Multidrug-Resistant Organisms in Solid Organ Transplantation

11

Meenakshi M. Rana, Paolo Grossi, and Shirish Huprikar

11.1 Introduction

Multidrug-resistant (MDR) bacterial infections are responsible for significant morbidity and mortality in solid organ transplant (SOT) recipients worldwide. Although there has been an increasing recognition of the threat of antimicrobial resistance over the last decade, SOT recipients remain vulnerable to infections with MDROs (multidrug-resistant organisms). Most commonly, these infections are seen early after transplantation when healthcare-associated risk factors, surgical complications, and donor-derived factors predominate.

MDR bacteria are defined as bacteria that are resistant to at least one agent in three different antibiotic classes [1]. These organisms can be further classified as extremely drug-resistant (XDR) or pan-drug-resistant (PDR). In XDR infections, bacteria are only susceptible to two classes of antimicrobials. In PDR infections, bacteria are resistant to all active antimicrobials. The most common organisms that "escape" the effects of antimicrobials and become MDROs are *Enterococcus faecium*, *Staphylococcus aureus*, *Clostridium difficile*, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, commonly known as the ESCAPE organisms [2].

M. M. Rana
Department of Medicine, Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: meenakshi.rana@mountsinai.org

P. Grossi
Division of Infectious Diseases, University of Insubria, Varese, Italy
e-mail: paolo.grossi@uninsubria.it

S. Huprikar (✉)
Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: Shirish.Huprikar@mssm.edu

O. Manuel, M. G. Ison (eds.), *Infectious Diseases in Solid-Organ Transplant Recipients*, https://doi.org/10.1007/978-3-030-15394-6_11

Infections with MDROs often result in increased hospital length of stay, higher costs, exposure to medications with adverse effects and decreased graft, and patient survival. Mortality rates are higher in these patients, often compounded by inappropriate empiric antimicrobial therapy. Lastly, insufficient clinical data in how to treat SOT recipients with MDR infections, specifically in the setting of resistant Gram-negative infections, frequently contribute to higher mortality rates.

11.2 Gram-Positive Bacteria

Multidrug-resistant infections with Gram-positive organisms typically include methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). MRSA infections appear to be decreasing, likely in the setting of infection prevention and control strategies [3]. Newer antimicrobials have provided improved treatment options for the management of MRSA and VRE infections.

11.3 Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus colonizes the nares and skin, causing infection in the setting of a breach of mucosal barriers or skin such as in the setting of an intravascular catheter. The Centers for Disease Control and Prevention (CDC) reported that 47.9% of all Hospital acquired infections caused by *Staphylococcus aureus* were methicillin-resistant in 2014 [4]. MRSA bloodstream infections (BSIs) and surgical site infections (SSIs) have been associated with longer median duration of hospital stay, increased hospital costs, and higher mortality rates as compared to patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) infection [5, 6]. Despite this, overall rates of HAIs secondary to MRSA appear to be declining in both the United States and Europe, perhaps due to improved infection control measures [3].

MRSA infections in SOT recipients typically present in the first 3 months after transplant. They most commonly cause bloodstream infections in the setting of intravenous catheters, surgical site infections, and respiratory tract infections [7]. Donor-derived infections have also been described, specifically in recipients of donors with MRSA bacteremia and endocarditis. Despite appropriate use of antimicrobials active against MRSA in the recipient and negative blood cultures in the donor at the time of procurement, transmission still occurred as evidenced by whole genome sequencing [8, 9].

Risk factors for MRSA infections in SOT recipients have previously been reported, largely in liver transplant (LT) recipients. These include nasal colonization with MRSA, recent surgical intervention, CMV seronegativity, primary CMV infection, prior antibiotic exposure, and increased ICU length of stay [10–13]. In lung transplant recipients, mechanical ventilation greater than 5 days was a significant risk factor for MRSA infection [14].

Among these risk factors, MRSA colonization seems to confer a significantly increased risk for infection with MRSA after transplant. In a large single center study, liver transplant candidates and recipients with MRSA colonization had an increased risk of MRSA infection but not of death [15]. These findings were confirmed in a meta-analysis in which patients with pre- and posttransplant MRSA colonization had a sixfold and 11-fold increase in MRSA infections posttransplant, respectively. About 8.5% of SOT candidates were colonized with MRSA, similar to other high-risk populations such as those on hemodialysis [16].

The management of patients with MRSA infection involves appropriate antimicrobial therapy (Table 11.1) along with source control [17–19]. Vancomycin remains the most commonly used antimicrobial to treat patients with MRSA infection and is still recommended as a first-line therapy when the vancomycin MIC is less than 2 [20, 21]. The phenomenon of "MIC creep" seen with vancomycin is controversial and has been associated with increased treatment failure and mortality in some studies. However, a recent meta-analysis showed no significant difference in the risk of death when comparing patients with a vancomycin MIC ≥1.5 to MIC <1.5 [22].

Table 11.1 Treatment options for methicillin-resistant *Staphylococcus aureus* (MRSA) infections

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Vancomycin	15–20 mg/kg IV q12	Nephrotoxicity	• First-line therapy when the vancomycin MIC is less than 2 • Requires PK/PD monitoring to achieve an AUC/MIC ratio of 400 or a trough of 15–20 for bacteremia, endocarditis, osteomyelitis, meningitis
Daptomycin	6 mg/kg IV daily for bacteremia, endocarditis; some reports of using higher doses (8–10 mg/kg) in severe infections	Myopathy, rhabdomyolysis, weekly CPK should be monitored; eosinophilic pneumonia	• Bactericidal • Cannot be used for pulmonary infections because inactivated by surfactant
Linezolid	600 mg IV or PO q12	Myelosuppression Peripheral neuropathy Optic neuritis Lactic acidosis Serotonin syndrome (with other SSRIs)	• Approved for HAP, CAP, and SSTIs • Orally bioavailable

(continued)

Table 11.1 (continued)

