

New Antimicrobial Agents



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LEARNING OBJECTIVES

1. Distinguish the pharmacology, spectrum of activity, and practical applications of ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, and cefiderocol.
2. Demonstrate similarities and differences in the pharmacology, spectrum of activity, and practical applications of omadacycline, eravacycline, and plazomicin.
3. Apply knowledge of new antimicrobial agents to select optimal pharmacotherapy for patient-specific clinical scenarios and formulary considerations.

ABBREVIATIONS IN THIS CHAPTER

ABSSSI	Acute bacterial skin structure and skin infection
BAT	Best available therapy
CABP	Community-acquired bacterial pneumonia
CRE	Carbapenem-resistant Enterobacteriaceae
ESBL	Extended-spectrum β -lactamase
HAP	Hospital-acquired pneumonia
IMP	Imipenemase-type metallo- β -lactamase
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
MBL	Metallo- β -lactamase
MDR	Multidrug resistant
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NDM	New Delhi metallo- β -lactamase
VAP	Ventilator-associated pneumonia
VIM	Verona integron-based metallo- β -lactamase
VRE	Vancomycin-resistant enterococci
XDR	Extensively drug-resistant

[Table of other common abbreviations.](#)

INTRODUCTION

The Infectious Diseases Society of America in collaboration with federal regulatory agencies implemented the “10 × 20 Initiative” in 2010, with the goal to approve 10 novel systemic antibiotics by 2020. A recent report of this group questioned revising this goal to the possibility of 20 × 20 because, by and large, the initiative was successful in reversing the trend of declining new antibacterials approved before 2010. Although methicillin-resistant *Staphylococcus aureus* (MRSA) is still classified as a serious threat by the CDC, in the past decade, several new anti-MRSA agents have been approved for use in the United States such as delafloxacin, tedizolid, lefamulin, dalbavancin, oritavancin, and ceftaroline. However, infections caused by carbapenem-resistant gram-negative bacteria and vancomycin-resistant enterococci (VRE) have only been addressed more recently. Although newly approved antibiotics have revolutionized the management of most carbapenem-resistant Enterobacteriaceae (CRE) and multidrug-resistant (MDR) *Pseudomonas*, agents with reliable activity against MDR *Acinetobacter*, *Stenotrophomonas*, and strains producing metallo- β -lactamases (MBLs) remain limited. In addition, emergence of resistance to novel agents has been documented, emphasizing the ongoing need for the evolution of our antibacterial arsenal to agents having higher thresholds against the development of resistance. This chapter will review selected new antibacterials and their spectrum of activity, pharmacology, and place in therapy.

NEW β -LACTAM/ β -LACTAMASE INHIBITOR COMBINATIONS

Ceftolozane/Tazobactam

Pharmacology and Dosing

Ceftolozane is a novel oxyimino-aminothiazole cephalosporin that is structurally similar to ceftazidime. Like other cephalosporins, ceftolozane exerts bactericidal activity by inhibiting penicillin-binding proteins (PBPs), thereby disrupting the final steps of the peptidoglycan biosynthesis required for the bacterial cell wall. However, ceftolozane has affinities for various PBPs that are at least 2-fold higher and inhibits a broader set of PBPs (including PBP1b, PBP1c, and PBP3 present in *Pseudomonas aeruginosa*) than ceftazidime. Ceftolozane has low affinity for PBP4, which reduces the likelihood of inducing overexpression of chromosomal AmpC β -lactamases, further enhancing its activity against *P. aeruginosa*. Finally, ceftolozane is minimally affected by other resistance mechanisms in *Pseudomonas* such as porin loss and efflux pumps. Ceftolozane is combined with tazobactam, a well-established β -lactamase inhibitor, to expand coverage against most extended-spectrum β -lactamase (ESBL)-producing organisms and some anaerobes.

Ceftolozane has a mean plasma half-life of 2.3 hours, with more than 92% excreted unchanged in the urine; hence, dose adjustments are needed in moderate to severe renal

impairment. The efficacy of ceftolozane/tazobactam correlates with the percentage of time the free drug concentration is above the MIC ($\%fT>MIC$) of around 40% for a 1-log bactericidal effect. Ceftolozane/tazobactam is commercially available in a 2:1 ratio, with a 1.5-g dose consisting of 1 g of ceftolozane and 0.5 g of tazobactam. Ceftolozane/tazobactam is FDA approved for intra-abdominal infections (in combination with metronidazole) and complicated UTIs at a dose of 1.5 g intravenously every 8 hours and for hospital-acquired and ventilator-associated pneumonia (HAP/VAP) at a dose of 3 g intravenously every 8 hours, both infused over 1 hour. The higher dosage for pneumonia was based on pharmacokinetic/pharmacodynamic (PK/PD) data requiring this dose to have a more than 90% probability of attaining the target $fT>MIC$ of 40% against *P. aeruginosa* with an MIC of up to 8/4 mg/L (Xiao 2016). In clinical practice, ceftolozane/tazobactam is expected to be used in MDR infections with elevated MICs; thus, it may be prudent to use the higher dose of 3 g intravenously every 8 hours (assuming normal renal function) for all indications to ensure efficacy while minimizing emergent resistance. For an elevated ceftolozane/tazobactam MIC, a 4-hour infusion can be considered because the reconstituted solution is stable at room temperature for 24 hours. A 4-hour infusion of 3 g intravenously every 8 hours achieved a more than 90% probability of attaining an $fT>MIC$ of 40% up to an MIC of 32/4 mg/L, well above the current 2020 Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint of 4/4 mg/L or less (Natesan 2017).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the various classes of antimicrobials
- Fundamental classification of gram-positive and gram-negative bacteria
- General principles of bacterial culture and antimicrobial susceptibility testing
- Recognition of basic mechanisms of antimicrobial drug resistance and strategies to overcome them

[Table of common laboratory reference values](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- CDC. [Antibiotic Resistance Threats in the United States, 2019](#). Atlanta: CDC, 2019.
- Eichenberger EM, Thaden JT. [Epidemiology and mechanisms of resistance of extensively drug-resistant gram-negative bacteria](#). *Antibiotics (Basel)* 2019;8:E37.

Spectrum of Activity and Role Against MDR Bacteria

Ceftolozane/tazobactam generally has broad activity, including against streptococci, gram-negatives, and some anaerobic bacteria. The clinical niche for ceftolozane/tazobactam is in managing infections caused by β -lactam-resistant *P. aeruginosa*. In a study of over 1500 *P. aeruginosa* isolates from critically ill adults in 32 U.S. hospitals, ceftolozane/tazobactam was the most active agent among β -lactams, with 96.5% of strains considered susceptible (Shortridge 2019). Even against 118 strains of pan- β -lactam-resistant *P. aeruginosa* (strains nonsusceptible to cefepime, ceftazidime, piperacillin/tazobactam, and meropenem), susceptibility remained high at 72% and lower than only amikacin (88%) and colistin (99%). Of note, the CLSI susceptibility breakpoint of 4/4 mg/L or less is based on the lower approved dose. Use of the higher dose is expected to result in even better susceptibility rates, particularly if infused over 4 hours. Ceftolozane/tazobactam is therefore a potent option against *P. aeruginosa* resistant to conventional antipseudomonal β -lactams. Although ceftolozane/tazobactam is active against many ESBL-producing Enterobacteriaceae (88%), meropenem has higher susceptibility rates (99%), and carbapenems remain the drug of choice for such infections (Shortridge 2018). Ceftolozane/tazobactam is generally cleaved by all carbapenemases;

thus, it is not an option in the management of CRE and plays no role against MDR *Acinetobacter* or *Stenotrophomonas*.

Susceptibility Testing and Patient Outcomes

Susceptibility testing for ceftolozane/tazobactam should be performed whenever possible. As noted earlier, ceftolozane/tazobactam tested nonsusceptible in around 30% of *Pseudomonas* resistant to conventional antipseudomonal β -lactams. In a small study of 21 patients with MDR *P. aeruginosa* treated with ceftolozane/tazobactam, resistance emerged upon therapy in 3 patients (14%), which is of concern and requires further investigation (Haidar 2017). The 2020 CLSI breakpoints of 4/4 mg/L or less against *Pseudomonas* and 2/4 mg/L or less against Enterobacteriaceae are based on the dose of 1.5 g intravenously every 8 hours, though the dose best suited for MDR infections is 3 g intravenously every 8 hours.

Ceftolozane/tazobactam achieved FDA approval in the United States on the basis of the ASPECT-cUTI, ASPECT-cIAI, and ASPECT-NP trials (Kollef 2019; Solomkin 2015; Wagenlehner 2015). At a dose of 1.5 g intravenously every 8 hours, ceftolozane/tazobactam was noninferior to levofloxacin in the setting of complicated UTIs and, when used in combination with metronidazole (expanding its anaerobic coverage to parallel meropenem), noninferior to meropenem for complicated intra-abdominal infections. Using the dose of 3 g intravenously every 8 hours, it was also noninferior to meropenem in HAP/VAP.

Clinical studies are limited comparing the effectiveness of ceftolozane/tazobactam with best available therapy (BAT) in β -lactam-resistant *P. aeruginosa*. A retrospective study of 200 patients assessed outcomes with ceftolozane/tazobactam compared with combinations of polymyxins and/or aminoglycosides with other agents, typically carbapenems (Pogue 2019b). Clinical cure with ceftolozane/tazobactam was 81% compared with 61% with polymyxin- or aminoglycoside-based regimens ($p=0.002$; OR 2.72; 95% CI, 1.43–5.17). In addition, acute kidney injury was significantly lower with ceftolozane/tazobactam (6% vs. 34%; adjusted OR 0.08; 95% CI, 0.03–0.22). This supports that ceftolozane/tazobactam is preferred to the previous standard of polymyxin- or aminoglycoside-based combination regimens against *P. aeruginosa* nonsusceptible to conventional β -lactams.

Ceftazidime/Avibactam

Pharmacology and Dosing

Ceftazidime is an established third-generation cephalosporin with broad gram-negative activity. Avibactam is a non- β -lactam β -lactamase inhibitor that inhibits the activity of many ESBLs (e.g., CTX-M and TEM-1) as well as carbapenemases such as *K. pneumoniae* carbapenemase (KPC). Avibactam also inhibits AmpC and OXA-48 (carbapenemase) β -lactamases, conferring broad activity. However, avibactam is not active against MBLs (which are carbapenemases) such as New Delhi metallo- β -lactamase (NDM), Verona integron-based

metallo- β -lactamase (VIM), and imipenemase-type metallo- β -lactamase (IMP).

The PK/PD properties of ceftazidime/avibactam are consistent with those of ceftazidime, with a target $fT_{>MIC}$ of 50% for a 1-log kill. Both agents have low protein binding of less than 10% with good penetration into the epithelial lining fluid of the lungs, with half-lives of 2.8 hours after several doses. Both drugs are primarily eliminated renally, with the need for dose adjustments in moderate and severe renal impairment. Ceftazidime/avibactam is available in a 4:1 dose ratio, with the standard dose of 2.5 g intravenously every 8 hours infused over 2 hours consisting of 2 g of ceftazidime and 0.5 g of avibactam. Ceftazidime/avibactam's FDA-approved indications are HAP/VAP, complicated UTIs including pyelonephritis, and complicated intra-abdominal infections (in combination with metronidazole), but unlike with ceftolozane/tazobactam, the standard dose is recommended across all indications. This dose achieves a high (greater than 95%) probability of achieving the target $fT_{>MIC}$ of 50% against MICs of 8/4 mg/L or less, which is the current 2020 CLSI susceptibility breakpoint for both Enterobacteriaceae and *Pseudomonas* (Das 2019).

