implementation of screening measures at the moment of admission and weekly afterwards [151].

4.6.1. Consensus recommendations

- Hand hygiene with an alcohol based solution before and after touching the patient is essential (AII).

- Contact isolation measures should be implemented: single room or cohort isolation for all infected/colonized patients, wearing gowns and gloves before entering the room and using disposable or patient-specific materials (AII). Isolation measures should be maintained until two or three weekly separated sterile cultures have been obtained. Antibiotic treatment must have been stopped at least one week before (BIII).

- Active screening of colonization with MDR *P. aeruginosa* should not be performed in the case of an endemic setting (BIII).

4.7. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with MDR P. aeruginosa?

Most lung recipients with septic lung disease have chronic *P. aeruginosa* infection and are treated with nebulized antibiotics. A high percentage is MDR or XDR *P. aeruginosa*. Treatment with nebulized colistin, tobramycin or aztreonam will depend on the strain´s resistance pattern at the moment of transplantation [210, 211].

Colonization with *P. aeruginosa* in the immediate post-transplant period may lead an infection of the bronchial anastomosis and dehiscence of the suture. Moreover, it is a risk factor for pneumonia since these patients are immunosuppressed and their lungs, in this initial moment, are denervated and poorly perfused. As such, it is a common practice to prescribe nebulized colistin if *P. aeruginosa* is isolated from respiratory secretions of a LuT recipient in the immediate post-transplant period.

Different studies have shown that LuT recipients with chronic *P. aeruginosa* infection not only have a higher risk of developing chronic rejection, but also to develop it in an earlier stage [32, 212]. Treatment of chronic MDR or XDR *P. aeruginosa* infection is complicated, as the only available drugs (colistin, amikacin) have a high rate of nephrotoxicity. Chronic MDR or XDR *P. aeruginosa* infection has not been shown to decrease the survival of these recipients [5, 201, 213]. Therefore, in LuT, considering the lack of guidelines and data, and using as example chronic *P. aeruginosa* infection in patients diagnosed with cystic fibrosis, it is a common practice to prescribe nebulized

colistin for a prolonged period of time. Of note, cases of possible synergistic nephrotoxicity between inhaled tobramycin and calcineurin inhibitors in LuT recipients have been described [214, 215].

Non-lung SOT recipients colonized with MDR/XDR *P. aeruginosa* should be treated as a non-transplanted patient, considering the risk of nephrotoxicity associated with aminoglycosides and colistin. Most of these patients will have bronchiectasis, and nebulized antibiotic prescription will be recommended.

4.7.1. Consensus recommendations

- Most LuT recipients with septic lung disease and chronic *P. aeruginosa* infection, regardless of the antimicrobial resistance pattern, should receive nebulized antibiotics (colistin, tobramycin, or aztreonam) before transplantation (AIII).

- LuT recipients should start receiving nebulized colistin immediately after transplantation if *P. aeruginosa* is isolated from respiratory secretions, in order to protect the bronchial suture (CIII).

- After transplantation, nebulized colistin treatment regimens should be prescribed to recipients with chronic *P. aeruginosa* infection, in order to reduce the risk of chronic lung allograft dysfunction (CIII).

4.8. What is the first-line therapy for a patient with an infection caused by MDR P. aeruginosa? Is monotherapy or combination therapy recommended? When should empirical treatment be prescribed? What are the therapeutic options?

The level of evidence for all the issued recommendations on the treatment of severe MDR *P. aeruginosa* infections is very low, because most of the available data come from single case reports, case series or retrospective studies that have compared clinical treatment outcomes.

At least two recent retrospective comparative studies that included BSI caused by *P. aeruginosa*, with susceptible and MDR strains, have not shown that combination therapy improved survival with regard to monotherapy, provided that the empirical treatment included at least one active antibiotic against the strain [216, 217]. Two published meta-analysis have confirmed

these results [218, 219]. Patients with *P. aeruginosa* BSI could benefit from empirical combination antibiotic regimens, as they increase the probability that at least one antibiotic will be active against the strain [220, 221].