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Ceftaroline	600 mg IV q12	Similar to other cephalosporins (rash, diarrhea)	• Fifth-generation cephalosporin with activity against MRSA, VISA, and GNRs • Approved for SSTIs, CAP but has been used for bacteremia and in some case reports in combination with daptomycin for salvage therapy
Telavancin	10 mg/kg IV q24	Nephrotoxicity, QT prolongation, dysgeusia	• Approved for HAP and SSTIs but black box warning of increased mortality observed in patients with renal impairment • Combination with tacrolimus may prolong QT • Woman should have a pregnancy test prior to use
Dalbavancin	Two-dose regimen, 1000 mg IV followed by 500 mg IV 1 week later	Nausea/HA/ diarrhea	• Approved for SSTIs • Long half-life which allows for two doses 1 week apart
Tigecycline	100 mg IV × 1 followed by 50 mg IV q12	Nausea/vomiting	• Bacteriostatic • Achieves low plasma drug concentrations and thereby controversial in use for severe infections and bacteremia • Approved for SSTIs, IAB, or HAP
Clindamycin	600–1200 mg IV q6–8 h	Gastrointestinal, *C. difficile* infection	• Bacteriostatic with good tissue penetrations • Appropriate for SSTIs, not bacteremia or severe infections
Sulfamethoxazole-trimethoprim	8–10 mg/kg daily based on trimethoprim component in two divided doses (orally or IV)	Hematologic effects, hepatotoxicity, severe dermatologic reactions	• Avoid use in bacteremia • Can be used for SSTIs

Mg/kg milligrams/kilogram, *IV* intravenous, *MIC* minimum inhibitory concentration, *PK/PD* pharmacokinetic/pharmacodynamics, *AUC/MIC* area under the curve/minimum inhibitory concentration, *HAP* healthcare-associated pneumonia, *CAP* community-associated pneumonia, *SSTI* skin and soft tissue infection, *VISA* vancomycin-intermediate *Staphylococcus aureus*, *GNRs* Gram-negative rods, *IAB* intra-abdominal infection

Commonly used alternatives for treatment of MRSA infection include daptomycin and linezolid. Daptomycin, most commonly used for the treatment of bacteremia and right-sided endocarditis, is inactivated by surfactant and cannot be used for the treatment of pneumonia. MRSA isolates with higher vancomycin MICs may also exhibit higher MICs to daptomycin, and some recommend higher doses of daptomycin (8–10 mg/kg). Combination therapy, particularly the use of daptomycin with beta-lactams such as ceftaroline, may be used as salvage therapy to minimize the emergence of resistance with daptomycin alone [23, 24]. Linezolid is most commonly used in the treatment of pneumonia where it may have superior efficacy when compared to vancomycin [25].

Duration of treatment is typically 4–6 weeks of therapy in patients with complicated MRSA bacteremia. In patients with uncomplicated bacteremia (exclusion of endocarditis, no prosthesis, clearance of bacteremia in 2–4 days, defervescence within 72 h of initiating therapy, no evidence of metastatic sites of infection), 2 weeks of therapy may be considered [20]. MRSA abscess and complicated skin and soft tissue infections should be debrided, and intravascular catheters should be removed in the setting of bacteremia.

The emergence of heteroresistant populations of vancomycin intermediate strains (hVISA) and VISA (vancomycin intermediate *Staphylococcus aureus*) infections have also been documented, although uncommon. Heart transplantation in a patient with hVISA left ventricular assist device infection, mediastinitis, and bacteremia has previously been described as has the clonal spread of an hVISA strain in a cohort of liver transplant recipients [26, 27].

Aggressive infection prevention and control measures, such as active surveillance, have previously been shown to help curtail MRSA infections in SOT recipients [28]. Infection prevention and control measures such as hand hygiene, chlorhexidine bathing for ICU patients, and implementation of contact precautions for patients infected with MRSA have also been shown to reduce hospital-acquired MRSA infections [29]. Larger, multicenter studies are needed to evaluate the benefit of such practices as decolonization in SOT recipients [30].

11.4 Vancomycin-Resistant *Enterococcus* (VRE)

Enterococcus is a Gram-positive organism that commonly colonizes the gastrointestinal tract and frequently causes infections in abdominal organ transplant recipients. Vancomycin resistance, specifically in *Enterococcus faecium*, became increasingly recognized in liver transplant recipients in the 1990s. Although typically known as a less virulent organism, infection with VRE has been associated with increased morbidity and mortality in SOT recipients, especially prior to the widespread availability of newer antimicrobials [31, 32].

Risk factors for VRE infection in liver transplant recipients include prior antibiotic use, intra-abdominal surgical procedures, biliary complications, and previous colonization [33–35]. Compared to non-colonized patients, liver transplant candidates and recipients colonized with VRE have an increased risk of VRE infection and death [15]. A meta-analysis documented an increase in VRE infection in patients with pre- and posttransplant VRE colonization [16].

Treatment for VRE infections should include source control and implementation of an active antimicrobial agent against VRE (Table 11.2). The most commonly used agents in the treatment of VRE infection are linezolid and daptomycin. Linezolid, an oxazolidone, has been used with good success in SOT recipients [36, 37]. Prolonged

Table 11.2 Treatment options for vancomycin-resistant *Enterococcus* (VRE) infections

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Linezolid	600 mg IV or PO q12	Myelosuppression Peripheral neuropathy Optic neuritis Lactic acidosis Serotonin syndrome (with other SSRIs)	• Approved for VRE infection/ bacteremia • Orally bioavailable
Daptomycin	6 mg/kg IV daily but can be used in higher doses (see text)	Myopathy, rhabdomyolysis, weekly CPK should be monitored; eosinophilic pneumonia	• Frequently used for VRE infection/bacteremia • Bactericidal • Cannot be used for pulmonary infections because inactivated by surfactant
Quinupristin-dalfopristin	7.5 mg/kg IV q8	Phlebitis Myalgias/arthralgias Elevation in transaminases/bilirubin	• Approved for VRE in the late 1990s, largely a second-line drug given treatment-related adverse events and likely decreased efficacy compared to newer agents
Tigecycline	100 mg IV × 1 followed by 50 mg IV q12	Nausea/vomiting	• Bacteriostatic • Achieves low plasma drug concentrations and thereby controversial in use for severe infections and bacteremia • Approved for SSTIs, IAB, or HAP
Tedizolid	200 mg IV or PO once daily	Fewer reported AEs when compared to linezolid—specifically hematologic and gastrointestinal- and lacks drug interactions with other SSRIs	• Activity against MRSA in addition to VRE • Orally bioavailable
Oritavancin	1200 mg as a one-time infusion	Nausea, vomiting, headache	• Long half-life enables single dose administration • Activity against MRSA in addition to VRE • Approved for SSTIs

Mg/kg milligrams/kilogram, *IV* intravenous, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *HAP* healthcare-associated pneumonia, *SSTI* skin and soft tissue infection, *IAB* intra-abdominal infection, *AEs* adverse events, *SSRIs* selective serotonin reuptake inhibitor

therapy can be associated with thrombocytopenia and leukopenia. Other adverse effects include peripheral neuropathy, serotonin syndrome in patients receiving concomitant SSRIs and lactic acidosis. Earlier meta-analyses suggested linezolid may be associated with improved clinical outcomes when compared to daptomycin although the outcome of these studies may have been affected by suboptimal daptomycin dosing [38].