Spectrum of Activity and Role Against MDR Bacteria

The addition of avibactam expands on the spectrum of activity of ceftazidime to include activity against KPC-producing Enterobacteriaceae. In a review of over 36,000 clinical isolates of Enterobacteriaceae, ceftazidime/avibactam had potent activity with susceptibility rates of 99.9% overall, including 99.6% against ESBL-producing strains, 97.5% against CRE, and even 99.3% against ceftazidime-nonsusceptible *Enterobacter*, showing broad expansion of the activity of ceftazidime in Enterobacteriaceae (Sader 2017).

Ceftazidime/avibactam also provides activity against ceftazidime-nonsusceptible *P. aeruginosa* because AmpC overexpression is a common factor mediating ceftazidime resistance, and avibactam is a potent inhibitor of AmpC β -lactamases. In an analysis of almost 8000 clinical isolates of *P. aeruginosa*, ceftazidime/avibactam had 97.1% susceptibility overall, including 81.3% against ceftazidime-nonsusceptible isolates and 71.8% against strains nonsusceptible to any conventional antipseudomonal β -lactams. Adding avibactam therefore significantly expands the activity of ceftazidime against *P. aeruginosa*.

Another area for potential use of ceftazidime/avibactam is in combination with aztreonam against MBL-producing pathogens. Aztreonam is unique as a monobactam that is stable against MBLs such as NDM, VIM, and IMP expressed by some Enterobacteriaceae and *Pseudomonas* and the L1 MBL expressed by *Stenotrophomonas*. However, most bacteria expressing such MBLs simultaneously express other β -lactamases such as ESBL, KPC, AmpC, and OXA-48, conferring aztreonam resistance. Combining aztreonam with avibactam is therefore a unique approach in which avibactam

inhibits AmpC, ESBL, KPC, and OXA-48 β -lactamases, thereby allowing aztreonam, unaffected by the remaining MBLs, to become active (Biedenbach 2015). The combination of ceftazidime/avibactam and aztreonam is synergistic and produces several hundred- to thousand-fold reductions in MIC against MBL-producing gram negatives (Wenzler 2017). Currently, this combination can only be achieved using ceftazidime/avibactam plus aztreonam, but the investigational antimicrobial combination aztreonam/avibactam is in the latter stages of clinical development. Aztreonam/avibactam was active against 99.9% of Enterobacteriaceae (including KPC and MBL carbapenemase producers) and 82% of *Stenotrophomonas*, but predictably, it had minimal activity against ceftazidime-nonsusceptible *Pseudomonas* and *Acinetobacter* (where MBLs are uncommon). Until aztreonam/avibactam becomes commercially available, ceftazidime/avibactam plays a role against MDR *Stenotrophomonas* and MBL-producing Enterobacteriaceae when used in combination with aztreonam (Mojica 2017; Biedenbach 2015). However, use of this combination would be in the absence of in vitro susceptibility until aztreonam/avibactam susceptibility testing is commercially available.

Outside these clinical scenarios, ceftazidime/avibactam has activity against *Streptococcus* spp. and ESBL-producing organisms, though narrower-spectrum agents should be used in these settings to preserve the role of ceftazidime/avibactam. Ceftazidime/avibactam also has very little anaerobic coverage; thus, metronidazole should be added if anaerobic coverage is needed. Ceftazidime/avibactam also provides no appreciable activity against ceftazidime-resistant *Acinetobacter*.

Susceptibility Testing and Patient Outcomes

The 2020 CLSI susceptibility breakpoint for ceftazidime/avibactam is 8/4 mg/L or less for both Enterobacteriaceae and *Pseudomonas* on the basis of the standard 2-hour infusion of 2.5 g intravenously every 8 hours. Susceptibility testing should be performed when ceftazidime/avibactam is used against CRE and *Pseudomonas*. Although susceptibility rates against KPC-producing CRE are high, emergent resistance during treatment has been reported (Giddins 2018). Carbapenemase testing using assays such as Carba-R, which detects the presence of NDM, VIM, IPM, OXA-48, and KPC genes, is encouraged if results are rapidly available. Detection of any of the MBLs (NDM, VIM, or IPM) should prompt consideration for adding aztreonam to ceftazidime/avibactam, as noted earlier. When ceftazidime/avibactam is considered in the treatment of *P. aeruginosa* nonsusceptible to conventional antipseudomonal β -lactams, about 30%–50% are nonsusceptible. However, ceftolozane/tazobactam is likely better against β -lactam-nonsusceptible *Pseudomonas* because it has consistently higher susceptibility rates than ceftazidime/avibactam. In either case, in vitro susceptibility should be confirmed.

Ceftazidime/avibactam achieved FDA approval in 2015 by showing noninferiority to doripenem in the RECAPTURE-1 and RECAPTURE-2 trials for complicated UTIs, noninferiority in combination with metronidazole compared with meropenem in the RECLAIM-1 and RECLAIM-2 trials for complicated intra-abdominal infections, and noninferiority to meropenem in the REPROVE trial for HAP/VAP (Torres 2018; Mazuski 2016; Wagenlehner 2016). In addition, the manufacturer conducted the REPRIZE randomized trial, which specifically compared the efficacy of ceftazidime/avibactam with that of BAT in over 300 patients with complicated UTIs or intra-abdominal infections caused by ceftazidime-resistant Enterobacteriaceae and *Pseudomonas*. Most patients in the BAT group (96%) received carbapenem monotherapy, and patient outcomes were similar across both groups, with 91% clinical cure at test-of-cure in both groups.

Two studies have described patient outcomes with ceftazidime/avibactam against CRE, which is its primary niche. An observational study in the United States involved 38 patients who received ceftazidime/avibactam compared with 99 who received colistin, all of whom had CRE, of which 97% were *Klebsiella pneumoniae* (van Duin 2018). One-half of the patients had CRE bacteremia, whereas pneumonia and UTI were the next most common primary sources. In this study, 96% of strains for which genetic testing was performed harbored the KPC gene, with 96% susceptible to ceftazidime/avibactam and 88% susceptible to colistin. Almost 50% of the patients in the ceftazidime/avibactam group received combination therapy with other antibiotics, and 74% received combinations in the colistin arm. The most common agents used in combination in both arms were carbapenems, followed by tigecycline, or an aminoglycoside. After adjusting for confounders, the ceftazidime/avibactam group had a lower adjusted rate of in-hospital mortality (9% vs. 32%, $p=0.001$). In addition, the percentage of surviving patients who had renal failure was lower in the ceftazidime/avibactam arm (5% vs. 13%). The findings show that ceftazidime/avibactam is likely superior to colistin with a more favorable safety profile, though this should be bolstered by further studies.

The other study was a retrospective study conducted in Italy of 138 adults with KPC-producing *K. pneumoniae*, 75% of whom had bacteremia (Tumbarello 2019). All isolates were susceptible to ceftazidime/avibactam, whereas susceptibility to other agents was generally poor (tigecycline 32%, colistin 27%, gentamicin 41%, amikacin 16%). Patients receiving ceftazidime/avibactam were matched to patients on alternative regimens. Almost 80% of patients in the ceftazidime/avibactam arm received combination therapy, whereas all patients in the alternative treatment arm received combinations. Similar to the previous study, the most common agents in combination included carbapenems and/or aminoglycosides. The 30-day mortality rate was lower in the ceftazidime/avibactam arm than in the alternative treatment arm (36.5% vs. 55.8%, $p=0.005$). After propensity score adjustment, multivariate

analysis confirmed reduced mortality in the ceftazidime/avibactam group (OR 0.27; 95% CI, 0.13–0.57; $p=0.001$). This study again confirmed that ceftazidime/avibactam is associated with reduced mortality compared with alternative BAT regimens for KPC-producing CRE.

Meropenem/Vaborbactam

Pharmacology and Dosing

Meropenem is a well-known antipseudomonal carbapenem inherently stable against many β -lactamases, including AmpC and ESBL. Vaborbactam is a novel boronic acid–based β -lactamase inhibitor that is a particularly potent inhibitor of KPCs as well as ESBLs and AmpC β -lactamases. In contrast to avibactam, vaborbactam has no activity against OXA-48 β -lactamases, but the general profile of both avibactam and vaborbactam is otherwise similar. Neither avibactam nor vaborbactam has activity against MBLs (NDM, VIM, IPM).

Meropenem/vaborbactam is commercially available in a 1:1 ratio as 2-g vials containing 1 g of meropenem and 1 g of vaborbactam. The standard dose in normal renal function is 4 g intravenously every 8 hours as a 3-hour infusion and is FDA approved for the indication of complicated UTIs. Of note, the meropenem component of meropenem/vaborbactam is double the standard dose of meropenem alone and is administered as an extended infusion. This dosing strategy expands the range of MICs covered with meropenem/vaborbactam by optimizing the likelihood of achieving the $fT > MIC$ target of greater than 45% for a 2-log kill, even aside from the effect of vaborbactam. The standard meropenem/vaborbactam dose results in a more than 90% probability of achieving the $fT > MIC$ target of greater than 45% for Enterobacteriaceae and *P. aeruginosa* up to an MIC of 8/8 mg/L, which is above the current CLSI susceptibility breakpoint of 4/8 mg/L or less against Enterobacteriaceae (Bhavnani 2017). Both meropenem and vaborbactam are primarily renally eliminated; thus, dose adjustments are recommended in moderate or severe renal impairment.

Spectrum of Activity and Role Against MDR Bacteria

As noted earlier, adding vaborbactam expands the coverage of meropenem to include activity against KPC-producing Enterobacteriaceae, the most common mechanism of CRE in the United States. In a study of over 300 CRE isolates, meropenem/vaborbactam had susceptibility rates of 74% (Pfaller 2018). However, these rates differed significantly depending on carbapenemase expression. Susceptibility against KPC-producing strains was 99.5%, but susceptibility was poor against OXA-48–like β -lactamases (24%) and MBLs (4%). In addition, the study included 38 strains of CRE that were carbapenemase negative, against which meropenem/vaborbactam had 82% susceptibility compared with just 3% with meropenem alone. These strains likely expressed other carbapenemases that were not included in the testing but

were nonetheless inhibited by vaborbactam. Meropenem/vaborbactam is therefore an excellent choice against KPC-producing Enterobacteriaceae but should be avoided in the setting of CRE expressing OXA-48 and MBLs such as NDM, VIM, or IPM.

With respect to *P. aeruginosa*, adding vaborbactam does not significantly expand on the activity of equivalently dosed meropenem alone (Lapuebla 2015). This is because meropenem resistance in *Pseudomonas* is often not β -lactamase mediated but is instead the result of some combination of porin loss and efflux pumps. In addition, meropenem/vaborbactam does not appreciably expand the activity of meropenem against *Acinetobacter* or *Stenotrophomonas*, whose mechanisms of resistance often involve OXA-type β -lactamases and MBLs, respectively, which are unaffected by vaborbactam. Consequently, meropenem/vaborbactam plays no meaningful clinical role in the management of meropenem-resistant *Pseudomonas*, *Acinetobacter*, or *Stenotrophomonas*.

Finally, meropenem/vaborbactam may play a role in combination with aztreonam against MBL-producing Enterobacteriaceae and *Stenotrophomonas*. One small in vitro study of eight NDM-producing Enterobacteriaceae showed that aztreonam plus meropenem/vaborbactam was synergistic, similar to aztreonam plus ceftazidime/avibactam, except for co-production of OXA enzymes, against which vaborbactam is not active (Biagi 2019).