There are published data on the use of ceftolozane-tazobactam for the treatment of severe infections caused by MDR *P. aeruginosa* [119, 222-225]. Some published case reports and an ongoing clinical trial suggest that it may be more appropriate, from the pharmacokinetic point of view, to use a dosing regimen of 2 g of ceftolozane and 1 g of tazobactam every 8 h [223, 224, 226]. Aztreonam has been used for the treatment of *P. aeruginosa* susceptible to this antibiotic but resistant to other β-lactams [227, 228]. For strains with intermediate susceptibility, it is recommended to administer the antibiotic by intravenous continuous infusion (**Table 5**).

4.8.1. Consensus recommendations

- High-dose ceftolozane-tazobactam could be prescribed to SOT recipients diagnosed with BSI and/or pneumonia caused by *P. aeruginosa* resistant to carbapenems and other β-lactams, as long as the strain shows *in vitro* susceptibility (AIII).

- Aztreonam is another therapeutic option for strains susceptible to this antibiotic (AIII).

- For strains with intermediate susceptibility to aztreonam, it is recommended to administer the antibiotic by intravenous continuous infusion (AIII).

- Intravenous aminoglycosides (amikacin, gentamicin, tobramycin) are recommended for SOT recipients diagnosed with complicated UTI (including pyelonephritis) caused by *P. aeruginosa* resistant to carbapenems and other β-lactam antibiotics, provided that the strain is susceptible and the risk of nephrotoxicity is acceptable (AII).

- Colistimethate sodium is the recommended treatment for SOT recipients diagnosed with severe infections caused by *P. aeruginosa* resistant to carbapenems and other β-lactams, and to whom ceftolozane-tazobactam, aztreonam or aminoglycosides cannot or should not be prescribed (AIII).

- Combination treatment is not recommended for SOT recipients with a severe infection caused by *P. aeruginosa* resistant to carbapenems and other β-lactams if the directed treatment includes an active first-line antibiotic (BIII).

- Empiric treatment against MDR *P. aeruginosa* is recommended to all SOT recipients with clinical signs of severe infection and recent history of colonization or infection by this type of strains. It should also be prescribed when infections produced MDR *P. aeruginosa* have been detected in the healthcare setting (AIII).

- Empirical combination antibiotic therapies could be recommended, with the goal of including in the treatment regimen an active antibiotic against the strain (AIII).

5. Infections produced by MDR *A. baumannii*

5.1. What are the risk factors for developing MDR A. baumannii infections after SOT?

A. baumannii infection in SOT recipients is above all a healthcare-associated infection. Its incidence varies widely depending on the center´s epidemiological data, ranging from 8% to 50% [18, 41, 185, 229-233]. *A. baumannii* infections are more prevalent among transplant recipients than among other non-transplanted patients admitted to the ICU after undergoing surgery [34].

Although SOT recipients frequently have infections caused by MDR microorganisms, data in this population are limited. The risk factors for MDR *A. baumannii* infection in SOT recipients are: previous antibiotic therapy, specifically carbapenems or piperacillin-tazobactam, retransplantation, septic shock at onset, prolonged mechanical ventilation, cardiothoracic transplantation, kidney failure after transplantation, intra-abdominal infection, prolonged cold ischemia time, fulminant hepatic failure as reason for

transplantation, high MELD score and *A. baumannii* pre-transplant colonization [5, 18, 20, 185] (listed in **Table 4**).

In a prospective study with LT recipients, infection/colonization by MDR *A. baumannii* before transplantation was associated with an increased risk of developing infection by this microorganism after transplantation. In the majority of cases, infection was caused by the same strain that had been isolated in the pre-transplant period [233]. Other authors have found similar results [234]. An ischemia time for more 400 minutes has been associated with a higher risk of SSI after LT [235-237].

Patients transplanted due to fulminant hepatitis usually have a higher MELD score, and longer hospital and ICU stay [231, 235, 238].

