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Multidrug-resistant Enterobacteriaceae, *Pseudomonas aeruginosa*, and vancomycin-resistant enterococci: Three major threats to hematopoietic stem cell transplant recipients

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Abstract

Hematopoietic stem cell transplant (HSCT) recipients are uniquely threatened by the emergence of multidrug-resistant (MDR) bacteria because these patients rely on immediate active antimicrobial therapy to combat bacterial infections. This review describes the epidemiology and treatment considerations for three challenging MDR bacterial pathogens in HSCT recipients: MDR Enterobacteriaceae, including extended-spectrum β -lactamase (ESBL)-producing and carbapenem-resistant Enterobacteriaceae (CRE), *Pseudomonas aeruginosa*, and vancomycin-resistant *Enterococcus* (VRE). These bacteria are common causes of infection in this population and bacteremias caused by these organisms are associated with high mortality rates. Carbapenems remain the treatments of choice for serious infections due to ESBL-producing Enterobacteriaceae in HSCT recipients. Administration of β -lactam agents as an extended infusion is associated with improved outcomes in patients with severe infections caused by *P. aeruginosa*. Older agents used for the treatment of CRE and MDR *P. aeruginosa* infections, such as polymyxins and aminoglycosides, have major limitations. Newer agents, such as ceftazidime-avibactam and ceftolozane-tazobactam have great potential for the treatment of *Klebsiella pneumoniae* carbapenemase-producing CRE and MDR *P. aeruginosa*, respectively, but more pre-clinical and clinical data are needed to better evaluate their efficacy. Daptomycin dosages 8 mg/kg/day are recommended to treat VRE infections in this population, particularly in the setting of increasing daptomycin resistance. Strategies to prevent these infections include strict adherence to recommended infection control practices and multidisciplinary antimicrobial stewardship. Lastly, gastrointestinal screening to guide empirical therapy and the use of polymerase chain reaction-

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based rapid diagnostics may decrease the time to administration of appropriate therapy for these infections, thereby leading to improved outcomes.

Keywords

carbapenemases; Enterobacteriaceae; extended-spectrum β -lactamases; hematopoietic stem cell transplantation *Pseudomonas aeruginosa*; vancomycin-resistant enterococci

1 INTRODUCTION

Hematopoietic stem cell transplant (HSCT) recipients are at high risk of bacteremia early after transplantation because of two major insults to their innate immune system. First, these patients have prolonged neutropenia after receipt of their conditioning regimen and thus lack the first and most important phagocytes to combat bacterial infections.^{1,2} Second, their conditioning regimen leads to marked gastrointestinal (GI) mucositis, and thus the integrity of their mucosal barrier is damaged. These two key insults establish a high-risk setting for bacteremia caused by enteric organisms and for severe complications from these infections.

Before the 1960s, empirical antibacterial therapy was not routinely administered to febrile neutropenic patients. This strategy of delaying therapy until culture results were available was associated with poor outcomes in neutropenic patients with gram-negative bacteremia. For example, bacteremia caused by *Pseudomonas aeruginosa* carried a 60%–80% mortality rate in this era.^{3,4} These outcomes improved dramatically after a critical change in practice to administer antibacterial agents with *in vitro* activity against prominent gram-negative bacteria to neutropenic patients immediately for fever or at the first sign of infection.^{4–6}

Current recommendations for the management of fever and neutropenia in oncology patients are to administer antimicrobial agents that are active against the three most common causes of gram-negative bacteremia in neutropenic patients: *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*.^{7–9} Recommended agents include ceftazidime, cefepime, piperacillin-tazobactam, or a carbapenem as monotherapy, based on results from randomized clinical trials that were conducted over a decade ago.^{10–14} However, over the last decade, multidrug-resistant (MDR) Enterobacteriaceae and *P. aeruginosa* have become increasingly prevalent among hospitalized patients.^{15,16} Furthermore, vancomycin-resistant *Enterococcus* has increasingly been reported as a common cause of bacteremia in HSCT recipients.^{17,18} This increase in resistance among the most common causes of bacteremia in neutropenic patients and HSCT recipients threatens the applicability of currently used algorithms.

The objective of this review is to delineate the current epidemiology and treatment considerations for three of the most challenging bacterial pathogens in HSCT recipients: MDR Enterobacteriaceae, including extended-spectrum β -lactamase (ESBL) and carbapenemase producers, *P. aeruginosa*, and vancomycin-resistant *Enterococcus* (VRE). We also discuss strategies to curb the threat posed by these pathogens, including an evaluation of preventative measures and strategies to minimize delays in administration of appropriate therapies for infected patients.

2 ESBL-PRODUCING ENTEROBACTERIACEAE (ESBL-E)

2.1 Epidemiology

ESBLs are enzymes that are capable of hydrolyzing penicillins, monobactams, and extended-spectrum cephalosporins.¹⁹ Multiple reports from oncology centers in North America, Europe, and Asia have identified ESBL prevalence rates of 17%–37% among bloodstream isolates of Enterobacteriaceae from patients with hematologic malignancies (Table 1^{9,20–26}). Not only did these reports demonstrate a high prevalence of ESBL-E in this population, but many also reported higher mortality rates associated with ESBL-E bacteremia compared to bacteremia caused by non-ESBL-producing Enterobacteriaceae. For example, in a study of 14 Italian hematologic oncology centers, the 21-day mortality rate was 26% after bacteremia caused by third-generation cephalosporin-resistant Enterobacteriaceae, most of which were likely ESBL-E, compared to 5% after bacteremia caused by third-generation cephalosporin-susceptible Enterobacteriaceae.⁹

Furthermore, ESBL-E have expanded their host range into HSCT recipients. In a report from Korea, 44% of *E. coli* bacteremias in HSCT recipients were ESBL producers and having an HSCT was a risk factor for ESBL-E bacteremia.²⁴ HSCT centers from Italy and Turkey reported that 18% and 23%, respectively, of *E. coli* bloodstream isolates and 86% and 22%, respectively, of *K. pneumoniae* bloodstream isolates were ESBL-producing strains.^{20,26} At our own HSCT center in New York City (NYC), 29 of 89 (33%) *E. coli* bloodstream isolates from 2011–2016 had a phenotypic profile suggestive of ESBL production (ceftriaxone resistant, meropenem susceptible).