Susceptibility Testing and Patient Outcomes

Susceptibility testing should generally be performed when meropenem/vaborbactam is used, particularly if carbapenemase testing is not performed. Against KPC-producing isolates, susceptibility rates are expected to be excellent (greater than 99%). The CLSI susceptibility breakpoint of 4/8 mg/L or less is for Enterobacteriaceae only because there is no established breakpoint against other gram-negative isolates. The susceptibility breakpoint for meropenem alone against *Pseudomonas* is 2 mg/L or less, but this is based on a meropenem dose of 1 g intravenously every 8 hours and cannot be applied to meropenem/vaborbactam with double the dose as an extended infusion.

Meropenem/vaborbactam achieved FDA approval by showing noninferiority to piperacillin/tazobactam in patients with complicated UTIs in the TANGO I randomized trial (Kaye 2018). However, this study included few patients with CRE. This limitation was addressed in the TANGO II randomized trial, which assessed outcomes with meropenem/vaborbactam compared with BAT in 77 patients with CRE of various sources from eight countries (Wunderink 2018). Almost 90% of patients had infections caused by *K. pneumoniae*, 73% of which were KPC producing. Best available therapy included antibiotic combinations in 67% of patients, typically a carbapenem with an aminoglycoside or polymyxin. The meropenem/vaborbactam arm received monotherapy according to protocol. Clinical cure at end of therapy was higher with

meropenem/vaborbactam (66% vs. 33%, $p=0.03$), and upon exclusion of patients with prior antibiotic failure, 28-day all-cause mortality was lower with meropenem/vaborbactam (4% vs. 33%, $p=0.02$). Meropenem/vaborbactam also had fewer adverse events overall, particularly renal adverse events (4% vs. 24%).

Because meropenem/vaborbactam and ceftazidime/avibactam both have potent activity against CRE, one multicenter retrospective study compared these agents in 131 patients (Ackley 2020). In the ceftazidime/avibactam group, 61% received combination therapy compared with only 15% in the meropenem/vaborbactam group. The groups did not differ with respect to clinical success, length of stay, mortality, or adverse events. However, emergence of resistance occurred in 3 of 41 patients (7%) in the ceftazidime/avibactam arm but in none of the 64 patients receiving meropenem/vaborbactam. Although preliminary, these findings suggest that meropenem/vaborbactam has an advantage over ceftazidime/avibactam by means of a higher threshold for the development of resistance. This finding corroborates that in other studies assessing mechanisms of treatment-emergent resistance with these agents (Pogue 2019a). Ceftazidime/avibactam was FDA approved 2 years before meropenem/vaborbactam. Therefore, the difference may arise from the amount of time the agents have been in use to allow for emergence of resistance, but further studies are needed. Continued use of both antibiotics in clinical practice over time will better substantiate or refute this finding, but this remains a note of caution that may differentiate the two agents. In addition, early data suggest CRE with resistance to one agent are still susceptible to the other.

Imipenem/Relebactam

Pharmacology and Dosing

Imipenem is an established antipseudomonal carbapenem co-formulated with cilastatin, a renal dehydropeptidase-1 inhibitor required to prevent the breakdown of imipenem. Imipenem/relebactam is also co-formulated with cilastatin for this reason. Relebactam is a β -lactamase inhibitor of similar chemical structure to avibactam that effectively inhibits ESBL, KPC, and AmpC β -lactamases. In contrast to avibactam, relebactam has minimal activity against any OXA-type β -lactamases, including OXA-48. Relebactam also has no activity against MBLs such as NDM, VIM, IPM, or L1.

The PK/PD properties of imipenem/relebactam are similar to those of imipenem, with efficacy best described by an $fT>MIC$ of imipenem of at least 30% to achieve a 1-log kill. Assuming normal renal function, imipenem/relebactam is dosed at 1.25 g intravenously every 6 hours as a 30-minute infusion and consists of 500 mg of imipenem, 500 mg of cilastatin, and 250 mg of relebactam. This dose has a more than 90% probability of achieving the target $fT>MIC$ of greater than 30% up to an MIC of 2 mg/L (Lucasti 2016). Similar to

previously discussed agents, dose adjustments are required with renal impairment, and imipenem/relebactam is unique because dose reductions are recommended even with CrCl values less than 90 mL/minute.

Spectrum of Activity and Role Against MDR Bacteria

The primary effect of adding relebactam to imipenem is expansion of coverage to include KPC-producing Enterobacteriaceae and many imipenem-nonsusceptible *P. aeruginosa*. This is similar to ceftazidime/avibactam. Of note, imipenem has inherently diminished activity against members of the tribe Proteeae (*Proteus*, *Providencia*, *Morganella*) compared with other carbapenems, which is not alleviated by adding relebactam. In a study of non-Proteeae Enterobacteriaceae, imipenem/relebactam had susceptibility to 78% of imipenem-nonsusceptible isolates (Karlowsky 2019a). Of these isolates, imipenem/relebactam tested susceptible against 96% of KPC-producing isolates. The strains not susceptible to imipenem/relebactam expressed OXA-48 β -lactamases or MBLs or were strains of *Serratia marcescens* against which the agent had low activity. Imipenem/relebactam is therefore an excellent choice against KPC-producing Enterobacteriaceae but should not be used against strains of imipenem-nonsusceptible *Proteus* spp., *Providencia* spp., *Morganella* spp., or *Serratia* spp. or in isolates expressing MBLs (NDM, VIM, IPM) or OXA β -lactamases.

In *P. aeruginosa*, the primary mechanism of imipenem resistance is a combination of porin (OprD) loss and AmpC overexpression, both of which are required for imipenem resistance (Livermore 1992). Adding relebactam therefore expands the activity of imipenem/relebactam against *Pseudomonas* by inhibition of AmpC β -lactamases. In a study of over 3700 clinical isolates of imipenem-nonsusceptible *P. aeruginosa* from 53 countries, 70% of strains were susceptible to imipenem/relebactam at the FDA-approved breakpoint of 2 mg/L or less (Karlowsky 2018). When considering the 251 isolates from within the United States, imipenem/relebactam susceptibility was slightly better at 81% (Lob 2017). Given these findings, imipenem/relebactam is more active than ceftazidime/avibactam against *P. aeruginosa* nonsusceptible to conventional β -lactams at a level similar to that of ceftolozane/tazobactam according to one study (Karlowsky 2020).

As with meropenem/vaborbactam, the combination of aztreonam with imipenem/relebactam is expected to have synergistic activity against MBL-producing isolates, except for co-production of OXA β -lactamases. This has not yet been confirmed in any studies and remains theoretical. Other than the two scenarios of KPC-producing Enterobacteriaceae and imipenem-nonsusceptible *Pseudomonas*, imipenem/relebactam has minimal additional clinical roles. Imipenem/relebactam does not significantly expand on the activity of imipenem against *Acinetobacter* (often OXA producing) or *Stenotrophomonas* (L1 MBL producing).

Susceptibility Testing and Patient Outcomes

Although there are currently no CLSI interpretive criteria for imipenem/relebactam, the FDA-approved susceptibility breakpoints are 1/4 mg/L or less against Enterobacteriaceae and 2/4 mg/L or less against *Pseudomonas*, which are the same breakpoints the CLSI recommends for imipenem alone. When possible, susceptibility testing using an E-test should be performed when imipenem/relebactam is used, particularly against imipenem-nonsusceptible *Pseudomonas*.

Imipenem/relebactam achieved FDA approval by showing noninferiority to imipenem in complicated UTIs and intra-abdominal infections (Sims 2017; Lucasti 2016). As with other agents, these trials lacked significant isolates with imipenem nonsusceptibility, the scenario for which imipenem/relebactam should be reserved. The RESTORE-IMI 1 double-blind, randomized trial included 47 patients with imipenem-nonsusceptible HAP/VAP, complicated UTIs, or intra-abdominal infections (Motsch 2019). Patients were assigned to either imipenem/relebactam or colistin plus imipenem. The most common pathogens were *P. aeruginosa* (77%) primarily expressing AmpC β -lactamases and *Klebsiella* spp. (16%) expressing KPCs. The groups had similar rates of overall favorable response: 71% with imipenem/relebactam and 70% with colistin plus imipenem. However, among the patient subset with *P. aeruginosa*, favorable overall response was higher with imipenem/relebactam (81% vs. 63%), and 28-day all-cause mortality was lower with imipenem/relebactam (10% vs. 30%), as was nephrotoxicity (10% vs. 56%). Further studies with imipenem/relebactam will better clarify its role in clinical practice, particularly compared with other β -lactam/ β -lactamase inhibitor agents.

Cefiderocol

Pharmacology and Dosing

Cefiderocol was FDA approved in November 2019 and is a novel cephalosporin antibiotic with a unique mechanism of action as a siderophore. Iron in humans is highly sequestered and generally protein bound primarily to transferrin. Bacteria infecting or colonizing humans are therefore adapted to survive in relatively iron-deficient environments. A key mechanism by which this adaptation occurs is by siderophores, which are a series of compounds produced by bacteria that act to bind iron and form a siderophore-iron complex that is actively transported into the bacterial cell. Because of its siderophore chemical structure, cefiderocol takes advantage of this mechanism and is actively transported into bacterial cells (colloquially called a Trojan horse mechanism and hence the brand name), in addition to the passive diffusion through porin channels used by other antibiotics. Once inside the cell, the cephalosporin core of cefiderocol has side chains similar to those of cefepime and ceftazidime and binds PBPs and inhibits peptidoglycan biosynthesis similar to these cephalosporins. However, cefiderocol's binding affinities for PBPs are generally higher than for other β -lactams, and its structure is

stable against a broad array of β -lactamases, including KPCs, OXA-type β -lactamases, and MBLs. In addition, cefiderocol's increased uptake into bacterial cells as a siderophore overcomes resistance as a result of porin loss or efflux pumps (Ito 2017). These unique attributes make cefiderocol the broadest-spectrum anti-gram-negative β -lactam on the market.

Cefiderocol's PK/PD properties are similar to those of other β -lactam antibiotics. More than 90% of unchanged drug is eliminated renally, necessitating dose adjustment in moderate to severe renal impairment, and the pharmacodynamic parameter that best predicts activity is the $fT > MIC$. The standard dose is 2 g intravenously every 8 hours as a 3-hour infusion, and it is FDA approved for complicated UTIs, including pyelonephritis. Of interest, a dose increase to 2 g intravenously every 6 hours is recommended for patients with augmented renal clearance with a CrCl of 120 mL/minute or more. An $fT > MIC$ target of 75% or more has achieved a bactericidal effect in animal models. Monte Carlo simulations showed a greater than 90% probability of achieving this target using recommended doses across various degrees of renal function up to an MIC of 4 mg/L, the 2020 CLSI susceptibility breakpoint for Enterobacteriaceae, *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas* (Katsube 2016).