Post-transplant kidney failure which required renal replacement therapy has been associated with an increased risk of healthcare-associated infection by CRAB [233]. The use of invasive procedures and prolonged ICU stay may justify this trend [18, 185].

Similar to immunocompetent patients, exposure to antibiotics is associated with MDR *A. baumannii* colonization in SOT recipients [18, 185].

5.1.1. Consensus recommendations

- The risk factors for developing MDR *Acinetobacter baumannii* infections in SOT are: previous exposure to antibiotic therapy, specifically carbapenems or piperacillin-tazobactam, retransplantation, septic shock at onset, prolonged mechanical ventilation, cardiothoracic transplantation, kidney failure after transplantation, intra-abdominal infection, prolonged cold ischemia time, fulminant hepatic failure as reason for transplantation, high MELD score, and *A. baumannii* pre-transplant colonization (BII).

5.2. What are the most important mechanisms of antimicrobial resistance in MDR A. baumannii? How can MDR A. baumannii be identified through an antibiogram?

The resistance mechanisms with greater clinical importance in *A. baumannii* are the ones that reduce susceptibility to carbapenems and colistin. Resistance to carbapenems is multifactorial: carbapenemases and, to a lesser extent,

permeability changes and overexpression of efflux pumps of the RND family (AdeABC, AdeFGH and AdeIJK) [239-241]. The most important carbapenemases in *A. baumannii* are acquired oxacillinases (class D), which belong to 4 different groups: a) OXA-23-like, b) OXA-24-like, c) OXA-58, and OXA-143-like. The most prevalent is OXA-23 [242, 243]. OXA-51 is a chromosome intrinsic oxacillinase with a small carbapenemase activity, and plays a questionable role in carbapenem resistance. MBLs (class B), and class A carbapenemase are other less frequent carbapenemase associated to *A. baumannii* [240-243]. *A. baumannii* also produces a class C chromosomal cephalosporinase with an irrelevant role in establishing resistance to carbapenems.

CRAB is easily detected in antimicrobial susceptibility testing systems, especially when the strains produce OXA-23-like or OXA-24-like oxacillinases, because of their usually high MIC values. Detection of OXA-58-producing strains may be more troublesome because they often show hetero-resistance to carbapenems and express relatively lower MIC values; for a correct identification, a high inoculum size, which is not used in automated systems, is required. Nevertheless, these strains are easily detectable if diffusion methods are used [244, 245].

Acquisition of mutations in genes of the pmrAB system (pmrAB mutants), which encodes an enzyme that adds phosphoethanolamine residues to the lipid A of the lipopolysaccharide, is the most frequent mechanism of colistin resistance in *A. baumannii* [246-248]. Mutations in metabolic genes involved in lipid A biosynthesis (*lpx* mutants) have also been described. Nevertheless, they are less frequent because of the biological cost associated with the loss of the lipopolysaccharide. Both mechanisms of resistance are chromosomal, so dissemination of colistin resistance in *A. baumannii* is clonal. Detection of colistin resistance can be problematic due to factors associated to the microorganism (hetero-resistance) or to the method used. The recommended test method for determining colistin susceptibility is broth microdilution [248, 249]. Disk diffusion is an unreliable method due to its lack of reproducibility, and is not recommended [250].

5.2.1. Consensus recommendations

- Carbapenem-resistance in *A. baumannii* strains is multifactorial; class D (OXA) carbapenemases are the most relevant (AIII).
- Carbapenem-resistance is easily detectable because of the high MIC values (AIII).
- The most important mechanisms of colistin resistance in *A. baumannii* are chromosomal. As such, dissemination is usually clonal (AIII).
- The detection of colistin resistance can be troublesome. Susceptibility should be determined by broth microdilution (BIII).

