Management of Severe Infections

Multidrug-Resistant and Carbapenem-Resistant Gram-Negative Bacteria

Federico Perez, MD, MS[a,b,c,*], Nadim G. El Chakhtoura, MD, MPH[a,c], Robert A. Bonomo, MD[b,c,d,e]

KEYWORDS

• *Acinetobacter baumannii* • Carbapenem-resistant Enterobacterales • Carbapenems • Carbapenemase-producing Enterobacterales • Cefiderocol • Metallo-β-lactamase • *Pseudomonas aeruginosa* • β-lactam/β-lactamase inhibitors

KEY POINTS

- Multidrug-resistant carbapenem-resistant gram-negative bacteria pose major challenges in antibiotic management. Understanding the basic mechanisms of antibiotic resistance is vital for effectively treating these infections.
- Novel β-lactam/β-lactamase inhibitors are effective against Enterobacterales producing *Klebsiella pneumoniae* carbapenemase (KPC) and oxacillin-hydrolyzing carpapenemase (OXA)-48-like, and the combination of ceftazidime-avibactam plus aztreonam is an option for Enterobacterales that produce metallo-β-lactamases.
- Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam target difficult-to-treat *Pseudomonas aeruginosa.*
- Sulbactam-durlobactam is preferred for treating carbapenem-resistant *Acinetobacter baumannii.*
- Cefiderocol is an alternative for metallo-β-lactamase-producing gram-negative bacteria.

[a] Geriatrics Research Education and Clinical Center, Louis Stokes Cleveland Department of Veterans Affairs, Cleveland, OH, USA; [b] Department of Medicine, Division of Infectious Diseases, Case Western Reserve University, Cleveland, OH, USA; [c] CWRU-Cleveland VAMC Center for Antimicrobial Resistance and Epidemiology (CARES), Case Western Reserve University, Cleveland, OH, USA; [d] Departments of Pharmacology, Molecular Biology and Microbiology, Biochemistry, and Proteomics and Bioinformatics, Case Western Reserve University, Cleveland, OH, USA; [e] Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH, USA

* Corresponding author. Louis Stokes Cleveland Department of Veterans Affairs Medical Center, 10701 East Boulevard, Cleveland, OH 44106.
E-mail address: federico.perez@va.gov

Med Clin N Am 109 (2025) 735–747
https://doi.org/10.1016/j.mcna.2025.01.003
0025-7125/25/Published by Elsevier Inc.
medical.theclinics.com

Abbreviations	
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem-resistant Enterobacterales
ESBL	extended-spectrum β-lactamase
KPC	*Klebsiella pneumoniae* carbapenemase
MBL	metallo-β-lactamase
MDR	multidrug resistant
PBP	penicillin-binding protein

INTRODUCTION

We depend on the availability of effective and safe antibiotics to protect our patients from the morbidity and mortality related to severe bacterial infections. When we encounter seriously ill patients with sepsis due to pneumonia or bloodstream infections, we recognize that the timely administration of active antibiotic therapy is crucial to their survival.[1] Antibiotic-resistant bacteria, therefore, pose a significant therapeutic challenge, with implications that extend beyond the medical field and resonate throughout society. A frequently cited, alarmist yet realistic warning we reflect on is that, unless we deepen our understanding of antibiotic-resistant bacteria, a return to the pre-antibiotic era could be a plausible scenario.[2]

Shortly after its introduction in the mid-twentieth century, penicillin, the first β-lactam antibiotic, became the cornerstone for treating severe bacterial infections caused by gram-positive bacteria such as *Streptococcus pneumoniae* and *Staphylococcus aureus,* at least until resistance emerged.[3] However, penicillin proved ineffective against gram-negative bacteria, including lactose fermenters like *Escherichia coli* and *Klebsiella pneumoniae*, as well as non-lactose fermenters such as *A baumannii* and *P aeruginosa*, a need fulfilled by polymyxins and aminoglycosides. Eventually, β-lactams with structural modifications that enabled them to penetrate the outer membrane and resist the β-lactamases of gram-negative bacteria were developed.[4] This advancement was followed by the introduction of β-lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam, which have proven to be a highly effective strategy for protecting and enhancing the action of β-lactams.[5] Next came the discovery of carbapenems and cephalosporins with an expanded spectrum of activity against gram-negative bacteria. However, while these developments marked a "golden age" of β-lactam antibiotic therapy for severe gram-negative bacterial infections, resistance has progressed even faster.[6] Understanding the most significant antibiotic resistance mechanisms is crucial for effectively treating and reducing the impact of severe infections caused by multidrug-resistant (MDR) gram-negative bacteria. Knowledge of these resistance mechanisms also helps maximize the effectiveness of current antibiotics and envision future treatment options.[7]