Spectrum of Activity and Role Against MDR Bacteria

Cefiderocol has extremely broad-spectrum activity against an array of notoriously drug-resistant gram-negative aerobic bacteria. Cefiderocol tested susceptible in vitro against 98% of meropenem-nonsusceptible Enterobacteriaceae, *Pseudomonas*, and *Acinetobacter* (Kazmierczak 2019). This activity was preserved against more than 99% of carbapenemase-negative strains and more than 95% of strains positive for the MBLs L1, IPM, and VIM, as well as OXA-type and KPC β -lactamases. Cefiderocol also tested susceptible against 9 of 14 NDM-producing isolates (64%). Of note, cefiderocol's activity remained high against strains with resistance related to porin loss (OprD, OmpK35, OmpK36) and efflux pumps (MexAB-OprM). In a large study of clinical isolates of gram-negative bacteria from North America and Europe, cefiderocol tested susceptible against more than 99% of meropenem-nonsusceptible Enterobacteriaceae, *Pseudomonas*, and *Stenotrophomonas*; 96% of meropenem-nonsusceptible *Acinetobacter*; and 87% of *Burkholderia* (Karlowsky 2019b). Although resistance to cefiderocol is rare, it has been attributed to some combination of β -lactamase overexpression and mutations in bacterial iron transport systems. In a recent study of 9205 isolates, 39 (0.4%) were cefiderocol nonsusceptible, of which 28 were PER-producing (an ESBL) *Acinetobacter* and 5 were NDM producing (Yamano 2019). Of interest, in the 34 non-NDM-producing isolates, the addition of ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem had strong synergistic activity. Synergy with meropenem is likely because of its stability against ESBL enzymes, and synergy with other

agents is likely because of β -lactamase inhibition. This suggests that cefiderocol can be used in combination with ceftazidime/avibactam in the setting of non-NDM-producing Enterobacteriaceae with elevated cefiderocol MICs. However, this finding is preliminary and needs to be clinically evaluated. As a limitation to its spectrum of activity, cefiderocol has minimal to no activity against gram-positive or anaerobic bacteria; hence, its role is exclusively in the management of resistant gram-negative infections.

In contrast to the previously discussed agents, cefiderocol is the only β -lactam with broad activity against bacteria producing OXA-type β -lactamases and MBLs and MDR *Stenotrophomonas maltophilia*, *Acinetobacter* spp., and *Burkholderia* spp. The only isolates with diminished activity were NDM-positive isolates, though activity was still respectable at 64%, and such strains would be better treated with aztreonam/avibactam in the absence of documented cefiderocol susceptibility.

Susceptibility Testing and Patient Outcomes

Because of cefiderocol's mechanism of action, susceptibility testing requires use of iron-depleted cation-adjusted Mueller-Hinton broth as recommended by the CLSI. Use of conventional growth media minimizes bacterial dependence on the siderophore mechanism of iron uptake and results in falsely elevated cefiderocol MICs. The CLSI has set provisional susceptibility breakpoints for cefiderocol of 4 mg/L or less against Enterobacteriaceae, *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas*. This is in contrast to the FDA's susceptibility breakpoints of 2 mg/L or less against Enterobacteriaceae and 1 mg/L or less against *Pseudomonas*. Given a high probability of pharmacodynamic target attainment up to an MIC of 4 mg/L, the reasons for this discrepancy are unclear. Cefiderocol became commercially available in the United States in early 2020, and currently, susceptibility testing can only be performed by reference laboratories. For now, clinicians will have to consider its use in the absence of routine susceptibility testing, though specialized microbiology laboratories may be able to do susceptibility testing. However, cefiderocol susceptibility is highly likely (greater than 90%) outside NDM-producing isolates.

Cefiderocol achieved FDA approval by showing noninferiority to imipenem in adults with complicated UTIs, where bacterial isolates included ESBL producers (Portsmouth 2018). Another trial (APEKS-NP) of adults with HAP/VAP showed cefiderocol to be noninferior to meropenem with isolates predominantly *K. pneumoniae* (31%), *P. aeruginosa* (16%), and *Acinetobacter baumannii* (16%).

The CREDIBLE-CR trial was more akin to scenarios in which cefiderocol is intended and was a randomized, open-label trial comparing cefiderocol with BAT in carbapenem-resistant gram-negative infections. The patient population had 45% HAP/VAP cases, 31% bacteremia or sepsis cases, and 24% complicated UTI cases with a median Acute Physiology and

Chronic Health Evaluation II (APACHE II) score of 15. A total of 101 patients received cefiderocol 2 g intravenously every 8 hours as a 3-hour infusion, and 49 patients received BAT at provider discretion. Monotherapy was received by 83% in the cefiderocol arm compared with just 29% in the BAT group. Of those who received combination therapy, 70% received colistin in combination with tigecycline, ampicillin/sulbactam, or fosfomycin, among others. Baseline demographics were similar between the groups. The microbiologic intent-to-treat population consisted of 118 patients, and *A. baumannii* (46%), *K. pneumoniae* (37%), and *P. aeruginosa* (24%) were the most common pathogens. Clinical cure at test-of-cure was similar across groups at 53% with cefiderocol and 50% with BAT and remained consistent by infectious source. However, all-cause mortality at days 14, 28, and 49 was higher with cefiderocol. Stratified by indication, all-cause mortality at the end of study for cefiderocol versus BAT was higher for nosocomial pneumonia (42% vs. 18%) and bacteremia/sepsis (37% vs. 18%) but lower for complicated UTIs (15% vs. 20%). Of concern, the day 49 mortality difference continued to be higher with cefiderocol than with BAT in the very infections where it is likely to be considered, namely *Acinetobacter* (49% vs. 24%) and *Pseudomonas* (35% vs. 17%), and in sicker patients with an APACHE II score of 16 or more (46% vs. 23%). These findings prompted the FDA-approved labeling for cefiderocol to carry a warning for increased mortality in patients with carbapenem-resistant gram-negative infections. Reasons for the divergent findings of APEKS-NP and CREDIBLE-CR are unclear, but the CREDIBLE-CR included only carbapenem-resistant isolates, had higher baseline mortality, and had a higher incidence of *Acinetobacter*. In addition, CREDIBLE-CR compared primarily cefiderocol monotherapy with combinations of BAT. Nonetheless, reasons for increased mortality with cefiderocol require investigation.

Other than the earlier trials, only a few case reports of its compassionate use have been published in the setting of OXA-positive *Klebsiella*, extensively drug-resistant (XDR) *Acinetobacter*, and NDM-producing *P. aeruginosa* with positive outcomes, though publication bias is likely.

In summary, cefiderocol has exceptional in vitro activity against many gram-negative strains with limited options (Table 1). However, early clinical trials have dampened excitement for cefiderocol, with increased mortality observed in the populations it was primarily intended for. Cefiderocol's role is therefore limited to salvage therapy when other agents are not viable.

NEW TETRACYCLINE ANTIMICROBIALS

Omadacycline

Pharmacology and Dosing

Omadacycline was FDA approved in 2018 and is a novel tetracycline-class antibiotic that is classified as an

Table 1. Comparison of In Vitro Activity of Novel β -Lactam Antibiotics

Drug	Activity Against β -Lactamases						Coverage Against β -Lactam-Resistant ^a Isolates of:					
	KPC	OXA-48	Other OXA	NDM	VIM	IMP	KPC+ CRE	MBL+ CRE	Pseudom	Acineto	Steno	
Ceftolozane/ tazobactam	–	–	–	–	–	–	–	–	+	–	–	
Ceftazidime/ avibactam	+	+	–	–	–	–	+	–	+	–	–	
Meropenem/ vaborbactam	+	–	–	–	–	–	+	–	–	–	–	
Imipenem/ relebactam	+	–	–	–	–	–	+ ^b	–	+	–	–	
Cefiderocol	+	+	+	+/-	+	+	+	+	+	+	+	
Aztreonam/ avibactam	+	+	–	+	+	+	+	+	–	–	+	

^a β -lactam resistant refers to resistance to all of the following: cefepime, ceftazidime, meropenem, imipenem, piperacillin/tazobactam, and ampicillin/sulbactam.

^bException: Imipenem/relebactam has no activity against most imipenem-resistant *Proteus*, *Providencia*, or *Morganella* spp.

Acineto = *Acinetobacter*; CRE = carbapenem-resistant Enterobacteriaceae; IMP = imipenemase-type metallo-beta-lactamase; KPC+ = *K. pneumoniae* carbapenemase positive; MBL+ = metallo- β -lactamase positive; NDM = New Delhi metallo- β -lactamase; OXA = oxacillinase; Pseudom = *Pseudomonas*; Steno = *Stenotrophomonas*; VIM = Verona integron-encoded metallo- β -lactamase.

aminomethylcycline, structurally different from the glycylicycline tigecycline and the fluorocycline eravacycline. As a tetracycline, omadacycline exerts generally bacteriostatic effects by binding to the 16S ribosomal RNA (rRNA) component of the bacterial 30S ribosomal subunit to inhibit protein synthesis. Efflux pumps (Tet(A), Tet(B), Tet(K), Tet(L)) and ribosomal protection proteins (Tet(M), Tet(O)) are common mechanisms of resistance to older-generation tetracyclines such as tetracycline and doxycycline, but omadacycline's structural modifications allow it to evade these common mechanisms of resistance. Unlike tigecycline and eravacycline, omadacycline is more orally bioavailable (35%) and is marketed in both intravenous and oral formulations. Of importance, the oral formulation should be taken on an empty stomach because coadministration with food drastically reduces bioavailability.

As with other tetracyclines, the PK/PD parameter that best predicts omadacycline's in vivo efficacy is the ratio of the 24-hour AUC to the MIC, or AUC_{0-24}/MIC . The target AUC_{0-24}/MIC for omadacycline varies from 23.2 for *Streptococcus pneumoniae* to 59.4 for *K. pneumoniae* (Rodvold 2020). Because of its long half-life of 16–17 hours, omadacycline can be administered once daily but requires a loading dose. For community-acquired bacterial pneumonia (CABP), the recommended dose is a loading dose on day 1 of either 200 mg intravenously over 60 minutes or 100 mg intravenously over 30 minutes every 12 hours. The subsequent maintenance dose is either 100 mg intravenously over 30 minutes once daily or 300 mg

orally once daily. Dosing is similar for the indication of acute bacterial skin structure and skin infections (ABSSSIs) except the loading dose can be administered orally as 450 mg once daily on days 1 and 2 of therapy. Oral administration should be separated by at least 4 hours from the intake of any food, dairy, antacid, multivitamin, or mineral supplement. Omadacycline is generally well tolerated, with the most common treatment-related adverse events being nausea and vomiting. However, omadacycline has a lower incidence of nausea and vomiting than tigecycline, with most events occurring during loading doses with oral administration. Omadacycline requires no dose adjustments in the setting of renal or hepatic impairment. After intravenous administration, 27% is excreted unchanged in the urine, with 14% excreted unchanged after oral administration.

Spectrum of Activity and Role Against MDR Bacteria

Given its FDA-approved indications of CABP and ABSSSIs, omadacycline has broad gram-positive coverage. Omadacycline has excellent in vitro activity against *S. aureus* (including MRSA), streptococci, enterococci (including VRE), *Bacteroides fragilis*, *Clostridioides*, and atypical pathogens. However, omadacycline also has broad gram-negative coverage, including against *Haemophilus influenzae*, *Moraxella catarrhalis*, MDR *Acinetobacter*, and *Stenotrophomonas* as well as non-Proteaeae Enterobacteriaceae, including ESBL-positive

Patient Care Scenario

A 53-year-old man is in your ICU for septic shock requiring mechanical ventilation and vasopressors on admission. He was initiated on cefepime, metronidazole, and vancomycin intravenously empirically. He was admitted to the hospital 1 month ago for a chronic obstructive pulmonary disease exacerbation, and his medical history includes type 2 diabetes. On ICU day 2, both blood cultures and a

urine culture resulted with gram-negative rods. Today, ICU day 3, his renal function has stabilized, but he remains mechanically ventilated on vasopressors with persistent leukocytosis. His current microbiology results are as follows. What antibacterial regimen is best to recommend for this patient?