5.3. Can a colonized or infected patient with MDR A. baumannii be accepted as an organ donor?

Organ donors are usually hospitalized in the ICU, and are inevitable exposed to MDR microorganisms. However, there is very little data on the eligibility of these organs for transplantation. In 2009, the Israeli Society for Infectious Diseases and the Israel Transplant Center developed a systematic national system for the use of organs from donors colonized with MDR microorganisms, including *A. baumannii*. The working group recommendations were based on previous data on the use of organs from donors with BSI and on their own experience.

Their recommendations were: 1. Donors with a positive rectal swab for any MDR GN microorganism: all organs could be accepted for transplantation. 2. Donors with MDR GN microorganisms isolated from airway secretions (colonized/infected), without an adequate antibiotic treatment for pneumonia: the lungs should not be accepted, but all other organs are appropriate for transplantation. If, on the other hand, there is an adequate antibiotic treatment for pneumonia, and to which the MDR GN strain is susceptible, then all organs could be accepted for transplantation. 3. Donors with a positive urine culture for MDR GN microorganisms: all organs could be accepted, except for the kidneys.

Mularoni et al. [61] in a study conducted in Italy in 2012-2013, reported that there was no donor-derived disease transmission in the case of respiratory tract colonization with *A. baumannii*.

5.3.1. Consensus recommendations

- The organs from donors with a positive rectal swab for *MDR A. baumannii* can be accepted for transplantation (AII).
- Except for the kidneys, the organs from donors diagnosed with MDR *A. baumannii* urinary colonization can be accepted for transplantation, provided that there is an effective antibiotic therapy (AII).
- The organs from donors diagnosed with respiratory tract colonization with MDR *A. baumannii* can be accepted for transplantation, except for the lungs if no effective antibiotic therapy is available in the case of developing pneumonia (AII).

5.4. Can a patient colonized with MDR A. baumannii be accepted for transplantation?

Numerous groups agree that infection by MDR *A. baumannii* is more frequent in SOT recipients than in non-transplanted patients and that the associated mortality is high [18, 34, 251-253]. Nevertheless, pre-transplant colonization or infection of a SOT candidate with *A. baumannii* has rarely been associated with morbidity after transplantation, though its true impact is not known [254]. A retrospective study reported that 32% of patients that developed an infection by *A. baumannii* had been previously colonized. Moreover, colonized patients were more likely to develop recurrent infections. Colonization rates by MDR *A. baumannii* were similar between all types of transplantation, but invasive infections were more frequent among cardiothoracic recipients [20].

5.4.1. Consensus recommendations

- Rectal, urinary or respiratory tract colonization with *A. baumannii* does not constitute an absolute contraindication for SOT (AIII).

5.5. Should a different surgical prophylaxis, with carbapenems or colistin, be prescribed to SOT recipients colonized with A. baumannii?

No study has specifically focused on analyzing whether the surgical prophylactic regimen should be different in a MDR *A. baumannii* colonized patient. Due to its long-lasting absence, recommendations are only issued according to the following indirect data.

Prior colonization with *A. baumannii* is a risk factor for developing an infection by this microorganism in SOT [20]. The incidence of SSI caused by *A. baumannii* after transplantation is highly variable, and is directly related to the epidemiological setting of the healthcare center. RESITRA studies with 292, 1400, and 1222 HT, KT and LT recipients, reported an incidence of SSI of 0%, 0.2% and 0.5% respectively [29, 145, 146]. On the other hand, the incidence of SSI reached 10% in a report that included 196 LT recipients from a center with a rate of *A. baumannii* colonization/infection of 53.6% [255].

The antibiotics usually recommended for surgical prophylaxis in SOT [233] are ineffective against *A. baumannii*. As such, carbapenems or colistin, depending on the degree of resistance, would be the antibiotics of choice. The efficacy of these antibiotics as antimicrobial prophylaxis, for both general surgery and SOT, is not known. The only data were limited to four LT recipients, colonized with CRAB before transplantation, who received perioperative prophylaxis with colistin. Despite the use of colistin, the patients developed SSI. Moreover, there is the potential risk of developing adverse effects to each antibiotic and antibiotic resistance. Nephrotoxicity reaches up to 51% in patients with *A. baumannii* pneumonia [256], but its incidence could be higher in SOT considering the concomitant administration of other nephrotoxic drugs and the increased susceptibility to kidney failure in KT.