Daptomycin, a bactericidal agent, is frequently used off-label as treatment for VRE infections and has been successfully used in SOT recipients [39]. However, the optimal dosing strategy of daptomycin for VRE infections still remains unclear. A recent retrospective cohort study of patients with VRE bloodstream infections (BSI) found that patients treated with daptomycin doses greater than 8 mg/kg had significantly improved microbiological clearance of infection; patients treated with even higher doses of daptomycin (≥10 mg/kg) had improved survival. There was no significant increase in CPK in the patients treated with higher-dose daptomycin [40]. Another prospective study from Taiwan found all-cause 14-day mortality was improved in patients receiving either high-dose daptomycin (9 mg/kg) or linezolid as compared to those receiving low-dose daptomycin (6–9 mg/kg) [41]. Higher doses of daptomycin may therefore be safely used to treat VRE infections although larger studies in SOT recipients are lacking. Combination therapy with beta-lactams has also been used in treatment of VRE infections, specifically in endocarditis [42–44].

Single-center studies have documented both daptomycin and linezolid resistance in patients with VRE infections. In a single center study of 14 liver transplant recipients with daptomycin non-susceptible *Enterococcus faecium* infections, all except one had previous exposure to daptomycin, and there was a 71% overall mortality rate [45]. Other studies have also described liver transplant recipients with linezolid-resistant VRE infections [46].

A comprehensive prevention strategy against VRE includes judicious use of antimicrobial agents and implementation of infection prevention and control measures such as hand hygiene and chlorhexidine bathing in the ICU. Routine surveillance is not indicated; however, in units with high prevalence rates or outbreak settings, active surveillance and use of contact precautions may be helpful to prevent cross-transmission and guide perioperative prophylaxis at the time of transplant [31, 32, 47]. Limited data exists regarding the use of decolonization strategies for rectal carriage of VRE, and larger studies are needed [48].

11.5 Gram-Negative Bacteria

Increasing resistance among Gram-negative bacteria in the last decade has accounted for a significant rise in antimicrobial resistant infections worldwide and presents a serious public health threat. The three most common Gram-negative organisms to "escape" the effects of antimicrobials are *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*.

11.6 Carbapenem-Resistant *Enterobacteriaceae* (CRE)

Infections with carbapenem-resistant *Enterobacteriaceae* (CRE) have been increasingly described in SOT recipients. ß-lactamases which hydrolyze carbapenems are responsible for CRE infections. These are largely classified by molecular structure as described in the Ambler classification (Table 11.3). Types of carbapenemases among *Enterobacteriaceae* include Ambler class A (KPC), class B (zinc-dependent metallo-B-lactamases, VIM, IMP, NDM), and class D (OXA type). The most commonly described carbapenemase is KPC (Ambler class A), which accounts for a large proportion of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections. KPC-producing isolates account for most CRE infections seen in the United States, Israel, Europe, China, and South America [49]. They hydrolyze all ß-lactams and are usually resistant to other classes of drugs such as fluoroquinolones and aminoglycosides. More recently in 2009, infections with the New Delhi metallo-beta-lactamase 1 (NDM-1) were described in South Asia and the United Kingdom. These have subsequently been described worldwide, largely in immigrants from South Asia. Lastly, infections with oxa-48 carbapenemase have been described in Europe, Turkey, North Africa, and India [49–52].

In the United States, CRE accounts for about 9300 infections annually and 600 deaths a year [53]. The incidence of CRKP varies by center and type of transplant. Various studies have reported rates between less than 1 and as high as 20% although the incidence of CRKP infection in LT recipients is likely around 5% in endemic areas [49, 50, 54]. LT recipients typically present with primarily intra-abdominal infections or bacteremia, whereas kidney transplant (KT) recipients present with urinary tract infections. Respiratory tract infections are more commonly seen in heart and lung recipients [50]. Necrotizing skin and soft tissue infections has also been described in transplant recipients [55]. Mortality rates in SOT recipients with CRKP vary by report but are usually between 30 and 50% with some studies describing mortality rates as high as 70% [49, 50, 56–58].

SOT recipients with CRE infection often have multiple risk factors that predispose them to infection including prolonged hospital and ICU stay, antimicrobial use, and mechanical ventilation [49, 59]. Transplantation itself has been an independent risk factor for CRKP [59]. In LT recipients, risk factors for CRKP have included MELD score at LT, re-transplantation, biliary leak, renal replacement therapy, and mechanical ventilation [60–62]. In KT recipients, risk factors have also included receipt of antimicrobials (other than sulfamethoxazole-trimethoprim) and increased transplant admission length of stay and use of ureteral stent [63, 64].

Table 11.3 Ambler classification of ß-lactamases

Ambler classification	ß-lactamases	Examples
A	Penicillinases	KPC, TEM, SHV, CTX-M
B	Metallo-ß-lactamases	IMP, VIM, NDM
C	Cephalosporinases	Amp-C
D	Oxacillinases	OXA

Pretransplant and posttransplant colonization has also been shown to be associated with posttransplant infection [56, 62, 65]. However, in a recent multicenter study, patients who were colonized with CRKP had 1-year survival rates approaching 80% posttransplant. Colonization with CRE may therefore not be considered an absolute contraindication to transplant [66].

Donor-derived infections with CRKP have also been reported. In one report, four recipients received tissue from a donor with CRKP, but there was evidence of transmission to only one recipient. In this case, timely communication and early involvement of transplant infectious disease specialists resulted in all four recipients receiving perioperative prophylaxis with antimicrobial agents directed toward the donor's KPC isolate resulting in only one transmission [67].

Treatment of CRE infections is largely based on observational clinical studies and should include source control and susceptibility-directed antimicrobial therapy (Table 11.4) [2, 68–70]. Source control is essential to improved clinical outcomes and mortality [59]. Tigecycline can be used for the treatment of intra-abdominal, skin and soft tissue and pulmonary infections but may be less effective in treating bloodstream or urinary tract infections because it does not achieve good serum or urinary levels. The polymyxins are some of the most active agents against CRE and require complex dosing schemes that have only recently been elucidated [2]. Polymyxin B, which differs from colistin or polymyxin E by amino acid structure, appears to be associated with less nephrotoxicity than colistin [71]. Neurotoxicity is also less common with more recent formulations. Fosfomycin has been used in combination therapy successfully but is only available in IV formulation in Europe [72].