Blood Culture (2 of 2) Identification: <i>K. pneumoniae</i>			Reflexed Carba-R Assay	
Drug	MIC	Interp	Enzyme	Result
Amikacin	≤ 16	S	IPM	Negative
Aztreonam	> 16	R	KPC	Negative
Cefepime	> 16	R	OXA-48	Positive
Ceftriaxone	> 32	R	VIM	Negative
Ciprofloxacin	0.5	I	NDM	Negative
Ertapenem	> 2	R		
Gentamicin	2	S		
Levofloxacin	1	I		
Meropenem	> 4	R		
Piperacillin/tazobactam	> 64	R		
Tobramycin	≤ 4	S		

ANSWER

The first step is to look at the susceptibility of β -lactams. In this case, all β -lactams are resistant, including ceftriaxone and carbapenems (CRE). Ceftolozane/tazobactam is not an option because it does not cover CRE. Non- β -lactam options are only the aminoglycosides, which would not be appropriate as monotherapy for bacteremia in a critically ill patient. Although the most likely carbapenemase would be KPC, the reflexed Carba-R is positive

for OXA-48, against which meropenem/vaborbactam and imipenem/relebactam are not active. Cefiderocol is likely to be active but should be reserved for salvage therapy. Ceftazidime/avibactam would be best because OXA-48 is inhibited by avibactam. Although the likelihood of susceptibility is high, it should be confirmed, if not, on automated susceptibility panels.

1. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/avibactam, meropenem/vaborbactam, or both? Clinical and formulary considerations. *Clin Infect Dis* 2019;68:519-24.
2. Shortridge D, Pfaller MA, Castanheira M, et al. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. hospitals (2013-2016) as part of the surveillance program: program to assess ceftolozane-tazobactam susceptibility. *Microb Drug Resist* 2018;24:563-77.

strains. Like other tetracyclines, omadacycline does not have reliable in vitro activity against *Pseudomonas*, *Proteus*, *Providencia*, *Morganella*, or *Burkholderia*. In an in vitro study of 49,000 clinical isolates from Europe and the United States, omadacycline inhibited 99% of *S. aureus* (MIC_{50/90} 0.12/0.25 mg/L), including 96% of MRSA, 98% of *S. pneumoniae* (MIC_{50/90} 0.06/0.12 mg/L), and 98% of *Enterococcus* (MIC_{50/90} 0.12/0.25 mg/L) including 96% of VRE (Pfaller 2020). Against gram negatives, omadacycline inhibited 88% of Enterobacteriaceae (excluding *Proteus*), including 76% of ESBL-producing

and 72% of carbapenem-resistant (most likely KPC producing) *Klebsiella* (MIC_{50/90} 2/8 mg/L). Omadacycline was also active against *Acinetobacter* and *Stenotrophomonas* (MIC_{50/90} 4/8 mg/L), but susceptibility rates cannot be determined because breakpoints have not been established. Omadacycline has some activity similar to tigecycline against selected anaerobes. Omadacycline therefore has a broad spectrum of activity and plays a role in the management of VRE and β -lactam-resistant *A. baumannii* and *S. maltophilia*, though susceptibility breakpoints are not established for these pathogens.

The availability of omadacycline as an oral formulation separates it from other options in the management of these pathogens in the setting of MDR.

Another role for omadacycline is in the treatment of MDR nontuberculous mycobacterial infections. Nontuberculous mycobacteria, particularly *M. abscessus*, often require prolonged treatment courses of up to 1 year, and tigecycline has historically played a role in the setting of resistance. However, tigecycline is only available intravenously and has significant dose-limiting adverse effects because of nausea and vomiting; hence, omadacycline has the advantage of an oral formulation with a better tolerability profile. In a recent in vitro study, omadacycline had activity equivalent to, or better than, tigecycline against strains of *M. abscessus*, *M. chelonae*, and *M. fortuitum* (Shoen 2019). In addition, nontuberculous mycobacteria commonly cause pulmonary infections, and omadacycline has around a 3-fold higher AUC than tigecycline in epithelial lining fluid and alveolar cells (Gotfried 2017). Omadacycline is therefore promising to replace tigecycline in the management of MDR nontuberculous mycobacterial infections, but further studies are needed.

Susceptibility Testing and Patient Outcomes

There are currently no interpretive criteria from the CLSI for omadacycline, but there are FDA-approved susceptibility breakpoints, depending on indication. The FDA susceptibility breakpoint of 0.12 mg/L or less applies to *S. pneumoniae* in CABP and to *Staphylococcus lugdunensis*, *S. anginosus*, and *S. pyogenes* in ABSSSI. For CABP, the susceptibility breakpoint for methicillin-susceptible *S. aureus* is 0.25 mg/L or less, whereas for ABSSSI, it is 0.5 mg/L or less for all *S. aureus*, including MRSA. For Enterobacteriaceae, the susceptibility breakpoint is 4 mg/L or less, but this only applies to *K. pneumoniae* for CABP and to *K. pneumoniae* and *Enterobacter cloacae* in ABSSSIs.

Omadacycline was noninferior to linezolid in patients with ABSSSIs in the OASIS-1 and OASIS-2 randomized, double-blind trials (O’Riordan 2019a, 2019b). The two trials were similarly designed except that OASIS-2 used only oral regimens, whereas OASIS-1 used intravenous regimens for at least the first 3 days. Overall success rates were high, including against MRSA and *Enterococcus faecalis*. Nausea and vomiting were more common with omadacycline than with linezolid in OASIS-2 (nausea 30% vs. 8%; vomiting 17% vs. 3%), but rates were similar in OASIS-1 (nausea 12% vs. 10%; vomiting 5% in both groups). Most of the nausea and vomiting events in both groups were transient and mild and occurred primarily with the higher oral loading doses (450 mg once-daily) during the first 2 days with omadacycline in OASIS-2. Other than the oral loading dose, maintenance doses of omadacycline (intravenous or oral) had rates of nausea and vomiting similar to linezolid.

Omadacycline was also noninferior to moxifloxacin in CABP in the OPTIC randomized, double-blind trial (Stets

2019). Dosing was similar to that in OASIS-1, with intravenous administration initially and a possible transition to oral after at least 3 days. Nausea and vomiting occurred in around 2% of patients in both arms, but diarrhea was more common with moxifloxacin (8% vs. 1%). Although rare and not statistically significant, mortality was higher with omadacycline (2.1% vs. 1%). All deaths occurred in patients older than 65. This finding prompted a warning in the FDA-approved labeling for omadacycline regarding higher mortality with omadacycline in CABP and the need for close monitoring in older adult patients.

No clinical studies have evaluated omadacycline in scenarios where it is most likely to be used, namely against VRE, *Acinetobacter*, *Stenotrophomonas*, and nontuberculous mycobacteria. The only exception is a case report of a patient with a pulmonary infection secondary to *M. abscessus* successfully treated with omadacycline 150 mg orally once daily (lower than the FDA-approved dose) in combination with intravenous amikacin and aztreonam for 4 weeks. As omadacycline becomes used in more real-world scenarios, further data may help guide its place in therapy.

Eravacycline

Pharmacology and Dosing

Eravacycline was FDA approved in August 2018 and is a novel fluorocycline-class tetracycline. Similar to omadacycline, eravacycline also has structural modifications that allow evasion of resistance as a result of efflux pumps and ribosomal protection proteins that commonly confer resistance to tetracycline and doxycycline. Although eravacycline has a slightly lower bioavailability than omadacycline (28% vs. 35%), eravacycline is only marketed as an intravenous formulation because of nausea and vomiting with oral administration.

With several doses, eravacycline’s mean steady-state half-life was 20 hours. As with other tetracyclines, the 24-hour free drug $fAUC_{0-24}/MIC$ was the pharmacodynamic parameter that best correlated with efficacy at a target $fAUC_{0-24}/MIC$ of 28–33, depending on the pathogen. The FDA-approved dose of eravacycline is 1 mg/kg intravenously every 12 hours as a 60-minute infusion, and it is available as 50-mg vials. Eravacycline is primarily metabolized by the liver and interacts with CYP3A4 substrates. Renal elimination is low because only 20% is excreted unchanged in the urine. Dose reduction to 1 mg/kg intravenously every 24 hours starting on day 2 is suggested in the setting of severe (Child-Pugh class C) hepatic impairment because of a 110% increase in $AUC_{0-\infty}$. Eravacycline is generally well tolerated, with the most common adverse reactions being infusion site reactions (7.7%), nausea (6.5%), and vomiting (3.7%). Although eravacycline has a large volume of distribution (V_d) of 4 L/kg, it is less than tigecycline’s 7–9 L/kg. Tigecycline carries a warning for increased mortality, particularly with bacteremia, believed to be because of low serum concentrations secondary to its large V_d . Although not expected to be a concern with eravacycline, this has not been evaluated.

Table 2. Comparison of In Vitro Activity of Novel Non-β-Lactam Antibiotics

Drug	ESBL+ CRE	KPC+ CRE	MBL+ CRE	MDR Pseudom	MDR Acineto	MDR Steno	MRSA	VRE
Omadacycline	+ ^a	+ ^a	ND ^a	–	+	+	+	+
Eravacycline	+ ^a	+ ^a	+ ^a	–	+	+	+	+
Plazomicin	+	+	+/-	– ^b	– ^b	–	+	–

^aException: Tetracyclines have little to no activity against *Proteus*, *Providencia*, and *Morganella*.

^bDenotes minimal to no additional activity beyond that of older-generation aminoglycosides such as amikacin.

ESBL = extended-spectrum β-lactamase; MDR = multidrug resistant; ND = no data; VRE = vancomycin-resistant enterococci.

Spectrum of Activity and Role Against MDR Bacteria

Similar to omadacycline, eravacycline has a broad spectrum of activity, including against gram-positive and gram-negative organisms. However, eravacycline has broader anaerobic activity, including against *Bacteroides*, *Clostridioides*, and *Prevotella*. Like other tetracyclines, eravacycline has no appreciable activity against *Pseudomonas*, *Proteus*, *Providencia*, *Morganella*, or *Burkholderia*. Eravacycline has potent activity equivalent to, or 2- to 4-fold greater than, tigecycline against common gram-positive bacteria, including *S. aureus* and MRSA (MIC_{50/90} 0.06/0.12 mg/L), streptococci, and enterococci including VRE (MIC_{50/90} 0.06/0.12 mg/L) as well as non-Proteaceae Enterobacteriaceae, including ESBL-producing and carbapenem-resistant *Escherichia coli* and *Klebsiella* (Zhanell 2018). In addition, eravacycline has lower MICs against *Acinetobacter* and *Stenotrophomonas* than tigecycline and even omadacycline. Against carbapenem-nonsusceptible Enterobacteriaceae and *Acinetobacter*, including KPC- and MBL-producing strains, eravacycline has lower MICs than tigecycline (Livermore 2016). This suggests eravacycline is the most potent tetracycline-class antibiotic against gram-negative pathogens. However, the FDA susceptibility breakpoint for eravacycline against Enterobacteriaceae is lower than that for tigecycline (0.5 mg/L vs. 2 mg/L); subsequently, susceptibility rates are in fact similar (Morrissey 2020). Eravacycline therefore plays a clinical role against VRE and MDR Enterobacteriaceae (excluding *Proteus*, *Providencia*, and *Morganella*) infections, including ESBL-, KPC-, and MBL-producing strains, when novel β-lactams are not options because of anaphylactic β-lactam allergies. Eravacycline is also a reasonable choice against MDR *Acinetobacter* and *Stenotrophomonas*, despite the lack of susceptibility breakpoints, because few agents are options in such scenarios.