Previous exposure to carbapenems [257] and to colistin [258] is the main risk factor for developing resistance to these antibiotics. While five of 14 colistin-treated SOT recipients (36%) developed resistance [20], it was identified as the only independent risk factor for developing colistin-resistant *A. baumannii* infection in LT [253]. It is also a real collective risk factor, as *A. baumannii* is easily transmitted to other patients through the hands of healthcare personnel, and could lead to an outbreak situation [259].

5.5.1. Consensus recommendations

- Patients colonized with *A. baumannii* should receive the same surgical prophylaxis as non-colonized patients. This prophylaxis regimen should be active against the common pathogens of the skin, and therefore neither carbapenems nor colistin should be used (AII).

5.6. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with MDR A. baumannii?

The recommended measures to prevent transmission of *A. baumannii* include standard precautions, environmental decontamination, hand hygiene compliance and education of the healthcare personnel. Surgical face mask and goggles are also mandatory whenever a diagnostic or therapeutic procedure is performed on an infected/colonized respiratory tract [260, 261].

These control measures are of particular importance in the case of SOT recipients colonized with *A. baumannii*. SOT recipients receive antibiotics more frequently than non-SOT patients, and their antibiotic regimens are usually more prolonged. For this reason, they are considered as high-risk patients for developing antibiotic resistance. Since the hospitalization rate is also higher in this group of patients, they are a source of healthcare-associated infections caused by MDR bacteria, including *A. baumannii*.

Recently, the benefit of antimicrobial stewardship programs in reducing SSI in transplant recipients, combined with other infection control measures, has been described. This improvement was mainly due to a better compliance of the surgical prophylaxis protocol [261].

5.6.1. Consensus recommendations

- All *A. baumannii* infected or colonized SOT recipients require the standard universal and contact precautions. Surgical face mask and goggles are also mandatory whenever a diagnostic or therapeutic procedure is performed on an infected/colonized respiratory tract (AII).

5.7. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with MDR A. baumannii?

There is sufficient clinical evidence to recommend adjuvant therapy with inhaled colistin for severe respiratory tract infections caused by several colistin-susceptible microorganisms, together with an appropriate systemic antibiotic treatment. Although there is no clear evidence of its benefit in reducing the mortality rate, its use is clearly associated with an improvement in the rates of microbiological eradication at the respiratory tract [262]. Although MDR *A. baumannii* colonization of the respiratory tract in SOT recipients may increase the risk of subsequent infections, there is no available clinical data on the usefulness of inhaled or systemic anticipated treatment for the prevention of infections caused by this microorganism.

5.7.1. Consensus recommendations

- Inhaled antimicrobials –colistin or polymyxin B– as adjuvant therapy together with a systemic antimicrobial treatment, have not yet demonstrated to improve the clinical outcome of patients with respiratory tract infections caused by MDR *A. baumannii*, though it may offer superior rates of microbiological eradication (CIII).

- Inhaled antimicrobial therapy has not demonstrated any benefit in preventing infections caused by MDR *A. baumannii* in both colonized donors and SOT recipients (CIII).

5.8. What is the first-line therapy for a SOT recipient with an infection caused by MDR A. baumannii?

The recommendations for the treatment of SOT recipients diagnosed with infections caused by MDR *A. baumannii* have not been issued based on randomized controlled trials (RCT). As such, they have to be obtained from published data with heterogeneous group of patients, including different types of SOT recipients.

The efficacy of various antimicrobials with *in vitro* activity against MDR *A. baumannii* is well demonstrated. Monotherapy with colistin or polymyxin B, has

not proven to be more effective than their comparators in VAP caused by this microorganism [263-265]. The main limitation of these studies lies in the heterogeneity of the patients enrolled and in the variability of the colistin dosage. The use of colistin monotherapy can lead to hetero-resistant mutants [266] and failure in microbiological eradication can reach up to 30% [263, 265].