2.2 Treatment

The ESBL-E test highly susceptible to carbapenems and these agents are the treatments of choice for serious ESBL-E infections in HSCT recipients.¹⁹ ESBL-E have variable susceptibility to other first-line recommended therapies for fever and neutropenia, with susceptibility rates to ceftazidime, cefepime, and piperacillin-tazobactam of 20%–30%, 60%–70% and 70%–95%, respectively.^{27,28} However, even when ESBL-E test susceptible to cefepime or piperacillin-tazobactam, concerns have been raised about their use for treating invasive ESBL-E infections. One concern with cefepime and piperacillin-tazobactam is the “inoculum effect”, whereby these agents have increases in their minimum inhibitory concentrations (MICs) against ESBL-E when higher inocula are used for testing.^{29,30} Thus, many ESBL-E that are reported as susceptible based on a standard inoculum would test resistant if a higher inoculum were used. This inoculum effect is typically not seen with carbapenems.

Clinical data characterizing the use of cefepime for the treatment of ESBL-E bacteremia substantiate these *in vitro* concerns. Three cohort studies comparing cefepime to carbapenems for the treatment of ESBL-E bacteremia demonstrated increased mortality with cefepime, including in multivariable and propensity-score matched analyses.^{31–33} Thus, cefepime should be avoided for the treatment of ESBL-E infections in HSCT recipients.

The role of piperacillin-tazobactam for the treatment of ESBL-E infections is unclear, as no randomized clinical trials comparing piperacillin-tazobactam to carbapenems have been

completed. Two large multicenter observational studies of patients with ESBL-E bacteremia found that outcomes of patients treated empirically or as targeted therapy with β -lactam/ β -lactamase inhibitors were similar to those of patients treated with a carbapenem in multivariable analyses.^{34,35} However, a large single-center cohort study from the United States (U.S.) of patients with ESBL-E bacteremia demonstrated a two-fold increased risk of death in patients who received piperacillin-tazobactam empirically compared to those who received a carbapenem empirically, and this difference persisted in multivariable and propensity score-adjusted analyses.³⁶ In the first two studies demonstrating the equivalence of piperacillin-tazobactam and carbapenems, two-thirds of the bacteremias originated from the urinary or biliary tracts. Piperacillin-tazobactam may be more effective in these settings because it achieves high urinary and biliary tract concentrations and biliary infections are often treated concurrently with biliary tract decompression.³⁷ Furthermore, piperacillin-tazobactam was administered at dosages of 4.5 g every 6 hours or as a prolonged infusion in these studies. Conversely, in the study demonstrating the superiority of carbapenems, the source of the majority of bacteremias was central line-associated or intra-abdominal, and the most common dosage of piperacillin-tazobactam was 3.375 g every 6 hours. In addition, very few neutropenic patients or HSCT recipients were included in these studies. In summarizing results from these studies, it could be concluded that piperacillin-tazobactam, dosed at either 4.5 g every 6 hours or as a prolonged infusion, is appropriate for ESBL-E bacteremias that originate from the urinary or biliary tract in immunocompetent hosts, but for ESBL-E bacteremias from other sources, or bacteremias that occur in neutropenic patients or HSCT recipients, carbapenems remain the preferred treatment options.

Group 2 carbapenems (e.g., imipenem and meropenem) are typically utilized for the initial treatment of ESBL-E infections in HSCT recipients. Ertapenem, a group 1 carbapenem, has the advantage of once-daily dosing and has a narrower antimicrobial spectrum; unlike group 2 carbapenems, it does not have activity against *P. aeruginosa* and *Acinetobacter baumannii*.³⁸ Unlike group 2 carbapenems, which are almost uniformly active *in vitro* against ESBL-E, up to 10% of ESBL-E will not test susceptible to ertapenem using current Clinical and Laboratory Standards Institute (CLSI) breakpoints.^{27,39} Provided that the organism is susceptible to ertapenem, outcomes of patients with ESBL-E infections treated with ertapenem are comparable to those of patients treated with group 2 carbapenems.^{40,41} Thus, HSCT recipients with infections caused by ESBL-E can potentially be transitioned from a group 2 carbapenem to ertapenem once clinically stable, provided that they have no other bacterial infections and that the organism tests susceptible *in vitro*.

3 CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE)

3.1 Epidemiology

Over the last decade, the prevalence has had an unprecedented increase in Enterobacteriaceae that are not only resistant to penicillins and cephalosporins, but also are resistant to carbapenems.⁴² In the U.S., CRE were initially reported in the NYC area,^{43,44} but have now been identified in almost every state and are considered an urgent antibiotic resistance threat by the Centers for Disease Control and Prevention (CDC).^{45,46} CRE have become most common in *K. pneumoniae*. For example, the percentage of carbapenem

resistance among U.S. *K. pneumoniae* isolates causing central line-associated bloodstream infection (BSI) increased from <1% in 2000, to 8% in 2006–2007, to 12% in 2009–2010, to 13% in 2012–2013.⁴⁷ CRE have also become endemic in many countries in South America, Europe, Africa, and Asia, and thus pose an international public health threat.⁴⁸

This global emergence of CRE has been caused by the spread of plasmid-mediated enzymes that hydrolyze carbapenems (carbapenemases) and essentially all other β -lactamases.⁴⁹ Furthermore, these enzymes are not inhibited by traditional β -lactamase inhibitors. Thus, CRE typically test resistant to all first-line agents for fever and neutropenia, such as ceftazidime, cefepime, piperacillin-tazobactam, and carbapenems.⁷ *K. pneumoniae* carbapenemase (KPC) is the predominant carbapenemase among Enterobacteriaceae in the U.S. and in many parts of the world,⁵⁰ although other enzymes predominate in other regions (Table 2⁴⁶).