Similar to omadacycline, eravacycline may also play a role in the treatment of nontuberculous mycobacteria. The only study to investigate this was an in vitro comparison of tigecycline, omadacycline, and eravacycline against 28 drug-resistant isolates of *Mycobacterium abscessus*. Eravacycline

consistently had the lowest MICs, by 1 or 2 dilutions, against these strains compared with the other tetracyclines. In addition, eravacycline and omadacycline achieve higher serum concentrations than tigecycline, and omadacycline also has lower plasma protein binding; hence, both agents are likely to attain higher fAUC₀₋₂₄/MIC targets. Although omadacycline has an oral option, eravacycline remains a viable choice for treating drug-resistant nontuberculous mycobacteria, and further studies are warranted.

Susceptibility Testing and Patient Outcomes

The CLSI has no interpretive criteria for eravacycline, but the FDA-approved susceptibility breakpoints are 0.06 mg/L or less against gram positives (*S. aureus*, *Enterococcus*, and *S. anginosus* group) and 0.5 mg/L or less against non-Proteaceae Enterobacteriaceae and anaerobes.

Eravacycline achieved FDA approval for complicated intra-abdominal infections by showing noninferiority to ertapenem in the IGNITE1 and to meropenem in the IGNITE4 randomized, double-blind trials (Solomkin 2019, 2017). Cure rates were high even for pathogens against which the agents lacked in vitro activity. For instance, cure rates were high in carbapenem arms against carbapenemase producers and in eravacycline and ertapenem arms against *Pseudomonas*. This was likely because of adequate source control, given that intra-abdominal abscess was common in both trials. Eravacycline had higher rates of nausea (8.1% vs. 0.7% in IGNITE1 and 4.8% vs. 0.8% in IGNITE4) and phlebitis (3% vs. 0.4% in both trials). Rates of vomiting and serious adverse events were similar across groups. Eravacycline did not receive FDA approval for the indication of complicated UTIs because it failed to show noninferiority against levofloxacin in the IGNITE2 and IGNITE3 trials. The IGNITE2 compared eravacycline 1.5 mg/kg intravenously every 24 hours or levofloxacin 750 mg intravenously every 24 hours, with step-down to oral administration (eravacycline 200 mg orally every 12 hours and levofloxacin 750 mg orally daily) after 3 days. Cure rates with eravacycline and levofloxacin were 60% and 67%, respectively, and eravacycline failed to show noninferiority. However, in a subset of

patients who only received intravenous therapy, eravacycline had similar cure rates. This prompted the IGNITE3 trial, which compared eravacycline 1.5 mg/kg intravenously every 24 hours with ertapenem 1 g intravenously every 24 hours, without an oral step-down option. However, eravacycline again failed to show noninferiority with a cure rate of 85% compared with 95% with ertapenem. Likely reasons for failure in the setting of UTIs are low urinary elimination (20%) and once-daily dosing at a lower daily dose than the FDA-approved dose. Given these findings, eravacycline should not be used in the setting of UTIs. However, eravacycline remains a viable option against MDR infections such as *Acinetobacter* and *Stenotrophomonas* from non-urinary sources, where no agents have been clinically evaluated (except for cefiderocol, with increased mortality in this setting).

NEW AMINOGLYCOSIDE ANTIMICROBIALS

Plazomicin

Pharmacology and Dosing

Plazomicin is a novel aminoglycoside that inhibits bacterial protein synthesis by binding to the 16S rRNA of the 30S ribosomal subunit. Plazomicin separates from older-generation aminoglycosides by key structural differences that allow plazomicin to evade almost all aminoglycoside-modifying enzymes that confer resistance to other aminoglycosides. An exception is the aminoglycoside-modifying enzyme *N*-acetyltransferase (2')-I of *Providencia stuartii*, which confers resistance to many aminoglycosides, including plazomicin. Aminoglycoside-modifying enzymes are the most common mechanism of aminoglycoside resistance in Enterobacteriaceae; hence, plazomicin expands on the activity of other aminoglycosides in this setting. However, aminoglycoside resistance in *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas* is often mediated by efflux pumps or reduced outer membrane permeability against which plazomicin has no advantage over older aminoglycosides. In addition, 16S rRNA methyltransferases can modify the ribosome to result in resistance to all aminoglycosides, including plazomicin. Although β -lactamases do not directly affect aminoglycosides, these methyltransferases are particularly common in isolates expressing MBLs; thus, plazomicin activity is diminished in this setting.

The PK/PD parameter that best predicts the efficacy of plazomicin is the AUC_{0-24}/MIC ratio. Although the efficacy of aminoglycosides was previously believed to correlate best with the C_{max}/MIC ratio, there has been a shift toward AUC_{0-24}/MIC as the best predictor for aminoglycosides (Bland 2018). Pharmacodynamic modeling identified AUC_{0-24}/MIC values of 24 and 85 for bacterial stasis and a 1-log CFU reduction, respectively. Monte Carlo simulations showed a more than 90% probability of achieving these AUC_{0-24}/MIC targets up to an MIC of 2 mg/L for a 1-log CFU reduction or

up to an MIC of 4 mg/L for stasis using FDA-approved dosing (Bhavnani 2018). The standard dose of plazomicin is 15 mg/kg intravenously every 24 hours as a 30-minute infusion. As with other aminoglycosides, the dosing weight should be total body weight unless total weight exceeds 125% of ideal body weight, in which case adjusted body weight with a correction factor of 0.4 should be used. Plazomicin is almost exclusively renally eliminated (98% unchanged), and dose adjustments are recommended with CrCl values less than 60 mL/minute. Therapeutic drug monitoring is recommended if CrCl values are less than 90 mL/minute to maintain trough concentrations below 3 mcg/mL. The FDA-approved labeling recommends extending the dosing interval by 1.5-fold if trough concentrations exceed 3 mcg/mL, but pharmacists comfortable with pharmacokinetic dosing should consider estimating AUC and targeting an AUC_{0-24}/MIC of 80–100 in patients with serious infections. Although not formally evaluated, such a dosing strategy is likely to achieve PK/PD targets. This can be achieved by obtaining two plasma concentrations and extrapolating AUC or by obtaining one plasma concentration interpreted with Bayesian modeling software. A key limitation is that therapeutic drug monitoring of plazomicin is unavailable at most institutions, and timely attainment of serum concentrations is an impediment to its clinical use, particularly in the setting of renal impairment. As with other aminoglycosides, plazomicin labeling carries warnings for nephrotoxicity, ototoxicity, neuromuscular blockade, and teratogenicity.

Spectrum of Activity and Role Against MDR Bacteria

In a large study of 4680 clinical isolates in Europe, plazomicin had excellent activity against most Enterobacteriaceae, including ESBL producers and CRE. At the FDA susceptibility breakpoint of 2 mg/L or less, plazomicin tested susceptible against 99% of *E. coli*, 97% of *Klebsiella*, 100% of *Enterobacter*, 93% of *Serratia*, and 99% of *Citrobacter* (Castanheira 2018). Plazomicin had diminished activity against *Morganella* (69%), *Providencia* (68%), and *Proteus mirabilis* (75%). Almost 85% of CRE were susceptible to plazomicin, including 93% of KPC producers, 87% of OXA-48 producers, and 95% of carbapenemase-negative isolates. By comparison, gentamicin and amikacin were only active against 43% and 34% of CRE, respectively. Plazomicin activity was much lower (42%) against MBL-producing Enterobacteriaceae, which was identified as being the result of a higher frequency of ribosomal methyltransferase expression in these isolates. In a separate analysis of pooled data from various worldwide studies, including 488 MBL-producing isolates (58% NDM; 37% VIM), plazomicin susceptibility was as high as 76% but still much lower than with KPC- or OXA-mediated resistance (Serio 2019). Plazomicin's activity against MBL-producing Enterobacteriaceae therefore likely varies from one country or region to another. Plazomicin did not appreciably expand

on the antipseudomonal activity of amikacin, but at an MIC of 2 mg/L or less, plazomicin inhibited only 40% of *Acinetobacter*, which was significantly worse than with other aminoglycosides, though there are no established interpretive breakpoints. Plazomicin had some activity against *Staphylococcus* spp. as well, including MRSA. Similar to other aminoglycosides, plazomicin has little to no activity against streptococci, enterococci, *S. maltophilia*, and anaerobes. Plazomicin therefore plays a role against CRE, particularly KPC- and OXA-positive isolates, in the setting of UTIs when aminoglycoside monotherapy is reasonable and the pathogen is non-susceptible to older aminoglycosides. Plazomicin's activity against MBL-positive CRE appears variable and would need confirmed susceptibility before being considered. However, plazomicin has no place in therapy against MDR *Pseudomonas*, *Acinetobacter*, or *Stenotrophomonas*, against which older aminoglycosides have similar or better activity.

Susceptibility Testing and Patient Outcomes

Susceptibility testing is currently available by disk diffusion, by E-test, or on the Sensititre automated susceptibility platform, but not on VITEK 2 or MicroScan. There are no interpretive criteria from the CLSI, but the FDA susceptibility breakpoint against Enterobacteriaceae is 2 mg/L or less. Susceptibility testing should generally be performed if plazomicin is used in a clinical setting, particularly against MBL-producing isolates.

Plazomicin received FDA approval after showing non-inferiority to meropenem for complicated UTIs, including pyelonephritis, in the EPIC randomized, double-blind trial (Wagenlehner 2019). Of note, therapeutic drug monitoring was not performed in this trial. The composite outcome of clinical cure and microbiologic eradication at test-of-cure was higher with plazomicin (82% vs. 70%). This was driven by increased microbiologic eradication with plazomicin in isolates nonsusceptible to at least one aminoglycoside (79% vs. 69%) and in ESBL-positive isolates (82% vs. 75%). In addition, microbiologic recurrence at 24–32 days of follow-up was lower with plazomicin at 3.7% than with meropenem at 8.1%. Overall rates of adverse events were similar, but more patients receiving plazomicin had an increase in SCr of at least 0.5 mg/dL (7% vs. 4%).

The open-label CARE trial included 37 patients with CRE bacteremia, HAP, or VAP randomized to either plazomicin 15 mg/kg intravenously once daily or colistin 5 mg/kg of colistin base activity intravenously every 8–12 hours, both in combination with meropenem or tigecycline for 7–14 days (McKinnell 2019). Plazomicin was dosed to achieve an AUC_{0-24} of 200–400 mg × hour/L of between 75% and 150% of a target AUC_{0-24} of 262 mg × hour/L. All-cause 28-day mortality or clinically significant disease-related complications were lower with plazomicin: 4 of 17 (24%) compared with 10 of 20 (50%) with colistin. Among patients with bacteremia, this outcome was again lower with plazomicin at 2 of 14 (14%) than with

colistin at 8 of 15 (53%). Cumulative probability of survival at day 60 favored plazomicin (HR 0.47; 95% CI, 0.19–1.19). Finally, 2 of 12 patients (17%) with plazomicin experienced a 0.5-mg/dL or more increase in SCr compared with 8 of 16 (50%) with colistin.

In summary, plazomicin has high cure rates as monotherapy similar to meropenem in complicated UTIs, including ESBL-positive infections. Although outcomes in CRE bacteremia and HAP/VAP are encouraging, sample sizes were small. In addition, plazomicin would need to be used in combination with other agents for non-urinary sources of infection when aminoglycoside monotherapy is not indicated. As such, plazomicin can be considered as a narrower-spectrum β -lactam-sparing option for UTIs caused by ESBL- or KPC-positive Enterobacteriaceae, though alternative agents are still preferred to plazomicin because of the difficulty in obtaining timely therapeutic drug monitoring.