A recent RCT reported that treatment with sulbactam (ampicillin-sulbactam 9 g every 8 hours) compared to colistin for HCAP had similar adverse effects and similar clinical and microbiological outcomes [265]. Other observational studies have reported similar outcomes with different associations of sulbactam versus their comparators [267, 268].

The available data on the use of tigecycline alone for the treatment of infections caused by MDR *A. baumannii* is scarce. A large observational study with 386 patients diagnosed with an infection caused by strains only susceptible to colistin or tigecycline, reported that the 266 patients treated with tigecycline (monotherapy or combination therapy) had a significantly lower rate of unfavorable outcome (30.8% vs. 50%, p <0.0001). Moreover, when compared to the 120 patients treated with a combination of imipenem and sulbactam, no significant differences in the mortality rate at day 3 were described. The comparative analysis between both groups of patients suggested that those treated with tigecycline had a less severe clinical condition (lower ICU admission and lower incidence of renal impairment or sepsis) [269]. It is well established that the use of tigecycline alone can favor the appearance of resistance during treatment [270, 271]. Higher doses of tigecycline (loading dose of 200 mg, followed by a maintenance dose of 100 mg every 12 h) may be associated with an improvement in the clinical response rate, without an increase of adverse affects in critically ill patients [272].

Several antibiotics, such as rifampicin or fosfomycin, have shown *in vitro* activity against MDR *A. baumannii* [273]. Animal models and *in vitro* studies have proven that these drugs have synergistic activity, especially when combined with colistin [274]. However, monotherapy use of these antimicrobials is associated with a rapid emergence of resistant strains [275]. Glycopeptides (vancomycin, teicoplanin and telavancin) are able to inhibit the synthesis of peptidoglycan of the *A. baumannii* cell wall, although they are not able to penetrate through its outer membrane and, therefore, do not have specific *in*

vitro activity. However, disruption of the outer membrane by another active drug allows these antimicrobials to reach their therapeutic targets and show synergistic activity. Such is the case with colistin [276-278].

A retrospective observational study with 69 SOT recipients diagnosed with a MDR *A. baumannii* infection (mostly HCAP), reported that the use of colistin-carbapenem combination therapy provided an improvement in the clinical response and survival rate, although none of these patients were treated with colistin monotherapy [20].

Different observational studies have described a significant improvement in the clinical course of MDR *A. baumannii* infections treated with a combination of colistin and rifampicin [279-281]. However, two recent comparative studies failed to prove superiority of this combination, though higher rates of microbiological eradication in patients with respiratory tract infection was observed [282, 283]. A systematic review has confirmed the lack of clinical efficacy of this combination and increased hepatic toxicity [284].

Combination therapy of colistin and sulbactam has not demonstrated superior hospital survival rate compared to colistin monotherapy, although a higher rate of microbiological eradication has been observed in patients who received combination therapy [285, 286]. Combination of tigecycline and colistin or a carbapenem has not shown to reduce in the mortality rate [287].

The potent *in vitro* synergistic activity of combining colistin and a glycopeptide [288, 289] has not correlated with an improvement in clinical efficacy. A retrospective series of 57 patients diagnosed with severe *A. baumannii* infection failed to prove a better outcome, while an increase in the risk of renal failure was described [290].

There is reasonable clinical evidence to recommend the use a loading dose of 6-9 MU of colimycin, as a way to improve its pharmacokinetic parameters and achieve earlier therapeutic levels, which may improve the prognosis in the case of severe infections. Although renal elimination of colistin is very limited, its prodrug sodium colistimethate is eliminated by the kidneys. Therefore, maintenance doses should be adjusted according to renal function, with proportional dosage intervals increments, or by monitoring plasma drug levels. Recommendations for patients with renal replacement therapy are not well established [291] (**Table 5**).