Other data has suggested that combination therapy may have more efficacy in the treatment of CRE infections when compared to monotherapy. In one multicenter retrospective cohort study in Italy, triple combination therapy was associated with lower mortality; specifically, the use of a carbapenem was associated with improved survival [73]. Other studies have reported on combination therapies involving the use of colistin and a carbapenem, colistin and tigecycline, or even dual carbapenem therapy [74]. In vitro synergy studies have confirmed activity of dual carbapenem therapy against carbapenemase-producing strains as well as polymyxin and rifampin; rifampin however should be used with caution in transplant recipients as it decreases the levels of calcineurin inhibitors, mTOR inhibitors and triazole antifungals [49]. However, in a large, international retrospective cohort study that included 480 patients with CRE BSI, there was no difference between monotherapy and combination therapy except in patients who had severe infections and were considered to have a high mortality score [75]. Larger clinical trials are still needed to understand why and which combination therapy may be effective for severely ill patients and elucidate optimal treatments for CRE infection [74].

Ceftazidime-avibactam is a recently approved beta-lactam/beta-lactamase inhibitor combination with activity against CRE [68]. Recent observational data suggests that ceftazidime-avibactam may be superior to alternative treatments such as colistin [76–78]. However, resistance to ceftazidime-avibactam has already been reported [79]. Of note, ceftazidime-avibactam cannot be used for NDM-1 infections as avibactam does not inhibit metallo-B-lactamases.

Table 11.4 Treatment of multidrug-resistant (MDR) Gram-negative infections

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Commercially available			
Tigecycline	100 mg IV × 1 followed by 50 mg IV q12	Nausea/vomiting	• Bacteriostatic • Achieves low plasma drug concentrations and thereby controversial in use for severe infections and bacteremia • Approved for SSTIs, IAB, or HAP • Does not have activity against *Proteus*, *Providencia*, or *Pseudomonas*
Polymyxins	Colistin 5 mg/kg/day IV or polymyxin B 1.25 mg/kg IV q12	Nephrotoxicity Neurotoxicity	• Approved for GNR infections including *Pseudomonas* • Requires complex PK/PD dosing with a loading dose
Ceftazidime-avibactam	2.5 gm IV q8	Nausea/vomiting	• Approved for complicated IAB and UTIs • Inhibits the activity of class A, B, and D enzymes, but not against B
Ceftolozane-tazobactam	1.5 gm IV q8	Nausea/vomiting, headache	• Approved for complicated IAB and UTIs • Has activity against MDR/XDR *Pseudomonas* and ESBL organisms
Fosfomycin	3 gm orally × 1; IV formulation available outside of the United States		• Oral formulation should only be used for uncomplicated cystitis • Rapid development of resistance if IV formulation used as monotherapy
Aminoglycosides	5–7 mg/kg/day IV of tobramycin or gentamicin; 15 mg/kg/day IV of amikacin	Nephrotoxicity, ototoxicity, vestibular toxicity	• Needs peak and trough monitoring
Meropenem/vaborbactam	4 gm IV q8	Headache, infusion site reaction, diarrhea	• Recently approved for UTI/pyelonephritis • Inhibitor of class A and class C ß-lactamases
Drugs in the pipeline			
Imipenem/relebactam			• Inhibitor of class A and class C ß-lactamases with additional activity against *Pseudomonas*

Table 11.4 (continued)

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Plazomicin			• Aminoglycoside with activity against KPC- and OXA-producing organisms and MDR *Pseudomonas*
Eravacycline			• Fluorocycline tetracycline with activity against NDM- and KPC-producing organisms and CRAB

Mg/kg milligrams/kilogram, *IV* intravenous, *MIC* minimum inhibitory concentration, *PK/PD* pharmacokinetic/pharmacodynamics, *HAP* healthcare-associated pneumonia, *SSTI* skin and soft tissue infection, *GNRs* Gram-negative rods, *IAB* intra-abdominal infection, *UTI* urinary tract infection, *MDR* multidrug-resistant, *XDR* extremely drug-resistant, *ESBL* extended-spectrum beta-lactamase, *KPC Klebsiella*-producing carbapenamase, *NDM* New Delhi metallo-beta-lactamase, *CRAB* carbapenem-resistant *Acinetobacter baumannii*

Prevention of CRE in the healthcare setting often requires a combination of several infection control and prevention strategies. These include hand hygiene, cohorting of patients or staff, contact isolation precautions for patients infected or colonized with CRE, environmental cleaning, and focus on implementation of an effective antimicrobial stewardship program [80].

11.7 MDR *Pseudomonas aeruginosa*

Resistance mechanisms in *Pseudomonas aeruginosa* can be complex and often involve loss of outer membrane porins and upregulation of efflux pumps resulting in few therapeutic options [81]. *Pseudomonas aeruginosa* is a common cause of pneumonia and/or bacteremia early posttransplant [82, 83]. In one study, SOT recipients were 3.47 times more likely to have an MDR strain of *Pseudomonas* as compared to a non-SOT recipient [84]. Frequently, MDR *Pseudomonas* colonizes the lungs of CF patients pre- and posttransplant with colonization in 75% of lung transplant recipients in some reports [54, 83]. It is also the most common cause of bacterial pneumonia in lung transplant recipients, responsible for 25% of infections [54]. However, colonization with MDR *Pseudomonas* is not an absolute contraindication to lung transplant as overall rates of survival are similar in patients with or without colonization [54, 82, 85, 86].

The most significant risk factor for colonization or infection with MDR *Pseudomonas* remains prolonged exposure to antimicrobial therapies [54]. Other risk factors include ICU stay, previous transplantation, hospital-acquired BSI and septic shock [84, 87].

Treatment should utilize prolonged infusion of beta-lactam antimicrobials or increased doses of concentration-dependent therapy (i.e., fluoroquinolones) when susceptible. The polymyxins can also be utilized, and inhaled colistin or

aminoglycosides can be used in the treatment of pneumonia as adjunctive therapy [88]. The role of combination therapy especially in the management of XDR isolates remains controversial and can be used initially in severely ill patients prior to obtaining susceptibilities [31].