Although the global threat of CRE has been well documented, the emergence of CRE in patients with hematologic malignancies and HSCT recipients has only recently been described.^{49,51} Publications reporting at least 10 HSCT recipients with CRE infection are outlined in Table 3.^{52–56} Carbapenem-resistant *K. pneumoniae* (CRKP) has become a major cause of bacteremia in this patient population in Italy. In a prospective cohort study of 13 Italian hematologic oncology centers from 2010–2014, 161 (58%) of 278 episodes of *K. pneumoniae* bloodstream isolates were carbapenem-resistant.⁵² In a study of 52 Italian HSCT centers, the overall incidence of post-transplant CRKP infection from 2010–2013 was 0.4% after an autologous transplant and 2% after an allogeneic transplant.⁵⁴ For comparison, the 12-month cumulative incidence of aspergillosis and candidiasis in HSCT recipients in the Transplant-Associated Infection Surveillance Network was 1.6% and 1.1%, respectively.⁵⁷ CRE is also an established pathogen in hematologic oncology centers in NYC. Our center reported that CRE bacteremia occurred in 1.8% of HSCT recipients within 12 months after transplantation.⁵¹ In a study of BSIs in neutropenic patients with hematologic malignancies at two NYC oncology centers, 43 (2.2%) of 1992 BSI episodes were caused by CRE, CRE caused 4.7% of gram-negative bacteremias, and 18% of *K. pneumoniae* bacteremias were carbapenem-resistant.⁵⁵

Not only are CRE emerging causes of bacteremia in HSCT recipients, but also CRE bacteremia is associated with high mortality rates in this population. In fact, both overall and CRE bacteremia-related mortality rates in patients with hematologic malignancies and HSCT recipients are consistently >50% (Table 3). Trecarichi et al.⁵² found that the 21-day mortality rate in patients with hematologic malignancies was 53% after CRKP bacteremia, compared to 15% after carbapenem-susceptible *K. pneumoniae* bacteremia, and carbapenem resistance was independently associated with mortality. A CRKP infection-related mortality rate of 64% was reported in allogeneic HSCT (allo-HSCT) recipients.⁵⁴

A likely explanation for these high mortality rates is that CRE are resistant to recommended empirical therapies for fever and neutropenia in patients with cancer,⁷ and thus appropriate CRE-active therapy is delayed until the availability of organism identification and antimicrobial susceptibility testing (AST) results. In HSCT recipients with CRKP infection, CRKP-targeted empirical therapy has been associated with a nearly three-fold increase in

survival in multivariable analysis.⁵⁴ In our study, 86% of patients with CRE bacteremia did not receive empirical treatment with antimicrobial agents that had *in vitro* activity against their CRE bloodstream isolate and 21% died before AST results became available.⁵⁵ Those who survived to availability of AST results had a median of 52 hours between blood culture collection and active therapy. Only one of six patients who received CRE-active empirical therapy died within 30 days, compared to 22 of 37 (59%) patients who did not receive CRE-active empirical therapy. These data suggest that CRE-active empirical therapy should be considered in HSCT recipients at high risk of CRE infection, such as a neutropenic patient with known CRE colonization or who is at a center where CRE are exceptionally common bloodstream pathogens.

3.2 Treatment

Treatment options for CRE infections are extremely limited, as in addition to being resistant to β -lactam agents, CRE are also typically resistant to fluoroquinolones and trimethoprim-sulfamethoxazole.⁴⁹ Antimicrobial agents that have typically retained activity against CRE are outlined in Table 4.^{44,58–71} Unfortunately, these options all have significant shortcomings. Out of necessity, polymyxins have been the mainstay of therapy for CRE infections. However, polymyxins have high rates of nephrotoxicity,⁵⁸ they are historically less effective than β -lactam agents for the treatment of gram-negative bacteremia in oncology patients,⁷² and both chromosomally-mediated and plasmid-mediated polymyxin resistance is increasingly identified among CRE.^{73,74} Tigecycline is not bactericidal, achieves low bloodstream concentrations, and its use is associated with increased mortality in randomized clinical trials compared to other agents.^{63,64} Although an intravenous fosfomycin formulation is available in Europe, it is only available in the U.S. as a 3-g cachet that is mixed with water and ingested. Limited data suggest that oral fosfomycin may represent a treatment option for urinary tract infections caused by CRE, but this dosage is unlikely to achieve sufficient bloodstream concentrations to treat invasive CRE infections.^{66,75} Aminoglycosides are not consistently active against CRE and have the well-known limitations of nephrotoxicity and ototoxicity.^{44,67,68} Like polymyxins, aminoglycosides have also been associated with worse outcomes than β -lactam agents when used as monotherapy to treat gram-negative bacteremia in oncology patients.^{72,76}

Given the limitations of the above agents, combination therapy is often employed for the treatment of CRE infections. No randomized clinical trials have been completed to definitively evaluate the merits of combination therapy. Some observational studies of CRE bacteremia (mostly KPC-producing *K. pneumoniae*) in the general population have demonstrated a mortality benefit when two or more drugs with *in vitro* activity against the organism are used,^{77–79} whereas others have failed to detect a benefit to combination therapy.^{80,81} In a study of CRKP bacteremia specifically in neutropenic patients with hematologic malignancies, Tofas et al.⁵³ found that use of more than one CRE-active agent was independently associated with decreased mortality.

Carbapenems are often included in treatment regimens for CRE infections even though CRE are characterized as carbapenem-resistant *in vitro*. High-dose, prolonged infusions of meropenem (2 g over 3 hours, every 8 hours) can maintain serum concentrations above the

MIC for a sufficient portion of the dosing interval to achieve bacterial killing when MICs are 4–8 µg/mL (meropenem resistance is defined by the CLSI as an MIC ≥ 4 µg/mL).⁸² Clinical studies corroborate these models, demonstrating improved outcomes with the addition of high-dose, prolonged infusions of meropenem to an active agent for KPC-producing *K. pneumoniae* infections when the meropenem MIC is ≥ 8 µg/mL.⁷⁷ Unfortunately, the majority of CRE bloodstream isolates have meropenem MICs ≥ 16 µg/mL, limiting the utility of this approach.^{77,80.}

Ceftazidime-avibactam was approved by the U.S. Food and Drug Administration (FDA) in 2015 and represents the first β-lactam/β-lactamase inhibitor with activity against KPC-producing CRE (Table 5^{83,84}). This agent has demonstrated comparable efficacy to carbapenems in phase 3 clinical trials of complicated urinary tract and intra-abdominal infections.^{69–71} Given the excellent track record of β-lactam agents for the treatment of gram-negative infections in neutropenic patients and HSCT recipients, ceftazidime-avibactam is a promising treatment option for KPC-producing CRE infections in this patient population. However, almost all of the patients in clinical trials were infected with carbapenem-susceptible pathogens and few if any of these patients were neutropenic or a transplant recipient. Pre-clinical *in vivo* animal data and clinical data are urgently needed to assess the effectiveness of this promising compound for the treatment of CRE infections in these populations.