Adequate and early antimicrobial therapy is a key element for improving the prognosis of SOT recipients with severe infections caused by MDR *A. baumannii*. Several recent observational studies have shown that different factors are related to an unfavorable clinical course in this population, including mechanical ventilation, LT or liver-kidney transplantation and the late-onset of infection. Patients with high mortality risk admitted to units with an endemic MDR *A. baumannii* setting could benefit from empirical therapy with colistin or a combination of colistin and tigecycline [19, 20, 229].

5.8.1. Consensus recommendations

- Patients with infections caused by CRAB should receive antimicrobial therapy with intrinsic laboratory-proven activity. These include polymyxins (especially colistin), sulbactam and tigecycline (AII).

- Certain antimicrobials with *in vitro* activity against *A. baumannii*, such as rifampicin, glycopeptides or fosfomycin, may only be used in combination therapy with other active antibiotics, particularly colistin (AII).

- SOT recipients diagnosed with severe MDR *A. baumannii* infections, especially VAP, may benefit from combination therapy with antibiotics that have *in vitro* synergistic activity, especially colistin-carbapenem (meropenem or doripenem, both administered by extended infusion), rather than a monotherapy regimen with colistin (CII).

- Combination treatment of colistin and rifampicin has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR *A. baumannii*, although it offers a higher rate of microbiological eradication (BII).

- Combination treatment of colistin and sulbactam or tigecycline has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR *A. baumannii* (BIII).

- Combination therapy of colistin and vancomycin has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR *A. baumannii* and increases the risk of renal toxicity (EII).

- Colistin should be administered with a loading dose of 6-9 MU, regardless of renal function, to obtain adequate plasma levels within the first 24 hours. Maintenance dose should be individualized according to creatinine clearance or by monitoring plasma levels (BII).

- Previously colonized SOT recipients or with high clinical suspicion of CRAB infection, who have risk factors for poor clinical outcome (mechanical ventilation, LT or kidney-liver transplantation or late-onset of infection), may benefit from empirical therapy with colistin or colistin and tigecycline (CIII).

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Table 1. *Infectious Diseases Society of America* (IDSA) grading system for ranking recommendations

Strength of recommendation	A	Good evidence to support a recommendation for use
	B	Moderate evidence to support a recommendation for use
	C	Poor evidence to support a recommendation
	D	Moderate evidence to support a recommendation against use
	E	Good evidence to support a recommendation against use
Quality of evidence	I	Evidence from ≥1 properly randomized, controlled trial
	II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Table 2. Antimicrobial categories used to define MDR, XDR and PDR isolates according to specific Gram-negative bacilli (modified from Magiorakos et al. [13])

Microorganism	**Antimicrobial category**
Enterobacteriaceae	Penicillins, penicillins with β-lactamase inhibitors, antipseudomonal penicillins combined with β-lactamase inhibitors, first- and second-generation cephalosporins, third- and fourth-generation cephalosporins, fifth-generation cephalosporins, cephamycins, monobactams, carbapenems, aminoglycosides, fluoroquinolones, folate pathway inhibitors, tetracyclines, glycylcyclines, phenicols, phosphonic acids (fosfomycin) and polymyxins
Pseudomonas aeruginosa	Antipseudomonal penicillins combined with β-lactamase inhibitors, antipseudomonal cephalosporins, monobactams, antipseudomonal carbapenems, aminoglycosides, fluoroquinolones, phosphonic acids (fosfomycin) and polymyxins
Acinetobacter baumannii	Ampicillin-sulbactam, antipseudomonal penicillins combined with β-lactamase inhibitors, third- and fourth-generation cephalosporins, antipseudomonal carbapenems, aminoglycosides, fluoroquinolones, folate pathway inhibitors, tetracyclines and polymyxins.