Both new B-lactam/b-lactamase inhibitors, ceftazidime-avibactam and ceftolozane-tazobactam, have activity against MDR *Pseudomonas* isolates [31]. However, ceftolozane-tazobactam shows particular promise against MDR and XDR isolates of *Pseudomonas* due to stability against multiple resistance mechanisms [89]. Successful use of ceftolozane-tazobactam has been described in several case reports of SOT recipients with MDR and XDR *Pseudomonas* infections including one lung transplant recipient and another LVAD patient undergoing HT [90, 91]. It is also a promising treatment option for pneumonia due to good penetration into the epithelial lining.

11.8 Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

Prevalence data for carbapenem-resistant *Acinetobacter baumannii* (CRAB) in SOT recipients varies by transplant center and region [54]. *Acinetobacter* is a particularly resilient pathogen, and many carbapenem-resistant isolates are resistant to other available antimicrobials [92]. A recent prospective cohort study at a single center in Brazil found that 46% of their LT recipients were colonized with CRAB and CRAB was the most common MDR Gram-negative isolated on surveillance [65]. MDR and XDR *Acinetobacter* are frequently seen in ventilator-associated pneumonia in cardiothoracic patients; however, respiratory infections in LT recipients are also described [65, 92, 93]. Treatment of MDR and XDR *Acinetobacter* infections remains challenging. Sulbactam, a B-lactamase inhibitor, has intrinsic activity against *Acinetobacter* and should be used if susceptible. Other therapeutic options include tigecycline, minocycline, aminoglycosides, and polymyxins if susceptible. A single center demonstrated that combination therapy with colistin and carbapenems was effective in SOT recipients [92]. Cefiderocol (formerly S-649266), an investigational siderophore cephalosporin, demonstrated potent in vitro activity against a 2014–2016 worldwide collection of clinical isolates of MDR *A. baumannii* and other carbapenem non-susceptible Gram-negatives [94].

11.9 *Burkholderia cepacia*

The *Burkholderia cepacia (B. cepacia)* complex comprises multiple different subspecies and is most known for its significance in patients with cystic fibrosis (CF) and lung transplantation, where it has been associated with increased morbidity and mortality. Infection with *B. cepacia* can lead to a progressive necrotizing pneumonia, resulting in a decline in pulmonary function [95]. The subspecies, *B. cenocepacia*, in particular, has been associated with poor outcomes [54]. In one single center study, patients infected with *B. cenocepacia* before transplant were six times more likely to

die within 1 year of lung transplant compared to those infected with other *Burkholderia* species and eight times more likely to die than compared to patients who were not infected [96]. In addition, transplant recipients infected with *B. gladioli* had significantly higher mortality compared to patients who were not infected [97]. Other studies have shown that infection with other *B. cepacia* species, such as *B. multivorans*, may not be associated with increased mortality after lung transplant [98].

Guidelines from the International Society for Heart and Lung Transplantation (ISHLT) suggest that *B. cenocepacia* and *B. gladioli* may be considered a relative contraindication to lung transplant and that these patients should be referred to a transplant center with significant experience in managing these infections [99]. *B. cepacia* complex strains are intrinsically resistant to multiple antimicrobials and can acquire resistance through efflux pumps or beta lactamases. Effective antimicrobials include trimethoprim-sulfamethoxazole, ceftazidime, meropenem, levofloxacin, and minocycline, and oftentimes combination drug therapy is utilized in patients with MDR or XDR infections [100]. Ceftazidime-avibactam has also been shown to have potent activity against *B. cepacia* [101]. Transmission of *B. cepacia* in healthcare and non-healthcare settings has been described, including through poor adherence to handwashing and contaminated respiratory equipment. Infection control interventions such as education, use of contact precautions, segregation of patients with *B. cepacia* in single-patient rooms with showers, and environmental decontamination have been shown to reduce transmission among CF patients [102, 103].

11.10 Conclusion

SOT recipients are at risk for MDR infections in the early posttransplant setting due to an interplay of complex risk factors that include exposure to broad-spectrum antimicrobials, healthcare-associated exposures, and surgical risk factors. Of particular concern are increasing reports of resistant Gram-negative infections and their association with high mortality rates in SOT recipients. Infection prevention and control measures are important, but more data is needed specifically in SOT recipients. Source control is essential in the management of SOT recipients with MDR infections. Lastly, while newer antimicrobials are being developed, more randomized controlled trials are needed to determine the optimal therapeutic regimens for these patients.

References

1. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268–81.
2. Kaye KS, Pogue JM. Infections caused by resistant Gram-negative bacteria: epidemiology and management. Pharmacotherapy. 2015;35:949–62.
3. Calfee DP. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, and other Gram-positives in healthcare. Curr Opin Infect Dis. 2012;25:385–94.

4. Weiner LM, Fridkin SK, Aponte-Torres Z, et al. Vital signs: preventing antibiotic-resistant infections in hospitals – United States, 2014. Am J Transplant. 2016;16:2224–30.
5. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis. 2003;36:53–9.
6. Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, Briggs JP, Sexton DJ, Kaye KS. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. Clin Infect Dis. 2003;36:592–8.
7. Garzoni C, Vergidis P. Methicillin-resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus infections in solid organ transplantation. Am J Transplant. 2013;13:50–8.
8. Wendt JM, Kaul D, Limbago BM, et al. Transmission of methicillin-resistant Staphylococcus aureus infection through solid organ transplantation: confirmation via whole genome sequencing. Am J Transplant. 2014;14:2633–9.
9. Altman DR, Sebra R, Hand J, et al. Transmission of methicillin-resistant Staphylococcus aureus via deceased donor liver transplantation confirmed by whole genome sequencing. Am J Transplant. 2014;14:2640–4.
10. Florescu DF, McCartney AM, Qiu F, Langnas AN, Botha J, Mercer DF, Grant W, Kalil AC. Staphylococcus aureus infections after liver transplantation. Infection. 2012;40:263–9.
11. Singh N, Paterson DL, Chang FY, Gayowski T, Squier C, Wagener MM, Marino IR. Methicillin-resistant Staphylococcus aureus: the other emerging resistant Gram-positive coccus among liver transplant recipients. Clin Infect Dis. 2000;30:322–7.
12. Schneider CR, Buell JF, Gearhart M, Thomas M, Hanaway MJ, Rudich SM, Woodle ES. Methicillin-resistant Staphylococcus aureus infection in liver transplantation: a matched controlled study. Transplant Proc. 2005;37(2):1243–4.
13. Bert F, Bellier C, Lassel L, Lefranc V, Durand F, Belghiti J, Mentre F, Fantin B. Risk factors for Staphylococcus aureus infection in liver transplant recipients. Liver Transpl. 2005;11:1093–9.
14. Shields RK, Clancy CJ, Minces LR, et al. Staphylococcus aureus infections in the early period after lung transplantation: epidemiology, risk factors, and outcomes. J Heart Lung Transplant. 2012;31:1199–206.
15. Russell DL, Flood A, Zaroda TE, Acosta C, Riley MMS, Busuttil RW, Pegues DA. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. Am J Transplant. 2008;8:1737–43.
16. Ziakas PD, Pliakos EE, Zervou FN, Knoll BM, Rice LB, Mylonakis E. MRSA and VRE colonization in solid organ transplantation: a meta-analysis of published studies. Am J Transplant. 2014;14:1887–94.
17. Holmes NE, Tong SYC, Davis JS, Van Hal SJ. Treatment of methicillin-resistant Staphylococcus aureus: vancomycin and beyond. Semin Respir Crit Care Med. 2015;36:17–30.
18. Choo EJ, Chambers HF. Treatment of methicillin-resistant Staphylococcus aureus bacteremia. Infect Chemother. 2016;48:267–73.
19. Gudiol C, Cuervo G, Shaw E, Pujol M, Carratalà J. Pharmacotherapeutic options for treating *Staphylococcus aureus* bacteremia. Expert Opin Pharmacother. 2017;6566:1–17.
20. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011. https://doi.org/10.1093/cid/ciq146
21. Van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in Staphylococcus aureus infections: a systematic review and meta-analysis. Clin Infect Dis. 2012;54:755–71.
22. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with Staphylococcus aureus bloodstream infections: a systematic review and meta-analysis. JAMA. 2014;312:1552–64.