Despite its potent activity against ESBL-E and KPC-producing CRE, limitations of the antimicrobial spectrum of ceftazidime-avibactam should be noted. First, it is not active against metallo-β-lactamase-producing Enterobacteriaceae. This limitation is compounded by the fact that ceftazidime-avibactam is not currently on automated antimicrobial susceptibility platforms. Thus, AST for this agent requires additional manual testing and results are not available until at least 1 day after identification of a CRE. Knowledge of the most common carbapenem resistance mechanisms among Enterobacteriaceae in a given epidemiologic setting, therefore, becomes critical in selecting initial therapy once a CRE is identified. While ceftazidime-avibactam may be an appropriate choice for CRE in an area where KPC-producing CRE predominate, it would not be appropriate in an area where metallo-β-lactamase-producing Enterobacteriaceae are prevalent. A recent report from MD Anderson Cancer Center highlighted this point, finding that 7 of 10 oncology patients with CRE bacteremia had ceftazidime-avibactam-resistant isolates and six of these seven isolates produced New Delhi metallo-β-lactamase (NDM).⁸⁵ Even in areas where KPC-producing CRE predominate, ceftazidime-avibactam AST is critical, as reports of ceftazidime-avibactam resistance among these organisms have already emerged.^{86–88} It is also important to understand that, unlike most other β-lactam/β-lactamase inhibitors, ceftazidime-avibactam has only modest activity against streptococci and staphylococci and no activity against enterococci.⁸³ Furthermore, it is not consistently active against *Bacteroides* or *Clostridium* species, and thus metronidazole was added when ceftazidime-avibactam was evaluated in the treatment of complicated intra-abdominal infections.^{69,83}

4 PSEUDOMONAS AERUGINOSA

4.1 Epidemiology

Recommendations for empirical antibacterial therapy in neutropenic patients have largely focused on *P. aeruginosa* because of the high mortality rates observed in patients infected with this organism, who are not immediately treated with effective therapy.^{7,72} *P. aeruginosa* remains a common cause of gram-negative bacteremia in HSCT recipients, particularly in the pre-engraftment period, as recent studies demonstrate it is responsible for 9%–26% of gram-negative bacteremias in this setting.^{18,20,89–91}

Unfortunately, *P. aeruginosa* has a remarkable capacity to develop resistance, and many strains are now resistant to anti-pseudomonal β -lactam agents used for febrile neutropenia.⁹² For example, in a recent study of 66 *P. aeruginosa* bloodstream isolates from nine hematology wards in Italy, 55% were resistant to ceftazidime, 71% were resistant to meropenem, and 42% were resistant to piperacillin-tazobactam.⁹ This staggeringly high prevalence of resistance to anti-pseudomonal β -lactam agents is ominous, because inactive empirical therapy is consistently associated with increased mortality in neutropenic patients with gram-negative bacteremia.^{9,91,93} Not surprisingly, outcomes were poor in patients who were infected with MDR *P. aeruginosa* strains, who presumably did not receive active empirical therapy, as 42% of infected patients died within 21 days. Although these extremely high rates of resistance are likely not applicable to most U.S. HSCT centers, recent data suggest that β -lactam-resistance in *P. aeruginosa* is also emerging domestically. Of 279 *P. aeruginosa* central line-associated BSIs in patients on oncology units from 2009–2012 that were reported to the CDC's National Healthcare Safety Network, 20% of isolates were carbapenem-resistant and 14% were resistant to anti-pseudomonal cephalosporins.⁹⁴

4.2 Treatment

Given this substantial resistance to anti-pseudomonal β -lactam agents, invasive infections caused by *P. aeruginosa* in neutropenic patients should typically be treated with both an anti-pseudomonal β -lactam and an aminoglycoside or fluoroquinolone (if this agent is not being used prophylactically) while awaiting susceptibility data. If AST reveals that the organism is susceptible to an anti-pseudomonal β -lactam, the role of continuing combination therapy is less clear, as most observational studies have not identified a benefit to adding a second agent for *P. aeruginosa* bacteremia in oncology patients.^{10,12,76,95} However, the development of resistance while on therapy is a major problem, occurring in 10% of all *P. aeruginosa* infections and one-third of cases of *P. aeruginosa* pneumonia treated with carbapenems.^{96,97} Although *in vitro* models suggest that combination therapy with the addition of an aminoglycoside or fluoroquinolone can prevent the emergence of β -lactam resistance,^{98,99} currently no clinical data confirm these findings.

The administration of β -lactam agents as an extended infusion (over hours instead of over 30 minutes) is a strategy that has also been shown to decrease the emergence of resistance in *P. aeruginosa* in *in vitro* models.¹⁰⁰ Furthermore, extended infusion strategies maintain the time that the concentration of the antibiotic is above the MIC for a longer portion of the dosing interval than standard infusions, and this parameter is correlated with increased

bactericidal activity against *P. aeruginosa* in animal models.¹⁰¹ Although no randomized controlled trials have been conducted to definitively prove the benefit of this strategy for *P. aeruginosa* infections, two single-center observational studies demonstrated decreased mortality in critically ill patients with *P. aeruginosa* infection after switching from standard infusions of piperacillin-tazobactam and cefepime to extended infusions of these agents.^{101,102} These compelling *in vitro* and observational data provide rationale for using extended infusions of β -lactam agents for the treatment of invasive *P. aeruginosa* infections in HSCT recipients, provided that venous access is not an issue.

P. aeruginosa that is not susceptible to anti-pseudomonal β -lactam agents or fluoroquinolones has previously been treated with polymyxins or aminoglycosides as agents of last resort. Unfortunately, these antibiotics have high rates of toxicity and are less effective than β -lactam agents in oncology patients with *P. aeruginosa* bacteremia.^{72,76} Ceftolozane-tazobactam, an additional new cephalosporin/ β -lactamase inhibitor, is a promising alternative for the treatment of these MDR *P. aeruginosa* infections (Table 5). Approximately two-thirds of *P. aeruginosa* isolates that are resistant to extended-spectrum cephalosporins, piperacillin-tazobactam, and meropenem test susceptible to this new agent.¹⁰³ Murine models suggest that ceftolozane-tazobactam has potent *in vivo* bactericidal activity against MDR *P. aeruginosa* infections.¹⁰⁴ However, clinical trials of this agent have only demonstrated efficacy for the treatment of complicated urinary tract and intra-abdominal infections caused by carbapenem-susceptible *P. aeruginosa*.^{105,106} Its efficacy has not been evaluated in the setting of BSIs, infections caused by carbapenem-resistant *P. aeruginosa*, or in neutropenic patients or HSCT recipients. Nevertheless, given the major limitations of polymyxin and aminoglycoside monotherapy, ceftolozane-tazobactam should be considered for HSCT recipients with infections caused by *P. aeruginosa* strains that are resistant to other anti-pseudomonal β -lactam agents.