CLINICAL APPROACH AND FORMULARY CONSIDERATIONS

The agents discussed in this chapter each have a unique fit into the armamentarium of antibiotics to treat drug-resistant infections. As is common in infectious diseases, there is, and likely will continue to be, a paucity of high-quality randomized trials comparing these agents in scenarios where they are most needed. As such, the approach to select the best antibiotic on the basis of clinical scenarios requires collaboration with microbiology laboratories and an in-depth knowledge of each agent's underlying pharmacology and ability to overcome resistance mechanisms. Figure 1 provides a summary of a practical approach.

Although several agents have potent activity against KPC-producing CRE, meropenem/vaborbactam is likely the best choice among them. Ceftazidime/avibactam decreases in preference because it appears to have a higher propensity to develop resistance than meropenem/vaborbactam, and imipenem/relebactam's limitation is its diminished activity against *Proteus*, *Providencia*, and *Morganella*. Although cefiderocol is reasonable, the signal of increased mortality compared with colistin-based regimens in the CREDIBLE-CR randomized trial is of concern. In addition, randomized controlled trials have found meropenem/vaborbactam and imipenem/relebactam to have reduced mortality and renal adverse events compared with colistin- and aminoglycoside-based regimens against KPC-producing CRE. Although ceftazidime/avibactam has had similar findings, its evidence is limited to observational studies. These β -lactams are therefore preferred to other classes. However, eravacycline (for non-urinary sources) or plazomicin (for UTIs) is reasonable in patients intolerant of β -lactams.

For MBL-producing CRE, ceftazidime/avibactam plus aztreonam is the best choice among the agents discussed in this chapter, with aztreonam/avibactam likely taking

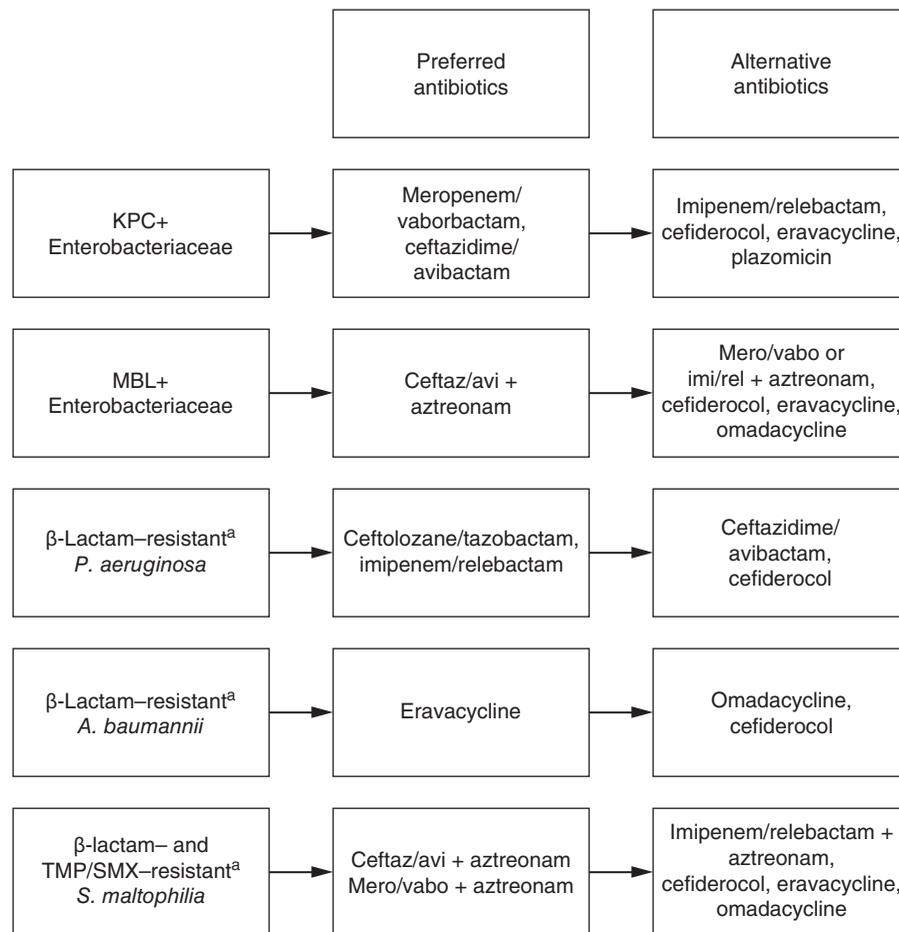


Figure 1. General approach to management of extensively drug-resistant (XDR) pathogens.

^a β -Lactam-resistant refers to resistance to all of the following: cefepime, ceftazidime, meropenem, imipenem, piperacillin/tazobactam, and ampicillin/sulbactam.

KPC = *K. pneumoniae* carbapenemase; MBL = metallo- β -lactamase; TMP/SMX = trimethoprim/sulfamethoxazole; VRE = vancomycin-resistant enterococci.

Information from: author's practice where data from comparative trials are unavailable. For rationale, see relevant sections in text.

its place once it becomes commercially available. This particular aztreonam combination is favored over that with meropenem/vaborbactam or imipenem/relebactam because of a larger body of in vitro evidence and its unique ability to cover OXA-48 β -lactamases. Cefiderocol again is hampered by the concern for increased mortality, and alternatives in patients intolerant of β -lactams include eravacycline and omadacycline for non-urinary sources. On a related note, for XDR *Stenotrophomonas* infections, aztreonam plus either ceftazidime/avibactam or meropenem/vaborbactam is equally viable to cover the pathogen's L1 MBL and L2 serine- β -lactamase. Imipenem/relebactam is considered secondary because its activity in combination with aztreonam has not yet been evaluated. Cefiderocol, eravacycline, and,

to a lesser extent, omadacycline are alternatives for XDR *Stenotrophomonas*.

Pseudomonas should be treated with a dose-optimized conventional β -lactam (cefepime, piperacillin/tazobactam, meropenem), if susceptible. Serious infections with strains nonsusceptible to typical β -lactams are best treated with ceftolozane/tazobactam or imipenem/relebactam. Both agents have similar and high susceptibility rates (around 70%–80%) against such strains of *P. aeruginosa* that are only lower than those with cefiderocol, which is again considered an alternative because of concern for increased mortality. Ceftazidime/avibactam is reasonable against *P. aeruginosa* if susceptibility is confirmed, but its likelihood of susceptibility is lower than that of the aforementioned agents. Of note,

imipenem/relebactam has the best evidence to support its use against imipenem-resistant *P. aeruginosa* because this was the primary pathogen (77%) in the RESTORE-IMI randomized trial in which the agent reduced mortality.

Options are particularly limited against *Acinetobacter* non-susceptible to conventional β -lactams (ampicillin/sulbactam, ceftazidime, meropenem). Cefiderocol appeared poised to fill this void because of unparalleled in vitro susceptibility (96%), but CREDIBLE-CR identified higher mortality than with colistin-based combinations in this scenario. Subsequently, the best choice for β -lactam-resistant *Acinetobacter* is eravacycline because of its better in vitro susceptibility rates compared with omadacycline. However, no studies have yet described clinical outcomes in this setting. As such, patients with serious *Acinetobacter* infections nonsusceptible to conventional β -lactams are best treated using combination therapy with a novel agent plus ampicillin/sulbactam, aminoglycosides, or colistin, depending on susceptibility results.

Considering the earlier factors, most institutions that encounter such XDR pathogens should have several agents on their formularies. Costs should be considered and negotiated by individual institutions, but, except for eravacycline, the average wholesale prices for 1 day of intravenous therapy with novel agents approach or exceed U.S. \$1000, as shown in Table 3.

In addition to costs, institutions should consider the local epidemiology of antimicrobial resistance. *Pseudomonas*, including resistant strains, tends to be common at most medium to large institutions; hence, ceftolozane/tazobactam should be on most formularies because it has the highest susceptibility rates other than cefiderocol. Although imipenem/relebactam can be considered, it is more expensive,

is dosed more frequently, and has a higher risk of seizures. Encountering KPC-producing Enterobacteriaceae is also likely in the United States; hence, meropenem/vaborbactam or ceftazidime/avibactam should be on most formularies. Meropenem/vaborbactam appears more stable to development of resistance, but ceftazidime/avibactam covers many XDR *Pseudomonas* isolates. It is probably prudent to have meropenem/vaborbactam on formulary while reserving case-by-case nonformulary consideration of ceftazidime/avibactam for patients with coinfections of XDR *Pseudomonas* and KPC-positive CRE. However, ceftazidime/avibactam may be the better formulary choice for institutions with a notable incidence of OXA-48 β -lactamases. It is therefore critical for institutions that regularly encounter CRE to implement methods to rapidly detect specific carbapenemases such as the Carba-R assay or the Verigene gram-negative panels. After decisions on these β -lactam/ β -lactamase inhibitors, eravacycline or omadacycline may be considered for formularies. Although omadacycline has the advantage of an oral option, eravacycline is probably the better choice because it is more potent against *Acinetobacter* and *Stenotrophomonas* and less expensive. The role of cefiderocol on formularies is unclear. As the most expensive agent with concern for increased mortality, cefiderocol may best be reserved for nonformulary salvage therapy. Plazomicin is a tempting β -lactam-sparing option for UTIs caused by KPC CRE in the setting of resistance to other aminoglycosides. However, the uncertain availability of therapeutic drug monitoring and susceptibility testing hinders its formulary addition. Ultimately, formulary decisions will need careful review of local resistance patterns in consultation with microbiologists and pharmacists with specialized infectious disease training.

Table 3. Comparison of AWP of 1 Day of IV Therapy

Drug	Dose for Daily Cost Estimation	AWP for 1 Day (\$)
Ceftolozane/tazobactam	3 g IV q8hr (6 × 1.5-g vial)	901
Ceftazidime/avibactam	2.5 g IV q8hr (3 vials)	1291
Meropenem/vaborbactam	4 g IV q8hr (6 × 2-g vial)	1188
Imipenem/relebactam	1.25 g IV q6hr (4 vials)	1284
Cefiderocol	2 g IV q8hr (2 × 1-g vial)	1320
Omadacycline	100 mg IV q12hr (2 vials)	828
Eravacycline ^a	1 mg/kg IV q12hr (2 × 50-mg vial)	235
Plazomicin ^a	15 mg/kg IV q24hr (2 × 500-mg vial)	756

^aBody weight = 70 kg was assumed for cost estimation purposes.

AWP = average wholesale price; IV = intravenous; q = every.

Information from: Red Book Online. Ann Arbor, MI: Truven Health Analytics. Accessed April 8, 2020.

Practice Points

- Management of KPC-producing CRE has been revolutionized as ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/relebactam have reduced mortality and renal adverse events than previous standards of care.
- In addition to KPC, ceftazidime/avibactam and imipenem/relebactam cover most carbapenem-resistant *Pseudomonas*, whereas meropenem/vaborbactam does not.
- Ceftazidime/avibactam is the only β -lactam/ β -lactamase inhibitor available that inhibits OXA-48 (but not other OXA) carbapenemases.
- Ceftolozane/tazobactam is the best β -lactam option to target *Pseudomonas* resistant to conventional β -lactams.
- Cefiderocol is the only β -lactam with in vitro activity that includes MBLs, OXA carbapenemases, and XDR *Acinetobacter*. However, cefiderocol was associated with increased mortality compared with colistin-based regimens against these highly drug-resistant infections.
- Ceftazidime/avibactam in combination with aztreonam is highly synergistic and can be used against MBL-producing CRE and XDR *Stenotrophomonas*. Meropenem/vaborbactam and imipenem/relebactam can also be used with aztreonam; however, they are narrower in spectrum than ceftazidime/avibactam because of the lack of OXA-48 activity.
- Eravacycline and omadacycline have similar spectrums of activity, including against MRSA, VRE, *Acinetobacter*, and *Stenotrophomonas*, though eravacycline is more potent in vitro against gram negatives, and omadacycline is available as an oral formulation.
- Serious infections caused by *Acinetobacter* are best treated with eravacycline in combination with ampicillin/sulbactam, aminoglycosides, or colistin.
- Eravacycline failed to show noninferiority to levofloxacin for complicated UTIs, and tetracyclines as a class are best avoided in UTIs.
- Plazomicin has potent activity against CRE, including against strains resistant to other aminoglycosides. However, plazomicin performs worse than other aminoglycosides against *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas*.