23. Purrello SM, Garau J, Giamarellos E, Mazzei T, Pea F, Soriano A, Stefani S. Methicillin-resistant Staphylococcus aureus infections: a review of the currently available treatment options. J Glob Antimicrob Resist. 2016;7:178–86.
24. Edwards B, Andini R, Esposito S, Grossi P, Lew D, Mazzei T, Novelli A, Soriano A, Gould IM. Treatment options for methicillin-resistant Staphylococcus aureus (MRSA) infection: where are we now? J Glob Antimicrob Resist. 2014;2:133–40.
25. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, McGee WT, Reisman A, Chastre J. Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis. 2012;54:621–9.
26. Swartz TH, Huprikar S, Labombardi V, Pinney S, Anyanwu A, Lee M, Patel G. Heart transplantation in a patient with heteroresistant vancomycin-intermediate Staphylococcus aureus ventricular assist device mediastinitis and bacteremia. Transpl Infect Dis. 2013. https://doi.org/10.1111/tid.12123
27. Bert F, Clarissou J, Durand F, Delefosse D, Chauvet C, Lefebvre P, Lambert N, Branger C. Prevalence, molecular epidemiology, and clinical significance of heterogeneous glycopeptide-intermediate Staphylococcus aureus in liver transplant recipients. J Clin Microbiol. 2003;41:5147–52.
28. Singh N, Squier C, Wannstedt C, Keyes L, Wagener MM, Cacciarelli TV. Impact of an aggressive infection control strategy on endemic Staphylococcus aureus infection in liver transplant recipients. Infect Control Hosp Epidemiol. 2006;27:122–6.
29. Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med. 2013;368:533–42.
30. Pergam SA. Infection prevention in transplantation. Curr Infect Dis Rep. 2016;18:1–10.
31. Hand J, Patel G. Multidrug-resistant organisms in liver transplant: mitigating risk and managing infections. Liver Transpl. 2016;22:1143–53.
32. Patel G, Snydman DR. Vancomycin-resistant Enterococcus infections in solid organ transplantation. Am J Transplant. 2013;13:59–67.
33. McNeil SA, Malani PN, Chenoweth CE, Fontana RJ, Magee JC, Punch JD, Mackin ML, Kauffman CA. Vancomycin-resistant enterococcal colonization and infection in liver transplant candidates and recipients: a prospective surveillance study. Clin Infect Dis. 2006;42:195–203.
34. Newell KA, Millis JM, Arnow PM, et al. Incidence and outcome of infection by vancomycin-resistant Enterococcus following orthotopic liver transplantation. Transplantation. 1998;65:439–42.
35. Gearhart M, Martin J, Rudich S, et al. Consequences of vancomycin-resistant Enterococcus in liver transplant recipients: a matched control study. Clin Transpl. 2005;19:711–6.
36. El-Khoury J, Fishman JA. Linezolid in the treatment of vancomycin-resistant Enterococcus faecium in solid organ transplant recipients: report of a multicenter compassionate-use trial. Transpl Infect Dis. 2003;5:121–5.
37. Radunz S, Juntermanns B, Kaiser GM, Treckmann J, Mathe Z, Paul A, Saner FH. Efficacy and safety of linezolid in liver transplant patients. Transpl Infect Dis. 2011;13:353–8.
38. Kohinke RM, Pakyz AL. Treatment of vancomycin-resistant Enterococci: focus on daptomycin. Curr Infect Dis Rep. 2017;19(10):33. https://doi.org/10.1007/s11908-017-0589-2.
39. Len O, Montejo M, Cervera C, et al. Daptomycin is safe and effective for the treatment of Gram-positive cocci infections in solid organ transplantation. Transpl Infect Dis. 2014;16:532–8.
40. Britt NS, Potter EM, Patel N, Steed ME. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of vancomycin-resistant enterococcal bacteremia among veterans affairs patients. Clin Infect Dis. 2017;64:605–13.
41. Chuang YC, Lin HY, Chen PY, Lin CY, Wang JT, Chang SC. Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose. Clin Microbiol Infect. 2016;22:890.e1–7.
42. Sierra-Hoffman M, Iznaola O, Goodwin M, Mohr J. Combination therapy with ampicillin and daptomycin for treatment of Enterococcus faecalis endocarditis. Antimicrob Agents Chemother. 2012;56:6064.