This article examines the most clinically significant gram-negative bacterial pathogens that display resistance to carbapenems and other key antibiotics, classifying them as MDR. First, it will explore the background of mechanisms related to antibiotic resistance, followed by a discussion on the antibiotic management of severe infections such as bacteremia and pneumonia. The focus will be on Enterobacterales resistant to carbapenems, as well as non-lactose fermenters like carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *P aeruginosa* that are paradigmatically "difficult to treat" due to their intrinsic and acquired resistance mechanisms. The goal is to provide a broad audience with a current, evidence-based, and practical overview of managing patients with severe infections caused by MDR carbapenem-resistant gram-negative bacteria. The antibiotics (and their recommended doses) mentioned

in this overview are listed in **Table 1**. Comprehensive and authoritative documents guide the treatment of various infections caused by these pathogens, including resources from the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases.[8,9]

BACKGROUND

Mechanisms of Resistance in Gram-Negative Bacteria

Carbapenem-resistant enterobacterales

The acquisition of carbapenemases, enzymes that inactivate carbapenems, is the main mechanism driving the emergence of carbapenem-resistant Enterobacterales (CRE). This phenotype first emerged in the United States with the isolation of a carbapenem-resistant *K pneumoniae* in 1996, which harbored a serine carbapenemase known as *Klebsiella pneumoniae* carbapenemase (KPC). This class A enzyme provides resistance to all cephalosporins, aztreonam, and β-lactamase inhibitors, including clavulanic acid and tazobactam. The genes that encode these carbapenemases are typically found on plasmids or other common mobile genetic elements, facilitating the acquisition of genes that confer resistance to additional antibiotic classes. Consequently, CRE isolates are MDR and extensively drug resistant. The mobility of these genetic elements has also led to the spread of bla_{KPC} into other Enterobacterales, including *E coli, Enterobacter, Serratia,* and *Salmonella* species.

KPC has spread globally and has become endemic beyond the United States, especially in Southern Europe and Israel, as well as South America and China. Historically, there has been a robust association between KPC-producing *K pneumoniae* and clones related to ST 258, although this continues to evolve.[10,11] Another globally significant mechanism of carbapenem resistance in CRE is oxacillin-hydrolyzing carbapenemase (OXA)-48, a class D carbapenemase, along with closely related enzymes (eg, OXA-181). OXA-48-like enzymes are widespread, particularly in Europe, the Middle East, and Northern Africa, but are less prevalent in the United States. The class B New Delhi metallo-β-lactamase (NDM) was first identified in *K pneumoniae* from a

Table 1
Conventional doses of antibiotics for the management of severe infections caused by multidrug and carbapenem-resistant gram-negative bacteria[9]

Antibiotic	Dose (Assuming Normal Renal and Hepatic Functions)
Ceftazidime-avibactam	2.5 g IV every 8 h infused over 3 h
Ceftazidime-avibactam + aztreonam	2.5 g IV every 8 h infused over 3 h + (given simultaneously) 2 g IV every 8 h infused over 3 h
Ceftolozane-tazobactam	3 g IV every 8 h infused over 3 h
Imipenem-relebactam	1.25 g IV every 6 h infused over 30 min
Meropenem-vaborbactam	4 g IV every 8 h infused over 3 h
Cefiderocol	2 g IV every 8 h infused over 3 h
Meropenem	2 g IV every 8 h infused over 3 h
Imipenem	500 mg IV every 6 h infused over 3 h
Sulbactam (given as ampicillin-sulbactam)	9 g IV every 8 h infused over 4 h
Minocycline	200 mg IV or PO every 12 h
Durlobactam-sulbactam	2 g IV every 6 h over 3 h (administer with meropenem or imipenem)

patient hospitalized in New Delhi and is now endemic throughout Asia and beyond, including Africa, Europe, and South America. Additionally, resistance to carbapenems arises from other enzymes, such as the metallo-β-lactamases (MBLs) VIM (verona integron-encoded MBL), and IMP (imipenemase), as well as the serine enzyme SME (*Serratia marcescens* enzyme). Although MBLs have been historically infrequent in the United States, it is important to recognize that they are becoming more common. Notably, the CRE phenotype may arise without carbapenemases due to alterations in outer membrane proteins and the production of extended-spectrum β-lactamases (ESBLs) or other cephalosporinases.[12,13]