Ceftazidime-avibactam represents an additional option for MDR *P. aeruginosa* infections. In addition to having *in vitro* activity against KPC-producing Enterobacteriaceae, it also has *in vitro* activity against MDR *P. aeruginosa* strains that is comparable to that of ceftolozane-tazobactam (Table 5).^{107,108} Preliminary *in vivo* murine models suggest that the addition of avibactam to ceftazidime enhances bacterial killing of *P. aeruginosa* infections compared to ceftazidime alone.¹⁰⁹ As with ceftolozane-tazobactam, additional pre-clinical and clinical data are urgently needed to better understand the role of this new agent for MDR *P. aeruginosa* infections.

5 VRE

5.1 Epidemiology

VRE is increasingly recognized as a major pathogen in HSCT recipients. In fact, some centers have reported that VRE is the most common cause of bacteremia early after allogeneic transplantation.^{17,18} The reported cumulative incidence of post-transplant VRE bacteremia in allo-HSCT recipients at U.S. centers is 6%–16%.^{17,18,110,111} VRE bacteremia in this population typically occurs in the setting of broad-spectrum antimicrobial exposures during the neutropenic period, which leads to an absence of normal enteric bacteria and intestinal domination with VRE.^{18,112}

VRE bacteremia after allogeneic transplantation has significant consequences. Although VRE is typically considered to be a relatively avirulent pathogen,¹¹³ it sometimes causes bacteremia and septic shock in neutropenic HSCT recipients.^{17,18,114} At our center, we found that VRE bacteremia led to septic shock and 7-day mortality at rates comparable to those observed after gram-negative bacteremia.¹⁸ Post-transplant VRE bacteremia has also been independently associated with increased mortality.^{110,111} However, whether this increased mortality is directly attributable to VRE infection or a marker for a complicated post-transplant course is unclear.

5.2 Treatment

In addition to vancomycin resistance, VRE are typically resistant to all β -lactam agents, leaving few available treatment options.¹¹³ Daptomycin and linezolid are most commonly used for the treatment of invasive VRE infections, although only linezolid has U.S. FDA approval for this indication. No randomized clinical trials are comparing the efficacy of these two agents for the treatment of VRE bacteremia, and observational studies have provided conflicting results as to which agent is superior.^{115,116}

Daptomycin is often preferred to linezolid for VRE bacteremia in HSCT recipients because it has bactericidal activity and a favorable safety profile. In contrast, linezolid is bacteriostatic, myelosuppressive, and associated with a slight delay in neutrophil recovery in oncology patients.¹¹⁷ Daptomycin is not an effective therapy for pneumonia because it is inactivated by alveolar surfactants.¹¹⁸ Furthermore, daptomycin resistance in VRE has been increasingly reported,¹¹⁹ particularly in patients with hematologic malignancies. One major cancer center reported that 15% of their VRE bloodstream isolates were daptomycin-non-susceptible.¹²⁰ Moreover, a recent multicenter study of *Enterococcus faecium* bacteremia, which included many HSCT recipients and neutropenic patients, questioned whether the current CLSI susceptible breakpoint of 4 $\mu\text{g/mL}$ for daptomycin is too high, implying an underreporting of daptomycin resistance.¹²¹ They found that patients with *E. faecium* bacteremia with daptomycin MICs of 3–4 $\mu\text{g/mL}$ by Etest had higher rates of microbiologic failure compared to cases with MICs of ≤ 2 $\mu\text{g/mL}$, even after adjusting for co-variables. Although the U.S. FDA-approved dosage of daptomycin is 6 mg/kg/day, higher dosages are recommended for VRE bacteremia because daptomycin MICs are higher for enterococci than for other gram-positive bacteria. Recent data suggest that daptomycin dosages of 8–10 mg/kg/day are well tolerated and two observational studies have demonstrated decreased mortality after VRE bacteremia with dosages of 9 mg/kg and 10 mg/kg, respectively, compared to lower doses.^{122–125} Some experts recommend using daptomycin in combination with β -lactam agents (e.g., ampicillin or ceftaroline) for VRE infections with elevated daptomycin MICs, as these combinations demonstrate marked *in vitro* synergy.¹²⁶ Weekly monitoring of serum creatinine phosphokinase levels is recommended during daptomycin therapy, as almost 3% of patients receiving daptomycin in clinical trials developed elevated creatinine phosphokinase levels.¹²⁷

Other agents with *in vitro* activity against VRE include quinupristin-dalfopristin, tigecycline, tedizolid, oritavancin, and telavancin.¹²⁸ Quinupristin-dalfopristin is rarely used because of high rates of adverse effects that lead to treatment discontinuation in nearly 20% of

patients.¹²⁹ Tigecycline has major limitations as outlined in Table 4, and sparse clinical data support the use of these alternative agents for VRE bacteremia. Tedizolid is a new oxazolidinone that appears to be less myelosuppressive than linezolid,¹³⁰ and thus is an attractive candidate for use in HSCT recipients. However, animal models have demonstrated that the efficacy of tedizolid is markedly reduced in the setting of neutropenia,¹³⁰ thus making it a less attractive alternative for VRE infections in neutropenic patients. Oritavancin may be an option for linezolid- and daptomycin-non-susceptible VRE infections, but *in vivo* and clinical data are extremely limited.