Table 3. Major infectious syndromes caused by multidrug resistant Gram-negative bacilli in solid organ transplantation

Syndrome	**Risk group**
Recurrent urinary tract infection	Kidney transplantation Kidney-pancreas transplantation
Renal cyst infection	Kidney transplantation in patients with polycystic disease and/or concomitant hepatic cysts
Recurrent respiratory tract infection	Lung transplantation Cardiopulmonary transplantation
Mediastinitis	Lung transplantation Heart transplantation Cardiopulmonary transplantation
Recurrent cholangitis	Liver transplantation Multivisceral transplantation
Infected biloma	Liver transplantation Multivisceral transplantation
Abdominal abscess and tertiary peritonitis	Liver transplantation Pancreas transplantation Intestinal and multivisceral transplantation

Table 4. Risk factors for developing infections by multidrug resistant Gram-negative bacilli in solid organ transplantation

Microorganism	**Associated risk factors**
ESBL-*Enterobacteriaceae*	Previous antibiotic exposure; pre-transplant colonization; perioperative prophylaxis; prolonged tracheal intubation; long-term hospitalization; urologic manipulation; kidney-pancreas transplantation; renal replacement therapy after transplantation; post-transplant urinary obstruction; recurrent UTI
CRE	Post-transplant renal replacement therapy; HCV infection; hepatoma; kidney-pancreas transplantation; ureteral stent placement
MDR *P. aeruginosa*	Previous transplantation; hospital-acquired infection; previous admission to ICU; septic shock
MDR *A. baumannii*	Pre-transplant colonization; previous exposure to antibiotic therapy, specifically carbapenems or piperacillin-tazobactam; retransplantation; septic shock at onset; prolonged mechanical ventilation; cardiothoracic transplantation; kidney failure after transplantation; intraabdominal infection; prolonged cold ischemia time; fulminant hepatic failure as reason for transplantation; high MELD score

CRE: carbapenem-resistant *Enterobacteriaceae*; ESBL: extended-spectrum β-lactamases; HCV: hepatitis C virus; ICU: intensive care unit; MDR: multidrug resistant; UTI: urinary tract infection

Table 5. Dose regimens of the most frequent antibiotics recommended for the treatment of multidrug resistant Gram-negative bacilli

Antibiotic	Dose
Amoxicillin-clavulanic acid[a]	2 g amoxicillin plus 0.2 g clavulanic acid, infused over 30 min every 8 h
Piperacillin-tazobactam[a]	4 g piperacillin plus 0.5 g tazobactam, infused over 30 min every 6 hours or 4 g piperacillin plus 0.5 g tazobactam, infused over 3-4 hours every 8 hours or 6 h in critically ill patients
Meropenem	2 g infused over 3 h every 8 h (6 g per day)
Aztreonam	6-8 g daily via an intravenous continuous infusion is recommended for strains with intermediate susceptibility
Tigecycline	200 mg loading dose followed by 100 mg/12 h should be considered for patients in septic shock, VAP or *Enterobacteriaceae* with MIC ≥ 1 mg/L
Fosfomycin[b]	4-6 g every 6 h or 8 g every 8 h
Ceftazidime-avibactam	2 g ceftazidime plus 0.5 g avibactam, administered via a 2-h intravenous infusion every 8 h
Ceftalozane-Tazobactam	2 g of ceftolozane plus 1 g of tazobactam, every 8 h
Colistin[c]	Loading dose of 6-9 MU followed by 4.5 MU every 12 h

[a]Most data derives from UTI caused by ESBL-producing *E. coli*. Data on other sources of infection or other *Enterobacteriaceae* are scarce

[b]Should always be considered as part of a combination regimen which includes at least one more active agent, preferably three-drug combination treatments

[c]The dose of colistin for patients with renal replacement therapy is not well established. Nevertheless, experts recommend, for patients undergoing IHD, 0.9 MU on non-IHD days and 1.5 MU on IHD days, after HD. In the case of CRRT, a dose of 2 MU every 8 hours is suggested

CRRT: continuous renal replacement therapy; ESBL: extended-spectrum β-lactamases; IHD: intermittent hemodialysis; MIC: minimum inhibitory concentration; UTI: urinary tract infection; VAP: ventilator-associated pneumonia