Carbapenem-resistant Acinetobacter baumannii

A baumannii exhibits low permeability to antibiotics due to its outer membrane porin content and efflux pumps that are constitutively expressed, which contribute to its intrinsic resistance to a wide range of antibiotics. *A baumannii* also possesses various β-lactamases, including AmpC enzymes known as *Acinetobacter*-derived cephalosporinases. Additionally, *A baumannii* harbors OXA-type enzymes, such as OXA-51, which are intrinsically characteristic of this species and may contribute to carbapenem resistance, depending on their expression levels and permeability. CRAB also acquires ß-lactamases, such as OXA-type carbapenemases from the OXA-23, OXA-24/40, and OXA-58 subfamilies.[14] Global clone 2 accounts for a large proportion of CRAB, leading to various subclones, but this situation is also evolving.[15,16] Additionally, *A baumannii* can acquire mutations in efflux pumps, along with changes in outer membrane proteins that affect permeability and reduce the intracellular concentration of various antibiotics.[17] Furthermore, alterations in the expression and structure of penicillin-binding proteins (PBPs), such as mutations in PBP3, result in sulbactam resistance and contribute to its MDR phenotype.[18] While less common than OXA class D enzymes, other carbapenemases, like NDM and KPC, may also be found in *A baumannii.*[19,20] Through horizontal gene transfer, *A baumannii* obtains resistance genes from different organisms. Fournier and colleagues reported a resistant *A baumannii* strain with an 86 kilobase genomic island (AbaR1) harboring resistance determinants from gram-negative organisms like *Salmonella, E coli,* and *Pseudomonas* spp. Of 52 identified resistance genes, 45 were localized to this island, showcasing the *Acinetobacter* species' ability to diversify, a hallmark of these resistant pathogens.[21]

Difficult to treat resistance in Pseudomonas aeruginosa

Difficult to treat resistance (DTR) in *P aeruginosa* is defined as isolates demonstrating resistance/intermediate resistance to these agents typically relied upon for the treatment of severe infections: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem, ciprofloxacin, and levofloxacin.[22] In the case of carbapenem-resistant strains, there is usually an interplay of mutations in the OprD porin (sufficient to exclude imipenem) and upregulation of drug-efflux pumps (generally necessary to exclude meropenem), as well as ß-lactamases: *P aeruginosa* is equipped with AmpC enzymes, known as *Pseudomonas*-derived cephalosporinases. Changes in the active site of these enzymes and especially their hyperexpression due to alterations in their regulatory system are critical, in conjunction with other mutational mechanisms, to the in vivo emergence of "pan-β-lactam resistance," including resistance to carbapenems.[23,24] Crucially, *P aeruginosa* also can acquire carbapenemases, such as MBLs. Historically, MBLs have only been detected infrequently in the United States. Still, as in the case of CRE, it is essential to acknowledge that MBLs are becoming more prevalent among carbapenem-resistant DTR *P aeruginosa.* In contrast, VIM-mediated carbapenem resistance in *P aeruginosa*

is endemic in all other regions.[25] Notably, *P aeruginosa* harboring the class A KPC (sometimes co-existing with VIM) has been found in Colombia and other Latin American countries.[26] Other more exotic β-lactamases may contribute to the DTR phenotype of *P aeruginosa*, such as GES (Guiana ESBL), VEB (Vietnamese ESBL), and *Pseudomonas* extended resistance.[9] An important notion is that the global dissemination of MDR/XDR *P aeruginosa* carrying acquired β-lactamases is linked to "high-risk clones" that continue to evolve.[27]

DISCUSSION

Current Evidence

Carbapenem-resistant enterobacterales

Guiding the treatment of severe infections caused by CRE should focus on the mechanisms of carbapenem resistance (**Fig. 1**). In the United States, KPC is the most commonly identified carbapenemase among CRE. The prevalence of NDM among CRE is approximately 10% overall, though it is higher in certain areas. Similarly, the prevalence of OXA-48 is also on the rise, nearing 5%. It is also possible for some CRE isolates to harbor 2 or more carbapenemases simultaneously. A history of travel to regions where these enzymes are prevalent may indicate the presence of NDM and/or OXA-48. If KPC is strongly suspected based on local molecular epidemiology or confirmed through molecular diagnostic methods, several treatment options are available within novel combinations of β-lactams and β-lactamase inhibitors: ceftazidime-avibactam, imipenem-relebactam, or meropenem-vaborbactam. Although most KPC-producing CRE remain susceptible to ceftazidime-avibactam—particularly in cases of prior exposure to this agent—there remains a risk of developing resistance. The predominant mechanism of resistance to ceftazidime-avibactam in KPC-producing Enterobacterales involves alterations to the loop in the enzyme's active site. Modifications in KPC, primarily D179Y and D179 YN, enhance ceftazidime

Mechanism/ Antibiotic	Carbapenem-resistant Enterobacterales					
	Non-carbapenemase producing	KPC	KPC D179Y variant	OXA-48	SME	Metallo-β-lactamase
Meropenem extended infusion						
Ceftazidime-avibactam						
Imipenem-relebactam						
Meropenem-vaborbactam						
Ceftazidime-avibactam + aztreonam	*	*	*	*	*	
Cefiderocol						