6 PREVENTION OF MDR BACTERIAL INFECTIONS IN HSCT RECIPIENTS

6.1 Prevention of transmission of MDR pathogens

The limited antimicrobial armamentarium against MDR Enterobacteriaceae, *P. aeruginosa*, and VRE, and the poor outcomes associated with these infections in HSCT recipients, highlight the importance of preventing these infections. Infection prevention efforts should focus on minimizing the risk of transmission of these MDR pathogens among patients located on HSCT units. In 2009, guidelines representing a collaborative effort from several organizations were published that provide an excellent resource for recommendations for preventing infectious complications in HSCT recipients.¹³¹ Infection prevention strategies that are most relevant to preventing transmission of MDR bacteria are ensuring strict adherence to hand hygiene and environmental cleaning practices, following evidence-based guidelines for proper insertion and care of intravascular catheters,¹³² implementation of contact precautions for patients known to be colonized with MDR bacteria, and use of single-patient rooms, where feasible. Although the effectiveness of each of these strategies in preventing MDR bacterial infections in HSCT recipients is unclear, they appear to be effective when implemented together.¹³³

6.2 Antimicrobial stewardship

Antimicrobial stewardship also plays an important role in preventing MDR bacterial infections in HSCT recipients. Broad-spectrum antimicrobial agents are consistently identified as risk factors for MDR gram-negative and VRE infections in oncology patients,^{18,21,55} and thus limiting unnecessary uses of these agents is an important goal. Although broad-spectrum antimicrobial therapy is often necessary in HSCT recipients, multidisciplinary stewardship teams that include transplant oncologists, infectious diseases physicians, microbiologists, and pharmacists should strive to implement the following recommend practices: de-escalation of broad-spectrum therapy in stable patients with a non-MDR pathogen, daily assessments for the need for continued antibacterial therapy, and optimization of antibacterial dosages.¹³⁴ Furthermore, this multidisciplinary team should review their HSCT unit's epidemiology and antibiogram on a regular basis and implement antimicrobial treatment algorithms for common scenarios, such as febrile neutropenia or sepsis.¹³⁵

6.3 GI screening for implementation of contact precautions and targeted decolonization

Active surveillance, where HSCT recipients are screened for colonization with MDR gram-negative bacteria and VRE, can be utilized to implement multiple interventions. First,

patients who are found to be colonized with an MDR pathogen can be placed on contact precautions, which may decrease the inpatient transmission of these organisms. Although this approach has led to reductions in CRE infection rates in certain settings,¹³⁶ data are sparse to indicate that this intervention decreases the nosocomial transmission of ESBL-E, *P. aeruginosa*, or VRE. In fact, a recent article demonstrated that discontinuation of a program of active surveillance for VRE and contact isolation of colonized patients had no effect on the incidence of VRE infection on a hematologic oncology unit.¹³⁷

Active surveillance can also be used to identify colonized patients who may be candidates for targeted decolonization strategies. Decolonization has primarily been evaluated using oral aminoglycosides and/or colistin to prevent ESBL-E and CRE infections in colonized patients. Although decolonization may reduce carriage of these organisms during therapy, this reduction is generally short-lived and can lead to resistance to the agents that are used.^{138–140} Furthermore, it may not decrease the risk of infection in colonized HSCT recipients. In a study of 15 patients undergoing HSCT who were colonized with CRKP, 8 patients developed post-transplant CRKP infection despite receiving decolonization therapy with oral gentamicin.¹⁴¹ Given the unclear clinical benefit of decolonization strategies in HSCT recipients, as well as the risk of increasing resistance to the few remaining antimicrobial agents for MDR bacterial infections, we cannot recommend implementation of decolonization protocols at this time.

7 ADDITIONAL STRATEGIES TO IMPROVE OUTCOMES OF INFECTED PATIENTS

7.1 GI screening as a guide for empirical antibacterial therapy

The emergence of MDR Enterobacteriaceae, *P. aeruginosa*, and VRE as causes of bacteremia in HSCT recipients warrants consideration of strategies to identify patients who are at high risk of developing infections caused by these pathogens. Such patients could potentially have their initial empirical therapy modified to ensure coverage of MDR bacteria with which they are at high risk of being infected. Active surveillance to identify hematologic oncology patients who are colonized with MDR bacteria may identify a high-risk group of patients. Investigators from Germany and Mexico found that 7% and 22%, respectively, of patients with hematologic malignancies who were colonized with ESBL-E by cultures of stool or perianal swabs developed subsequent ESBL-E bacteremia during admission for chemotherapy.^{142,143} At our center, we found that 6 of 13 allo-HSCT recipients who were colonized with ESBL-E on admission for transplant developed ESBL-E bacteremia during neutropenia, compared to none of 118 patients who were not colonized ($P<.001$).¹⁴⁴ A multicenter study of HSCT recipients in Italy also identified high rates of GI colonization to infection for CRKP. CRKP infection occurred after transplantation in 26% of colonized autologous HSCT recipients and 39% of colonized allo-HSCT recipients.⁵⁴

These data suggest that screening for GI colonization with MDR Enterobacteriaceae may be a useful tool to identify HSCT recipients who are at high risk of developing subsequent infection caused by these organisms, and who may benefit from an adjustment of their empirical therapy to cover for these pathogens. However, prospective clinical trials are

needed to evaluate the clinical impact of this strategy. Moreover, additional data are needed to assess whether screening should be performed on admission for transplant only or if it should be continued weekly during neutropenia. In addition, these screening strategies should only be considered in HSCT centers with a substantial incidence of infections caused by these organisms.

In contrast to MDR Enterobacteriaceae, assessment for GI colonization is not an effective tool in identifying patients at high risk for *P. aeruginosa* infection. In a study of 794 allo-HSCT recipients, the majority of patients who developed a *P. aeruginosa* infection did not have fecal colonization, suggesting a different source of infection.¹⁴⁵

Screening HSCT recipients for GI colonization with VRE may also identify patients at high-risk for post-transplant VRE infection. Studies of allo-HSCT recipients demonstrate that 14%–19% of patients who are colonized with VRE prior to their transplant develop VRE bacteremia early after transplantation, compared to only a 4%–6% incidence in patients who are not colonized pre-transplant.^{17,110,146} Notably, however, a substantial proportion of VRE bacteremias occur in patients who are not colonized pre-transplant, but acquire VRE during their transplant admission.¹⁷ Despite the increased risk of VRE bacteremia in colonized patients undergoing allo-HSCT, it is unclear whether VRE-colonized patients should have their empirical therapy modified when they present with fever and neutropenia, particularly given reports of increasing resistance to VRE-active agents like daptomycin.^{118,119} Unlike gram-negative infections, no data show that delays in treatment of VRE bacteremia are associated with worse outcomes in this population. However, a recent study of hospital-onset VRE bacteremia in the general inpatient population demonstrated that delay in active therapy of >48 hours was associated with increased mortality.¹⁴⁷ Thus, it is reasonable to initiate VRE-active therapy in colonized HSCT recipients who develop bacteremia with a Gram stain compatible with VRE (gram-positive cocci in pairs or short chains) or who present with severe sepsis.