43. Snyder AH, Werth BJ, Barber KE, Sakoulas G, Rybak MJ. Evaluation of the novel combination of daptomycin plus ceftriaxone against vancomycin-resistant enterococci in an in vitro pharmacokinetic/pharmacodynamic simulated endocardial vegetation model. J Antimicrob Chemother. 2014;69:2148–54.
44. Smith JR, Barber KE, Raut A, Aboutaleb M, Sakoulas G, Rybak MJ. β-Lactam combinations with daptomycin provide synergy against vancomycin-resistant Enterococcus faecalis and Enterococcus faecium. J Antimicrob Chemother. 2014;70:1738–43.
45. Lewis JD, Enfield KB, Cox HL, Mathers AJ, Sifri CD. A single-center experience with infections due to daptomycin-nonsusceptible Enterococcus faecium in liver transplant recipients. Transpl Infect Dis. 2016;18:341–53.
46. Niebel M, Perera MTPR, Shah T, Marudanayagam R, Martin K, Oppenheim BA, David MD. Emergence of linezolid resistance in hepatobiliary infections caused by Enterococcus faecium. Liver Transpl. 2016;22:201–8.
47. Banach DB, Peaper DR, Fortune BE, Emre S, Dembry LM. The clinical and molecular epidemiology of pre-transplant vancomycin-resistant enterococci colonization among liver transplant recipients. Clin Transpl. 2016;30:306–11.
48. Cheng VCC, Chen JHK, Tai JWM, et al. Decolonization of gastrointestinal carriage of vancomycin-resistant Enterococcus faecium: case series and review of literature. BMC Infect Dis. 2014;14:514.
49. Pouch SM, Satlin MJ. Carbapenem-resistant Enterobacteriaceae in special populations: solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. Virulence. 2017;8:391–402.
50. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014;58:1274–83.
51. Giani T, Conte V, Mandalà S, D'Andrea MM, Luzzaro F, Conaldi PG, Grossi P, Rossolinia GM. Cross-infection of solid organ transplant recipients by a multidrug-resistant Klebsiella pneumoniae isolate producing the OXA-48 carbapenemase, likely derived from a multiorgan donor. J Clin Microbiol. 2014;52:2702–5.
52. Grundmann H, Glasner C, Albiger B, et al. Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis. 2017;17:153–63.
53. CDC. Antibiotic resistance threats in the United States, 2013 | Antibiotic/Antimicrobial Resistance | CDC; 2013.
54. Van Duin D, Van Delden C. Multidrug-resistant Gram-negative bacteria infections in solid organ transplantation. Am J Transplant. 2013;13:31–41.
55. Rana MM, Sturdevant M, Patel G, Huprikar S. Klebsiella necrotizing soft tissue infections in liver transplant recipients: a case series. Transpl Infect Dis. 2013. https://doi.org/10.1111/tid.12103
56. Lübbert C, Becker-Rux D, Rodloff AC, Laudi S, Busch T, Bartels M, Kaisers UX. Colonization of liver transplant recipients with KPC-producing Klebsiella pneumoniae is associated with high infection rates and excess mortality: a case-control analysis. Infection. 2014;42:309–16.
57. Kalpoe JS, Sonnenberg E, Factor SH, del Rio Martin J, Schiano T, Patel G, Huprikar S. Mortality associated with carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients. Liver Transpl. 2012;18:468–74.
58. Barchiesi F, Montalti R, Castelli P, Nicolini D, Staffolani S, Mocchegiani F, Fiorentini A, Manso E, Vivarelli M. Carbapenem-resistant Klebsiella pneumoniae influences the outcome of early infections in liver transplant recipients. BMC Infect Dis. 2016;16:538.
59. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant Klebsiella pneumoniae Infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol. 2008;29:1099–106.
60. Freire MP, Oshiro ICVS, Pierrotti LC, et al. Carbapenem-resistant Enterobacteriaceae acquired before liver transplantation. Transplantation. 2017;101:811–20.

61. Pereira MR, Scully BF, Pouch SM, Uhlemann A-C, Goudie S, Emond JE, Verna EC. Risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients. Liver Transpl. 2015;21:1511–9.
62. Giannella M, Bartoletti M, Morelli MC, et al. Risk factors for infection with carbapenem-resistant Klebsiella pneumoniae after liver transplantation: the importance of pre- and post-transplant colonization. Am J Transplant. 2015;15:1708–15.
63. Freire MP, Abdala E, Moura ML, de Paula FJ, Spadão F, Caiaffa-Filho HH, David-Neto E, Nahas WC, Pierrotti LC. Risk factors and outcome of infections with Klebsiella pneumoniae carbapenemase-producing K. pneumoniae in kidney transplant recipients. Infection. 2015;43:315–23.
64. Pouch SM, Kubin CJ, Satlin MJ, Tsapepas DS, Lee JR, Dube G, Pereira MR. Epidemiology and outcomes of carbapenem-resistant Klebsiella pneumoniae bacteriuria in kidney transplant recipients. Transpl Infect Dis. 2015. https://doi.org/10.1111/tid.12450
65. Freire MP, Villela Soares Oshiro IC, Bonazzi PR, et al. Surveillance culture for multidrug-resistant Gram-negative bacteria: performance in liver transplant recipients. Am J Infect Control. 2017;45:e40–4.
66. Huprikar S, Casner L, Pierrotti LC, Nellore A, Madan R, Garcia-Diaz J, Jacobs S, Lee D, Trindade Clemente W, Alangaden G Outcomes associated with carbapenem-resistant Enterobacteriaceae infection after solid organ transplantation in a multicenter study. Progr. Abstr. 16th Am. Transpl. Congr. Am. Soc. Transpl. Surg. Am. Soc. Transplantation, Boston, MA; 2016.
67. Ariza-Heredia EJ, Patel R, Blumberg EA, et al. Outcomes of transplantation using organs from a donor infected with Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae. Transpl Infect Dis. 2012;14:229–36.
68. van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation β-lactam/β-lactamase inhibitor combinations. Clin Infect Dis. 2016;63:234–41.
69. Falagas ME, Mavroudis AD, Vardakas KZ. The antibiotic pipeline for multi-drug resistant Gram negative bacteria: what can we expect? Expert Rev Anti-Infect Ther. 2016;14:747–63.
70. Wright H, Bonomo RA, Paterson DL. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn? Clin Microbiol Infect. 2017;23:704–12.
71. Vardakas KZ, Falagas ME. Colistin versus polymyxin B for the treatment of patients with multidrug-resistant Gram-negative infections: a systematic review and meta-analysis. Int J Antimicrob Agents. 2017;49:233–8.
72. Mills JP, Wilck MB, Weikert BC, Porrett PM, Timko D, Alby K, Bonomo RA, Blumberg EA. Successful treatment of a disseminated infection with extensively drug-resistant Klebsiella pneumoniae in a liver transplant recipient with a fosfomycin-based multidrug regimen. Transpl Infect Dis. 2016;18:777–81.
73. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: importance of combination therapy. Clin Infect Dis. 2012;55:943–50.
74. Bonomo RA, Burd EM, Conly J, Limbago BM, Poirel L, Segre JA. Carbapenemase-producing organisms: a global scourge! Clin Infect Dis. 2017;66:1290–7.
75. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis. 2017;17:726–34.
76. van Duin D, Lok JJ, Earley M, et al. Colistin vs. ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2017. https://doi.org/10.1093/cid/cix783
77. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini R V., Doi Y, Kreiswirth BN, Clancy CJ. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. Antimicrob Agents Chemother. 2017. https://doi.org/10.1128/AAC.00883-17