Fig. 1. Antibiotics used for the management of severe infections caused by carbapenem-resistant Enterobacterales, according to the mechanism of resistance. Green indicates that the antibiotic is active and recommended. Yellow indicates that the antibiotic could be an alternative. Red indicates that the antibiotic is inactive. *Indicates redundancy of ceftazidime-avibactam + aztreonam with ceftazidime-avibactam alone.

hydrolysis and may, in certain instances, reduce hydrolytic efficiency against meropenem. In contrast, meropenem-vaborbactam is not impacted by these changes and is, therefore, a more dependable agent for treating KPC-producing Enterobacterales. A study comparing meropenem-vaborbactam and ceftazidime-avibactam for managing CRE demonstrates similar outcomes, with less emergence of resistance noted with meropenem-vaborbactam.[28] Imipenem-relebactam is also active against KPC-producing CRE that is resistant to ceftazidime-avibactam, although there is less clinical experience with this agent.

Severe infections caused by CRE sometimes lack an identified carbapenemase. These isolates are usually resistant to ertapenem but susceptible in vitro to meropenem and imipenem. Due to their optimized pharmacokinetic and pharmacodynamic profiles, extended infusions of meropenem or imipenem may be preferred over meropenem-vaborbactam or imipenem-relebactam. Clinical analysis shows that patients with ertapenem-resistant-only CRE infections rarely receive newer agents like ceftazidime-avibactam, meropenem-avibactam, or imipenem-relebactam but have similar outcomes to those with CRE resistant to multiple carbapenems who do receive them.[29]

In the case of carbapenem resistance mediated by OXA-48 in Enterobacterales, it is essential to note that neither vaborbactam nor relebactam, unlike avibactam, is a suitable inhibitor of OXA-48-like enzymes. Additionally, these enzymes are more effective carbapenemases than cephalosporinases. Thus, ceftazidime-avibactam is the preferred antibiotic for treating severe infections caused by OXA-48-producing Enterobacterales.[9] Of note, the rare SME (*Serratia marcescens* enzyme, a class A carbapenemase described in *Serratia* species) appears to be susceptible to ceftazidime (and more so with the addition of avibactam) and is well inhibited by vaborbactam, whereas adding relebactam to imipenem does not restore bactericidal activity against SME-producing strains.[30]

The currently available β-lactamase inhibitors (including avibactam, relebactam, and vaborbactam as well as tazobactam, sulbactam, and clavulanate) are inactive against MBLs. Therefore, the treatment of CRE (and other gram-negative bacteria) that produce MBLs (chiefly NDM, but also VIM, IMP, etc.) awaits the development and introduction into the clinic a β-lactam/β-lactamases inhibitor combination for that purpose. Notably, cefepime-taniborbactam may be close to achieving that goal.[31] Similarly, the combination of aztreonam and avibactam represents a promising option under development.[32] Although avibactam does not inhibit MBLs, aztreonam cannot be hydrolyzed by MBLs either. However, aztreonam is susceptible to hydrolysis by other β-lactamases (ESBLs, AmpCs, OXA-48, KPC) found in MBL-producing CRE. The role of avibactam is to inhibit these other β-lactamases (distinct from MBLs), thereby protecting aztreonam so it can reach its target among the PBPs of CRE. Given that the co-formulation of aztreonam and avibactam is not yet available in clinical practice, the current recommendation is to treat severe infections caused by MBL-producing CRE with aztreonam and ceftazidime-avibactam.[9] While not backed by data from randomized controlled trials, this combination has demonstrated success in multiple case series.[33]

Cefiderocol, a cephalosporin decorated with a catechol group that confers its siderophore activity, is stable against a broad range of β-lactamases, including MBLs, and readily penetrates the gram-negative cell wall. The in vitro activity of cefiderocol against MBL-producing CRE is complemented by promising clinical evidence.[34] Therefore, cefiderocol is an option for treating CRE, especially when combinations with β-lactamase inhibitors as described earlier are inactive or unavailable.[9] There are no direct comparisons of the clinical outcomes of treating

MBL-producing CRE either with ceftazidime-avibactam plus aztreonam versus cefiderocol. Therefore, the preferred treatment option for MBL-producing CRE is not firmly established. It is clear, however, that the novel tetracyclines, tigecycline and eravacycline, should not be used to treat severe CRE infections, given underlying resistance and their unfavorable pharmacokinetic and pharmacodynamic properties for treating bloodstream infection.