7.2 Rapid identification of bloodstream pathogens

An additional strategy to improve the outcomes of HSCT recipients who are infected with MDR Enterobacteriaceae, *P. aeruginosa*, and VRE is to implement new technologies in the clinical microbiology laboratory to more rapidly identify these pathogens. This, in turn, could lead to shorter delays in the administration of effective antimicrobial therapy. Real-time multiplex polymerase chain reaction systems are now available that detect a variety of bacteria, yeasts, and important resistance determinants directly from positive blood culture bottles within 2 hours of culture positivity. Both systems, the FilmArray® Blood Culture Identification Panel (Biofire Diagnostics, bioMérieux, Salt Lake City, UT USA) and the Verigene® gram-positive and gram-negative Blood Culture Tests (Nanosphere, Northbrook, IL USA) detect enterococci, the most common Enterobacteriaceae, and *P. aeruginosa*, in addition to other prominent bloodstream pathogens.^{148–150} It is important to note that both systems detect the *vanA* and *vanB* genes, which confer vancomycin resistance in enterococci, and *bla_{KPC}*, the most common gene that confers carbapenem resistance in Enterobacteriaceae in the U.S. and many other countries. In addition, the Verigene system detects genes that encode other carbapenemases and the most common ESBL, CTX-M.

Implementation of one of these systems should decrease the time to identification of MDR Enterobacteriaceae, *P. aeruginosa*, and VRE from 24–72 hours after culture positivity to only 2 hours after culture positivity. This improved speed of detection should lead to more timely therapy for infections caused by these bacteria, which will hopefully improve outcomes. However, it should be noted that these assays do not provide information to predict antimicrobial susceptibilities of *P. aeruginosa* bloodstream isolates. Furthermore, no data have evaluated the impact of these tools on clinical outcomes in HSCT recipients. One study performed in the general inpatient population, where the microbiology laboratory randomized positive blood cultures to conventional processing or the use of the FilmArray® Blood Culture Identification Panel, found that use of the polymerase chain reaction assay led to a decrease in use of broad-spectrum antimicrobial agents, but no improvements in clinical outcomes.¹⁵¹ Studies evaluating the clinical impact of these technologies are urgently needed in HSCT recipients.

7.3 Management of infected central venous catheters (CVCs)

Bacteremia caused by MDR Enterobacteriaceae and VRE in HSCT recipients is most commonly from GI translocation during chemotherapy-induced neutropenia.^{7,112,144} However, CVCs are occasionally the sources of bacteremia caused by these organisms. *P. aeruginosa* is less likely to originate from the GI tract than VRE and MDR Enterobacteriaceae and is more likely to cause CVC-related bacteremias.^{7,145} If blood cultures are collected from a peripheral vein and a CVC simultaneously, then culture positivity that occurs 2 hours earlier in the CVC culture compared to the peripheral culture is suggestive that the catheter is the source of the infection.¹⁵² Catheter removal is imperative for all CVC-related infections that involve the tunnel track or port pocket site or in the setting of hemodynamic instability.¹⁵³ In cases of CVC-related bacteremias in hemodynamically stable patients that do not involve a tunnel track or port pocket site, CVC retention can be considered, particularly in patients with refractory thrombocytopenia or lack of alternate intravenous access. If the CVC is retained, antimicrobial therapy should be administered through the infected catheter, potentially in combination with antibiotic lock therapy.⁷

8 CONCLUSIONS

In summary, MDR Enterobacteriaceae, *P. aeruginosa*, and VRE are becoming increasingly common bloodstream pathogens in HSCT recipients and outcomes of patients infected with these bacteria are worse than those of patients infected with more susceptible bacteria. Developing preclinical and clinical research data to guide the use of new antimicrobial agents for the treatment of these pathogens in the HSCT population is paramount. Identification of optimal strategies to prevent these infections is also an urgent need. Screening for GI colonization to guide empirical therapy and using rapid diagnostics may be approaches that lead to improved outcomes for infected HSCT recipients.

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TABLE 1

Prevalence and characteristics of bacteremia due to ESBL-producing Enterobacteriaceae in patients with hematologic malignancies and HSCT recipients.

First author Reference	Country	Years	Organisms	All patients with hematologic malignancies: % of isolates that were ESBL producers	HSCT recipients only: % of isolates that were ESBL producers	Mortality of ESBL BSI vs non-ESBL BSI	Mortality type
Mikulska (20)	Italy	2004–2007	<i>Escherichia coli</i> <i>Klebsiella pneumoniae</i>	HSCT only	41% (13/32)	NR	NR
Guidol (21)	Spain	2006–2008	<i>E. coli</i>	17% (13/76)	9% (1/11)	38% vs. 7% ¹	30-day
Cornejo-Juarez (22)	Mexico	2004–2009	<i>E. coli</i>	23% (205/670)	NR	34% vs. 19% ¹	Overall
Kang (23)	Korea	2008–2009	<i>E. coli</i> <i>K. pneumoniae</i>	33% (37/156)	NR	45% vs. 14% ¹	30-day
Ha (24)	Korea	2010–2012	<i>E. coli</i>	32% (42/130)	44% (15/34)	14% vs. 10%	30-day
Kim (25)	Korea	2007–2008	<i>E. coli</i> <i>K. pneumoniae</i>	26% (26/101)	38% (8/21)	15% vs. 5%	30-day
Trecarichi (9)	Italy	2009–2012	Enterobacteriaceae	37% (98/265) ²	NR	26% vs. 5% ¹	21-day
Yemi en (26)	Turkey	2000–2011	Enterobacteriaceae	HSCT only	21% (5/22)	NR	NR

¹ *P* value < .05 for this comparison.

² Third-generation cephalosporin resistance was used as a surrogate for ESBL production in this study.

HSCT, hematopoietic stem cell transplantation; ESBL, extended-spectrum beta-lactamase; BSI, bloodstream infection; NR, not reported.

Characteristics of prominent carbapenemases among carbapenem-resistant Enterobacteriaceae (CRE).

TABLE 2

Carbapenemase	Ambler Molecular Class	Requirement for Enzymatic Activity	# of U.S. states reporting CRE with this enzyme ^I	Global Distribution	Inhibited by Avibactam
KPC	A	Serine	49	U.S., Colombia, Brazil, Argentina, Italy, Greece, Israel, China	Yes
NDM	B	Zinc	25	India, Pakistan, Bangladesh, United Kingdom	No
VIM	B	Zinc	7	Greece, Italy, Spain	No
IMP	B	Zinc	5	Japan, Taiwan	No
OXA-48-types (OXA-48, OXA-181, OXA-232)	D	Serine	19	Turkey, Spain, Morocco, Algeria, Tunisia, India	Yes

^I As of April 2016 (46).

KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo- β -lactamase; VIM, Verona integron-encoded metallo- β -lactamase.

Carbapenem-resistant Enterobacteriaceae (CRE) infections in patients with hematologic malignancies and hematopoietic stem cell transplant (HSCT) recipients

TABLE 3

First author Reference	Location	Patients	HSCT recipients	Infection type	Organisms	Mortality rate	CRE bacteremia-related mortality rate
Trecarichi (52)	Italy: 13 centers	161	26	Bacteremia	<i>Klebsiella pneumoniae</i>	52% (21-day)	NR
Tofias (53)	Greece: 4 centers	50	NR	Bacteremia	<i>K. pneumoniae</i>	50% (14-day)	50%
Girmenia (54)	Italy: 45 centers	112	112	Bacteremia (<i>n</i> =100) Pneumonia (<i>n</i> =12)	<i>K. pneumoniae</i>	58% (90-day)	54%
Satlin (55)	New York City, USA	43	18	Bacteremia	<i>K. pneumoniae</i> (<i>n</i> =30) <i>Enterobacter cloacae</i> (<i>n</i> =8) Others (<i>n</i> =5)	53% (30-day)	51%
Hussein (56)	Israel	28	18	Bacteremia	<i>K. pneumoniae</i>	NR	NR

NR, not reported.

TABLE 4

Available antimicrobial agents with activity against CRE

Antimicrobial Agent (reference)	Recommended Dosages (normal renal function)	Limitations
Polymyxins (58–62)		
Polymyxin B (administered as the active compound)	<ul style="list-style-type: none"> 2.5 mg/kg loading dose, then 1.5 mg/kg every 12h¹ Do not need to adjust dosage for renal insufficiency 	<ul style="list-style-type: none"> Nephrotoxicity and neurotoxicity Low concentrations in the urinary tract
Colistin (administered as the prodrug colistin methanesulfonate)	<ul style="list-style-type: none"> 5 mg/kg/day of CBA (up to 300 mg), in 2 divided doses^{2,3} Adjust dosage for renal insufficiency 	Similar to polymyxin B, except: <ul style="list-style-type: none"> Inefficient conversion to active compound Active drug accumulates in the urinary tract More nephrotoxic than polymyxin B
Tigecycline (63–65)	<ul style="list-style-type: none"> 100 mg loading dose, then 50 mg every 12h Doses up to 100 mg every 12h have been evaluated in clinical trials and may be necessary for pneumonia 	<ul style="list-style-type: none"> Use associated with increased mortality in randomized trials Low bloodstream and urinary tract concentrations Gastrointestinal side effects
Fosfomycin (66)	<ul style="list-style-type: none"> U.S.: oral formulation only: 3 g in 3–4 oz. of water (once, or every 2–3 d for 3 doses for urinary tract infections) IV formulation: 8 g every 12h 	<ul style="list-style-type: none"> IV formulation not available in the U.S Used as adjunctive therapy for CRE infections where available Low barrier to development of resistance
Aminoglycosides (44,67,68) ⁴		
Gentamicin	<ul style="list-style-type: none"> Extended-interval: 5–7 mg/kg every 24h Conventional: 2–3 mg/kg loading dose, followed by 1.5–2 mg/kg every 8 hours 	<ul style="list-style-type: none"> Variable activity vs. CRE (40–60% of KPC producers in the U.S. are susceptible; most NDM producers are resistant) Nephrotoxicity and ototoxicity Suboptimal clinical efficacy when used as monotherapy
Amikacin	<ul style="list-style-type: none"> Extended-interval: 15 mg/kg every 24h Conventional: 7.5 mg/kg every 12 hours 	Similar to gentamicin, except: <ul style="list-style-type: none"> Less nephrotoxicity and ototoxicity Usually less active vs. KPC producers
Ceftazidime-avibactam (69–71)	2.5 g as a 2-hour infusion every 8h (2 g ceftazidime, 0.5 g avibactam)	See Table 5 for limitations

¹ 1 mg polymyxin B = 10,000 units polymyxin B.² 300 mg CBA is equal to approximately 9 million international units (MIU).

³ A loading dose of 300 mg (9 MIU) should be considered in severe infections.

⁴ Tobramycin is rarely active against CRE.

CRE, carbapenem-resistant Enterocateriaceae; CBA, colistin base activity; IV, intravenous.

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TABLE 5

Comparison of two new cephalosporin/ β -lactamase inhibitor combinations: ceftazidime-avibactam and ceftolozane-tazobactam (83)

Properties	Ceftazidime-avibactam	Ceftolozane-tazobactam
Spectrum of activity		
Enterobacteriaceae		
ESBL-producers	Excellent activity	Good activity against ESBL-producing <i>Escherichia coli</i> , but only modest activity against ESBL-producing <i>Klebsiella pneumoniae</i>
CRE	<ul style="list-style-type: none"> Active against KPC-producers and other serine carbenemase-producers Not active vs. metallo-β-lactamase producers (e.g., NDM) 	Not active
AmpC-hyperproducers	Excellent activity	Modest activity
<i>Pseudomonas aeruginosa</i>		Active <i>in vitro</i> against ~2/3 of strains that are resistant to CAZ, PTZ, and MER
<i>Acinetobacter baumannii</i>		Poor activity
Gram-negative anaerobes		Limited activity vs. <i>Bacteroides</i> species
MSSA		Limited activity
U.S. FDA-approved indications		Complicated urinary tract and intra-abdominal infections
Clinical data in HSCT recipients		No
Dosing	2.5 g every 8 hours (2 g ceftazidime, 0.5 g avibactam)	1.5 g every 8 hours (1 g ceftolozane, 0.5 g avibactam) ¹
Adjustment for renal insufficiency		Yes

¹ Ceftolozane-tazobactam is being evaluated in clinical trials as a 3 g every 8 hour dosage for nosocomial pneumonia (84).

CAZ, ceftazidime; CRE, carbenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β -lactamase; FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplant recipients; KPC, *Klebsiella pneumoniae* carbenemase; MER, meropenem; MSSA, methicillin-susceptible *Staphylococcus aureus*; NDM, New Delhi metallo- β -lactamase; PTZ, piperacillin-tazobactam.