78. King M, Heil E, Kuriakose S, et al. Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother. 2017. https://doi.org/10.1128/AAC.00449-17
79. Humphries RM, Yang S, Hemarajata P, Ward KW, Hindler JA, Miller SA, Gregson A. First report of ceftazidime-avibactam resistance in a KPC-3-expressing Klebsiella pneumoniae isolate. Antimicrob Agents Chemother. 2015;59:6605–7.
80. Centers for Disease Control and Prevention (CDC). Facility guidance for control of carbapenem-resistant Enterobacteriaceae (CRE). Natl Cent Emerg Zoonotic Infect Dis. 2015;24:700–9.
81. Arizpe A, Reveles KR, Patel SD, Aitken SL. Updates in the management of cephalosporin-resistant Gram-negative bacteria. Curr Infect Dis Rep. 2016. https://doi.org/10.1007/s11908-016-0552-7
82. Aguado JM, Silva JT, Fernández-Ruiz M, et al. Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. Transplant Rev. 2017. https://doi.org/10.1016/j.trre.2017.07.001
83. Cervera C, van Delden C, Gavaldà J, Welte T, Akova M, Carratalà J. Multidrug-resistant bacteria in solid organ transplant recipients. Clin Microbiol Infect. 2014;20(Suppl 7):49–73.
84. Johnson LE, D'Agata EMC, Paterson DL, Clarke L, Qureshi ZA, Potoski BA, Peleg AY. Pseudomonas aeruginosa bacteremia over a 10-year period: multidrug resistance and outcomes in transplant recipients. Transpl Infect Dis. 2009;11:227–34.
85. Dobbin C, Maley M, Harkness J, Benn R, Malouf M, Glanville A, Bye P. The impact of pan-resistant bacterial pathogens on survival after lung transplantation in cystic fibrosis: results from a single large referral centre. J Hosp Infect. 2004;56:277–82.
86. Hadjiliadis D, Steele MP, Chaparro C, Singer LG, Waddell TK, Hutcheon MA, Davis RD, Tullis DE, Palmer SM, Keshavjee S. Survival of lung transplant patients with cystic fibrosis harboring panresistant bacteria other than Burkholderia cepacia, compared with patients harboring sensitive bacteria. J Hear Lung Transplant. 2007;26:834–8.
87. Bodro M, Sabe N, Tubau F, Llado L, Baliellas C, Gonzalez-Costello J, Cruzado JM, Carratala J. Extensively drug-resistant Pseudomonas aeruginosa bacteremia in solid organ transplant recipients. Transplantation. 2015;99:616–22.
88. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. Inhaled antibiotics for Gram-negative respiratory infections. Clin Microbiol Rev. 2016;29:581–632.
89. Maraolo AE, Cascella M, Corcione S, Cuomo A, Nappa S, Borgia G, De Rosa FG, Gentile I. Management of multidrug-resistant *Pseudomonas aeruginosa* in the intensive care unit: state of the art. Expert Rev Anti-Infect Ther. 2017;15:861–71.
90. Peghin M, Maiani M, Castaldo N, Givone F, Righi E, Lechiancole A, Sartor A, Pea F, Livi U, Bassetti M. Ceftolozane/tazobactam for the treatment of MDR Pseudomonas aeruginosa left ventricular assist device infection as a bridge to heart transplant. Infection. 2017;46:263–5.
91. Stokem K, Zuckerman JB, Nicolau DP, Wungwattana M, Sears EH. Use of ceftolozane-tazobactam in a cystic fibrosis patient with multidrug-resistant Pseudomonas infection and renal insufficiency. Respir Med Case Rep. 2018;23:8–9.
92. Shields RK, Clancy CJ, Gillis LM, Kwak EJ, Silveira FP, Massih RCA, Eschenauer GA, Potoski BA, Nguyen MH. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant Acinetobacter baumannii Infections among solid organ transplant recipients. PLoS One. 2012;7(12):e52349. https://doi.org/10.1371/journal.pone.0052349.
93. Guo W, Sheng J, Gu Y, Xing T-H, Peng Z-H, Zhong L. Analysis and forecast for multidrug-resistant Acinetobacter baumannii Infections among liver transplant recipients. Transplant Proc. 2014;46:1448–52.
94. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahma DF. In vitro activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative Bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 study). Antimicrob Agents Chemother. 2017. https://doi.org/10.1128/AAC.00093-17

95. Hafkin J, Blumberg E. Infections in lung transplantation: new insights. Curr Opin Organ Transplant. 2009;14:483–7.
96. Alexander B, Petzold E. Survival after lung transplantation of cystic fibrosis patients infected with Burkholderia cepacia complex. Transplant. 2008;8:1025–30.
97. Murray S, Charbeneau J, Marshall BC, LiPuma JJ. Impact of Burkholderia infection on lung transplantation in cystic fibrosis. Am J Respir Crit Care Med. 2008;178:363–71.
98. Boussaud V, Guillemain R, Grenet D, Coley N, Souilamas R, Bonnette P, Stern M. Clinical outcome following lung transplantation in patients with cystic fibrosis colonised with Burkholderia cepacia complex: results from two French centres. Thorax. 2008;63:732–7.
99. Weill D. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Hear Lung Transplant. 2014;34:1–15.
100. Zhou J, Chen Y, Tabibi S, Alba L, Garber E, Saiman L. Antimicrobial susceptibility and synergy studies of *Burkholderia cepacia* complex isolated from patients with cystic fibrosis. Antimicrob Agents Chemother. 2007;51:1085–8.
101. Papp-Wallace KM, Becka SA, Zeiser ET, et al. Overcoming an extremely drug resistant (XDR) pathogen: avibactam restores susceptibility to ceftazidime for Burkholderia cepacia complex isolates from cystic fibrosis patients. ACS Infect Dis. 2017;3:502–11.
102. Saiman L, Siegel J. Infection control in cystic fibrosis. Clin Microbiol Rev. 2004;17:57–71.
103. O'Malley CA. Infection control in cystic fibrosis: cohorting, cross-contamination, and the respiratory therapist. Respir Care. 2009;54:641–57.