Carbapenem-resistant Acinetobacter baumannii

The management of severe infections caused by CRAB has recently been transformed by the introduction into the clinic of durlobactam-sulbactam, following its approval by the US Food and Drug Administration (**Fig. 2**). Durlobactam is an inhibitor of the class D carbapenemases (OXA-23, OXA-24, OXA-58), which typically confer carbapenem resistance in *A baumannii.* Sulbactam is included in the combination with durlobactam not as a β-lactamase inhibitor but rather because it targets PBPs (PBP 1a/1b and PBP3) of *A baumannii*. Furthermore, durlobactam itself targets additional PBPs. Therefore, sulbactam-durlobactam demonstrates excellent in vitro activity against carbapenem-resistant and sulbactam-resistant *A baumannii*.[35] A notable limitation of durlobactam-sulbactam is that it is inactive against *A baumannii* strains that produce MBLs. The ATTACK study was a multicountry randomized trial at 59 sites involving 177 patients with pneumonia from *A baumannii* complex, treated with sulbactam-durlobactam or colistin, both alongside imipenem.[36] The 28 day all-cause mortality was 19% for durlobactam-sulbactam and 32% for colistin. Nephrotoxicity was significantly lower in the durlobactam-sulbactam group (13% vs 38%). Notably, based on current knowledge, sulbactam-durlobactam should be given with imipenem (or meropenem) to mimic the ATTACK trial protocol, broaden antibiotic coverage, and enhance carbapenem interactions with PBPs.

The availability of durlobactam-sulbactam has replaced high-dose ampicillin-sulbactam (27 g daily) administered in combination with at least one other agent as the preferred treatment of CRAB. Determining the appropriate second agent to administer with sulbactam is challenging. High-dose minocycline (200 mg IV every 12 hours) has evidence supporting its use and a relatively mild profile of adverse effects, contrasting

Mechanism/ Antibiotic	Carbapenem-resistant *Acinetobacter baumannii*	
	OXA-23, OXA-40, OXA-58	Metallo-β-lactamase
Durlobactam-sulbactam (+ carbapenem)		
Cefiderocol (as part of combination regimen)		
Sulbactam (high dose) + minocycline		

Fig. 2. Antibiotics used for the management of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*, according to the mechanism of resistance. Green indicates that the antibiotic is active and recommended. Yellow indicates that the antibiotic could be an alternative. Red indicates that the antibiotic is inactive.

with polymyxin B and colistin, which are known to cause neurotoxicity and nephrotoxicity. The role of novel tetracyclines such as tigecycline and eravacycline in treating severe infections like bloodstream infections caused by CRAB is limited due to the pharmacokinetic and pharmacodynamic properties of both drugs, as well as the lack of clinical evidence supporting their use.

Cefiderocol, as described, is a cephalosporin linked to a siderophore that is considered an option for the treatment of severe infections caused by CRAB. Most CRAB strains show in vitro susceptibility to cefiderocol at a breakpoint of 4 mcg/mL. However, susceptibility evaluation is complicated by factors such as variable iron concentrations, non-reproducible MIC results, and heteroresistance (subpopulations with resistance). Moreover, the available clinical evidence indicates a higher mortality rate in patients with CRAB treated with cefiderocol compared to standard alternative therapies, especially in cases of pneumonia and bloodstream infections, and there is risk of recurrence.[37] Cefiderocol may be used cautiously after other alternatives have failed or are not considered an option due to resistance.[9] In this context, CRAB harboring MBLs is incredibly challenging since they are resistant to durlobactam-sulbactam, leaving nephrotoxic options like polymyxins. Cefiderocol, therefore, may offer an alternative, which should be used as part of a combination regimen.

Difficult to treat resistance in Pseudomonas aeruginosa

A key element in deciding how to manage severe infections caused by DTR *P aeruginosa* is the presence of carbapenemases, particularly MBLs (**Fig. 3**). This possibility is generally viewed as rare in the United States but should not be dismissed, especially in cases of health care received during travel or other instances of "medical tourism." In the absence of carbapenemases, *P aeruginosa* is resistant to antipseudomonal carbapenems

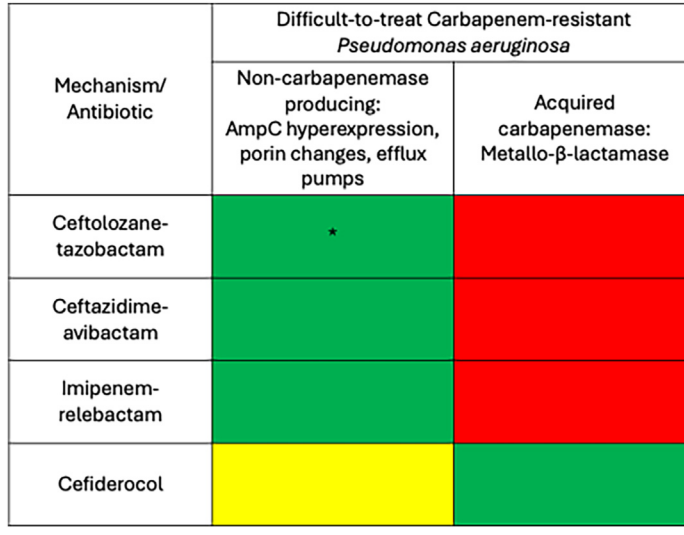

Fig. 3. Antibiotics used for the management of severe infections caused by difficult-to-treat carbapenem-resistant *Pseudomonas aeruginosa*, according to the mechanism of resistance. Green indicates that the antibiotic is active and recommended. Yellow indicates that the antibiotic could be an alternative. Red indicates that the antibiotic is inactive. *Indicates that the antibiotic is preferred for the treatment of pneumonia.

(meropenem and imipenem), cefepime, ceftazidime, and piperacillin-tazobactam due to varying combinations of 3 essential factors: porin changes, efflux pumps, and the production of AmpC and other β-lactamases. Ceftolozane withstands hydrolysis by AmpC and readily enters the cell despite porin changes and efflux pumps. Although coformulated with tazobactam, this β-lactamase inhibitor does not significantly enhance ceftolozane's activity against *P aeruginosa*. Avibactam and relebactam inhibit AmpC and other β-lactamases, respectively, restoring the effectiveness of ceftazidime and imipenem against DTR *P aeruginosa*. In contrast, vaborbactam fails to restore meropenem susceptibility in *P aeruginosa* because meropenem resistance stems from changes in efflux and permeability unaffected by vaborbactam.[38]

The consensus from the available data is that ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-relebactam agents are more effective and safer than options like aminoglycosides or polymyxins for treating severe infections like pneumonia or bacteremia caused by DTR *P aeruginosa*[39,40]. In the United States, ceftolozane-tazobactam is usually more active than its counterparts,[41] but this may vary depending on the geographic locale and previous exposure. It is, therefore, recommended that antimicrobial susceptibility testing be conducted for all options to confirm that the chosen treatment is effective. A multicenter, retrospective, observational study compared the outcomes of patients with MDR *P aeruginosa* pneumonia or bacteremia treated with ceftolozane-tazobactam or ceftazidime-avibactam.[42] The primary outcome was clinical success (defined as survival, resolution of signs and symptoms of infection, and no recurrent infection at day 30). Clinical success was observed in 61% of patients treated with ceftolozane-tazobactam and in 52% of patients treated with ceftazidime-avibactam, attributed to improved response rates in patients with pneumonia. However, there were no significant differences in mortality. Resistance developed in approximately 20% of patients treated with either agent.

Cefiderocol is an alternative option for managing DTR *P aeruginosa* when resistance, adverse effects, or unavailability preclude using the earlier discussed β-lactam-β-lactamase inhibitors. Moreover, cefiderocol is one of the few options for MBL-producing *P aeruginosa* and the preferred agent to treat severe infections by such pathogens, even though clinical data are limited.[9]

SUMMARY

The antibiotic management of severe infections, such as pneumonia and bacteremia caused by MDR and carbapenem-resistant gram-negative bacteria, presents a significant clinical challenge. Novel β-lactam/β-lactamase inhibitor combinations are preferred options for treating CRE. Meropenem-vaborbactam may have a preferential role in cases of KPC-producing Enterobacterales, particularly when resistance to ceftazidime-avibactam is a concern due to prior treatment. For OXA-48-producing Enterobacterales, ceftazidime-avibactam is the recommended treatment, while the combination of ceftazidime-avibactam and aztreonam is advised for MBL-producing Enterobacterales. Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam are viable options for severe infections caused by DTR *P aeruginosa*, although a retrospective study comparing ceftolozane-tazobactam and ceftazidime-avibactam suggests that the former may be advantageous, especially in pneumonia cases. For severe infections caused by CRAB, if MBLs are excluded, sulbactam-durlobactam (administered with imipenem or meropenem) is the preferred choice. Cefiderocol offers a reasonable alternative for treating severe infections caused by MBL-producing CRE, DTR *P aeruginosa*, and CRAB.

CLINICS CARE POINTS

CRE

- For patients with severe infection due to CRE, treatment is predicated upon mechanism of carbapenem resistance.
- If KPC is suspected or confirmed, meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-relebactam are alternatives.
- If there is concern for KPC variants resistant to ceftazidime-avibactam, meropenem-vaborbactam is preferred.
- If OXA-48 is suspected or confirmed, ceftazidime-avibactam is recommended.
- If MBL is suspected or confirmed, ceftazidime-avibactam and aztreonam in combination, or cefiderocol, are recommended.
- Extended infusions of meropenem or imipenem are an alternative for the treatment of infections caused by CRE without an identified carbapenemase.

Carbapenem-resistant *Acinetobacter baumannii*

- For patients with severe infection due to CRAB (in the absence of MBLs), durlobactam-sulbactam should be used, administered with a carbapenem (imipenem or meropenem).
- Cefiderocol is an alternative to CRAB where sulbactam-durlobactam is not an option due to resistance (including MBLs).

Difficult to treat *Pseudomonas aeruginosa*

- For patients with severe infection due to DTR *P aeruginosa* (in the absence of MBLs), ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam are options.
- Observational data may favor the use of ceftolozane-tazobactam especially for the treatment of pneumonia.
- If an MBL is suspected or confirmed, cefiderocol is a preferred option for the treatment of severe DTR *P aeruginosa* infections.

DISCLOSURES

Previous research funding from Merck, United States, Pfizer, United States, and Accelerate to Federico Perez.

REFERENCES

1. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34(6):1589–96.
2. Baker S. Infectious disease. A return to the pre-antimicrobial era? Science 2015; 347(6226):1064–6.
3. Gaynes R. The discovery of penicillin—new insights after more than 75 Years of clinical use. Emerging Infectious Diseases Journal CDC 2017;23:5.
4. Jones RN, Thornsberry C, Barry AL, et al. Piperacillin (T-1220), a new semisynthetic penicillin: in vitro antimicrobial activity comparison with carbenicillin, ticarcillin, ampicillin, cephalothin, cefamandole and cefoxitin. J Antibiot (Tokyo) 1977; 30(12):1107–14.
5. Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. Clin Microbiol Rev 2010;23(1):160–201.
6. Bonomo RA, Perez F, Hujer AM, et al. The real crisis in antimicrobial resistance: failure to anticipate and respond. Clin Infect Dis 2024;78(6):1429–33.
7. Perez F, Bonomo RA. Precision medicine and mysteries in clinical Microbiology: rationalizing epidemiology, genotype, and phenotype to guide therapeutics. Antimicrob Agents Chemother 2020;64(2):e02264–319.

8. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect 2022; 28(4):521–47.
9. Tamma PD, Heil EL, Justo JA, et al. Infectious Diseases society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis 2024;ciae403. https://doi.org/10.1093/cid/ciae403.
10. Perez F, Van Duin D. Carbapenem-resistant Enterobacteriaceae: a menace to our most vulnerable patients. Cleve Clin J Med 2013;80(4):225–33.
11. van Duin D, Arias CA, Komarow L, et al. Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study. Lancet Infect Dis 2020;20(6):731–41.
12. Boutzoukas AE, Komarow L, Chen L, et al. International epidemiology of carbapenemase-producing Escherichia coli. Clin Infect Dis 2023;77(4):499–509.
13. Wang M, Earley M, Chen L, et al. Clinical outcomes and bacterial characteristics of carbapenem-resistant Klebsiella pneumoniae complex among patients from different global regions (CRACKLE-2): a prospective, multicentre, cohort study. Lancet Infect Dis 2022;22(3):401–12.
14. Perez F, Hujer AM, Hujer KM, et al. Global challenge of multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2007;51(10):3471–84.
15. Iovleva A, Mustapha MM, Griffith MP, et al. Carbapenem-resistant acinetobacter baumannii in U.S. Hospitals: diversification of circulating lineages and antimicrobial resistance. mBio 2022;13(2):e0275921. https://doi.org/10.1128/mbio.02759-21.
16. Wang M, Ge L, Chen L, et al. Clinical outcomes and bacterial characteristics of carbapenem-resistant acinetobacter baumannii among patients from different global regions. Clin Infect Dis 2024;78(2):248–58.
17. Kornelsen V, Kumar A. Update on multidrug resistance efflux pumps in acinetobacter spp. Antimicrob Agents Chemother 2021;65(7):e0051421.
18. Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in Acinetobacter baumannii. Antimicrob Agents Chemother 2015;59(3):1680–9.
19. Bonnin RA, Poirel L, Naas T, et al. Dissemination of New Delhi metallo-β-lactamase-1-producing acinetobacter baumannii in Europe. Clin Microbiol Infect 2012;18(9):E362–5.
20. Martinez T, Martinez I, Vazquez GJ, et al. Genetic environment of the KPC gene in Acinetobacter baumannii ST2 clone from Puerto Rico and genomic insights into its drug resistance. J Med Microbiol 2016;65(8):784–92.
21. Fournier PE, Vallenet D, Barbe V, et al. Comparative genomics of multidrug resistance in Acinetobacter baumannii. PLoS Genet 2006;2(1):e7.
22. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-Treat resistance in gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis 2018; 67(12):1803–14.
23. Livermore DM. Multiple mechanisms of antimicrobial resistance in Pseudomonas aeruginosa: our worst nightmare? Clin Infect Dis 2002;34(5):634–40.
24. Montaner M, Lopez-Argüello S, Oliver A, et al. PBP target profiling by β-lactam and β-lactamase inhibitors in intact Pseudomonas aeruginosa: effects of the intrinsic and acquired resistance determinants on the periplasmic drug availability. Microbiol Spectr 2023;11(1):e0303822.

25. Reyes J, Komarow L, Chen L, et al. Global epidemiology and clinical outcomes of carbapenem-resistant Pseudomonas aeruginosa and associated carbapenemases (POP): a prospective cohort study. Lancet Microbe 2023;4(3):e159–70.
26. Correa A, Montealegre MC, Mojica MF, et al. First report of a Pseudomonas aeruginosa isolate coharboring KPC and VIM carbapenemases. Antimicrob Agents Chemother 2012;56(10):5422–3.
27. Del Barrio-Tofiño E, López-Causapé C, Oliver A. Pseudomonas aeruginosa epidemic high-risk clones and their association with horizontally-acquired β-lactamases: 2020 update. Int J Antimicrob Agents 2020;56(6):106196.
28. Ackley R, Roshdy D, Meredith J, et al. Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother 2020;64(5):e02313–9.
29. Weston G, Giri A, Komarow L, et al. Clinical outcomes in patients infected with ertapenem-only-resistant Enterobacterales versus multi-carbapenem-resistant Enterobacterales. J Antimicrob Chemother 2024;79(8):1929–37.
30. Biagi M, Shajee A, Vialichka A, et al. Activity of imipenem-relebactam and meropenem-vaborbactam against carbapenem-resistant, SME-producing Serratia marcescens. Antimicrob Agents Chemother 2020;64(4):e02255–319.
31. Wagenlehner FM, Gasink LB, McGovern PC, et al. Cefepime-taniborbactam in complicated urinary tract infection. N Engl J Med 2024;390(7):611–22.
32. Carmeli Y, Cisneros JM, Paul M, et al. Aztreonam-avibactam versus meropenem for the treatment of serious infections caused by Gram-negative bacteria (REVISIT): a descriptive, multinational, open-label, phase 3, randomised trial. Lancet Infect Dis 2024;S1473-3099(24):00499–507.
33. Marshall S, Hujer AM, Rojas LJ, et al. Can ceftazidime-avibactam and aztreonam overcome β-lactam resistance conferred by metallo-β-lactamases in Enterobacteriaceae? Antimicrob Agents Chemother 2017;61(4). https://doi.org/10.1128/AAC.02243-16.
34. Timsit JF, Paul M, Shields RK, et al. Cefiderocol for the treatment of infections due to metallo-B-lactamase-Producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 randomized studies. Clin Infect Dis 2022;75(6):1081–4.
35. Barnes MD, Kumar V, Bethel CR, et al. Targeting multidrug-resistant acinetobacter spp.: sulbactam and the diazabicyclooctenone β-lactamase inhibitor ETX2514 as a novel therapeutic agent. mBio 2019;10(2):e00159–619.
36. Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet Infect Dis 2023;23(9):1072–84.
37. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2021;21(2):213–25.
38. El Chakhtoura NG, Saade E, Iovleva A, et al. Therapies for multidrug resistant and extensively drug-resistant non-fermenting gram-negative bacteria causing nosocomial infections: a perilous journey toward "molecularly targeted" therapy. Expert Rev Anti Infect Ther 2018;16(2):89–110.
39. Gupta C, Lee SSJ, Sahu M, et al. Ceftazidime-avibactam versus other antimicrobial agents for treatment of Multidrug-resistant Pseudomonas aeruginosa: a systematic review and meta-analysis. Infection 2024;52(6):2183–93.

40. Pogue JM, Kaye KS, Veve MP, et al. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant Pseudomonas aeruginosa. Clin Infect Dis 2020;71(2):304–10.
41. Karlowsky JA, Lob SH, Bauer KA, et al. Activity of ceftolozane/tazobactam, imipenem/relebactam and ceftazidime/avibactam against clinical Gram-negative isolates-SMART United States 2019-21. JAC-Antimicrob Resist 2024;6(1): dlad152.
42. Shields RK, Abbo LM, Ackley R, et al. Effectiveness of ceftazidime-avibactam versus ceftolozane-tazobactam for multidrug-resistant Pseudomonas aeruginosa infections in the USA (CACTUS): a multicentre, retrospective, observational study. Lancet Infect Dis 2024;S1473-3099(24):00648–50.