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Self-Assessment Questions

1. A 52-year-old woman is admitted to the ICU with septic shock. Her medical history includes recurrent UTIs, hypertension, depression, and bladder outlet obstruction, for which she had a nephrostomy tube placed 6 months ago. She was discharged from the hospital 5 weeks ago after being treated for an *E. coli* UTI with ceftriaxone. She has been receiving intravenous cefepime, vancomycin, and ciprofloxacin for the past 2 days since admission and is still receiving norepinephrine for hemodynamic support. Her urine culture is positive for *E. coli*, as are her blood cultures (2 of 2). Susceptibilities are pending, but the Verigene BC-GN test on the blood isolate is positive for *E. coli* and CTX-M (an extended-spectrum β -lactamase [ESBL] enzyme). Which one of the following is best to recommend for this patient?
 - A. Discontinue vancomycin and ciprofloxacin. Continue cefepime.
 - B. Discontinue cefepime, vancomycin, and ciprofloxacin. Initiate ceftolozane/tazobactam.
 - C. Discontinue cefepime, vancomycin, and ciprofloxacin. Initiate ceftazidime/avibactam.
 - D. Discontinue cefepime, vancomycin, and ciprofloxacin. Initiate ertapenem.
2. A hemodynamically stable patient with normal renal function is being treated for ventilator-associated pneumonia (VAP). The patient's tracheal aspirate results are as follows:

Drug	<i>P. mirabilis</i>		<i>P. aeruginosa</i>	
	MIC	Interpretation	MIC	Interpretation
Amikacin	≤ 16	S	≤ 16	S
Aztreonam	> 16	R	> 16	R
Cefepime	> 16	R	32	R
Ceftazidime/avibactam	≤ 8/4	S	16/4	R
Ceftolozane/tazobactam	≤ 2/4	S	8/4	I
Ceftriaxone	> 32	R		
Ciprofloxacin	1	R	> 2	R
Ertapenem	≤ 0.5	S		
Gentamicin	2	S	8	I
Levofloxacin	1	I	> 4	R
Meropenem	≤ 1	S	> 8	R
Piperacillin/tazobactam	16/4	S	> 64/4	R
Tobramycin	≤ 4	S	≤ 4	S

Which one of the following is best to recommend for this patient?

- A. Ertapenem 1 g intravenously every 24 hours infused over 30 minutes plus tobramycin 7 mg/kg intravenously every 24 hours
 - B. Ceftolozane/tazobactam 3 g intravenously every 8 hours infused over 4 hours
 - C. Meropenem 2 g intravenously every 8 hours infused over 3 hours plus tobramycin 7 mg/kg intravenously every 24 hours
 - D. Imipenem/relebactam 1.25 g intravenously every 6 hours infused over 30 minutes
3. A man was discharged from the hospital 5 weeks ago after receiving an adequate course of ceftazidime/avibactam for bacteremia caused by carbapenem-resistant *K. pneumoniae*. He is now back to the hospital in septic shock, and his blood cultures are again positive for *K. pneumoniae*, with susceptibilities pending. Which one of the following is best to recommend empirically for this patient?
 - A. Ceftazidime/avibactam
 - B. Meropenem/vaborbactam
 - C. Cefiderocol
 - D. Meropenem plus colistin
 4. A 52-year-old man presents with abdominal pain, fever, and a liver abscess secondary to a liver biopsy performed 2 weeks ago. Abscess fluid culture grows *Morganella morganii* resistant to all conventional agents tested on automated susceptibility testing. Tests for susceptibility to novel agents have been sent to a reference laboratory. Which one of the following is best to recommend for this patient while awaiting these results?
 - A. Omadacycline
 - B. Imipenem/relebactam
 - C. Meropenem/vaborbactam
 - D. Extended-infusion meropenem plus plazomicin
 5. A ventilator-dependent patient presents from a nursing home with increased ventilator requirements and purulent secretions from his tracheostomy tube. His tracheal aspirate culture grows *P. aeruginosa* resistant to all conventional agents on automated susceptibility testing. Susceptibility testing to novel agents is unavailable at your rural community hospital. Which one of the following is best to recommend to treat this patient's VAP?
 - A. Ceftazidime/avibactam
 - B. Meropenem/vaborbactam
 - C. Ceftolozane/tazobactam
 - D. Cefiderocol

6. A patient has pyelonephritis caused by an isolate of *S. maltophilia* resistant to trimethoprim/sulfamethoxazole, β -lactams, and fluoroquinolones. Which one of the following is best to recommend for this patient?
- Plazomicin
 - Meropenem/vaborbactam
 - Ceftazidime/avibactam plus aztreonam
 - Eravacycline
7. During a patient care discussion, the attending physician asks for your guidance in explaining the role of novel antibacterials and their role against extensively drug-resistant (XDR) *P. aeruginosa*. Which one of the following best evaluates the broadened spectrum of activity of novel antibacterial agents against *P. aeruginosa*?
- Meropenem/vaborbactam significantly expands on the activity of meropenem.
 - Imipenem/relebactam significantly expands on the activity of imipenem.
 - Eravacycline significantly expands on the activity of minocycline.
 - Plazomicin significantly expands on the activity of amikacin.
8. For many novel β -lactam agents, adding a β -lactamase inhibitor confers expanded activity against *P. aeruginosa*. Which one of the following best matches the agent to the mechanism by which this is achieved?
- Ceftazidime/avibactam has expanded antipseudomonal activity because avibactam inhibits the AmpC β -lactamases often responsible for ceftazidime resistance in *P. aeruginosa*.
 - Ceftolozane/tazobactam has expanded antipseudomonal activity because tazobactam inhibits the AmpC β -lactamases often responsible for ceftolozane resistance in *P. aeruginosa*.
 - Meropenem/vaborbactam has expanded antipseudomonal activity because vaborbactam inhibits the *K. pneumoniae* carbapenemase (KPC) β -lactamases often responsible for meropenem resistance in *P. aeruginosa*.
 - Imipenem/relebactam has expanded antipseudomonal activity because relebactam inhibits the KPC β -lactamases often responsible for imipenem resistance in *P. aeruginosa*.
9. Because your institution has a high rate of carbapenem-resistant Enterobacteriaceae (CRE), the Carba-R assay was incorporated 2 years ago into the routine microbiology workflow for CRE. Reviewing all CRE cases since its incorporation reveals carbapenemase identification as 69% KPC, 24% OXA-48, 6% Verona integron-based metallo- β -lactamase (VIM), and 1% carbapenemase negative.

Which one of the following is best to recommend for formulary addition for CRE infections?

- Ceftolozane/tazobactam
 - Meropenem/vaborbactam
 - Imipenem/relebactam
 - Ceftazidime/avibactam
10. A patient presents with bacterial peritonitis caused by an isolate of *Proteus vulgaris* that is positive for KPC on the Carba-R assay. Susceptibility testing to novel agents is pending. Which one of the following is best to recommend for this patient?
- Plazomicin
 - Eravacycline
 - Imipenem/relebactam
 - Meropenem/vaborbactam
11. The antimicrobial stewardship committee at a large academic medical center identifies a relatively high incidence of β -lactam-nonsusceptible gram-negative infections and intends to add some combination of novel antibacterials to its formulary, together with clinical pathways to guide prescribers to their appropriate use. To make an informed decision, the microbiologist runs a report of all non-urinary gram-negative isolates that tested nonsusceptible to all conventional β -lactams in the past year with the following results:
- | | |
|---------------------------------|------------------|
| Total No. of Isolates | 537 |
| Enterobacteriaceae | 172 of 537 (32%) |
| Carba-R results of this subset: | |
| KPC | 99% |
| VIM | 1% |
| OXA-48 | 0 |
| IMP | 0 |
| NDM | 0 |
| <i>P. aeruginosa</i> | 256 of 537 (48%) |
| <i>A. baumannii</i> | 89 of 537 (17%) |
| <i>S. maltophilia</i> | 20 of 537 (4%) |
| <i>Burkholderia cepacia</i> | 0 |
- Considering the clinical use of novel agents and their associated costs, which one of the following combinations of agents and associated clinical pathways would be best suited for formulary addition against β -lactam-nonsusceptible isolates?
- Meropenem/vaborbactam for KPC-positive Enterobacteriaceae, ceftolozane/tazobactam for *P. aeruginosa*, and eravacycline for *A. baumannii* and *S. maltophilia*

- B. Cefiderocol for all β -lactam–nonsusceptible gram-negative infections
- C. Imipenem/relebactam for KPC-positive Enterobacteriaceae and *P. aeruginosa* and omadacycline for *A. baumannii* and *S. maltophilia*
- D. Ceftazidime/avibactam for KPC-positive Enterobacteriaceae and *P. aeruginosa* and cefiderocol for *A. baumannii* and *S. maltophilia*
12. A 48-year-old man currently receives plazomicin 900 mg intravenously every 24 hours as a 30-minute infusion for pyelonephritis caused by KPC-positive *K. pneumoniae*. Thirty minutes before his second dose, the plazomicin trough concentration is 5.2 mcg/mL. According to FDA-approved labeling, which one of the following is best to recommend for this patient?
- A. Continue plazomicin 900 mg intravenously every 24 hours.
- B. Change to plazomicin 600 mg intravenously every 24 hours.
- C. Change to plazomicin 600 mg intravenously every 36 hours.
- D. Change to plazomicin 900 mg intravenously every 36 hours.
13. The antimicrobial stewardship committee is deciding between cefiderocol, eravacycline, and omadacycline for formulary addition to have an option against XDR *A. baumannii*. Which one of the following best pairs the agent with its appropriate rationale for formulary addition?
- A. Cefiderocol should be added because it was associated with a trend toward decreased mortality in clinical trials that included patients with infections caused by *A. baumannii*.
- B. Eravacycline should be added because it has lower MICs against *A. baumannii* than omadacycline and is the least expensive option.
- C. Omadacycline should be added because it is available for oral administration and has shown noninferiority in clinical trials that included patients with infections caused by *A. baumannii*.
- D. The least-expensive agent should be selected because they all have similar in vitro activity but currently lack clinical data in infections caused by *A. baumannii*.
14. Despite awareness of in vitro data, an infectious disease physician is skeptical of the combination of ceftazidime/avibactam plus aztreonam against *S. maltophilia* and wants to understand the rationale behind this combination. Which one of the following is best to share with this colleague regarding how this combination overcomes resistance in *S. maltophilia*?
- A. *S. maltophilia* develops resistance to either aztreonam or ceftazidime/avibactam by up-regulated efflux pumps. In combination, however, avibactam preferentially saturates the efflux pumps, thereby restoring the activity of aztreonam.
- B. Aztreonam preferentially saturates the metallo- β -lactamase (MBL) of *S. maltophilia*, thereby enabling ceftazidime/avibactam to become active against its remaining KPC β -lactamases.
- C. *S. maltophilia* typically expresses an MBL and other enzymes such as ESBL or AmpC. In combination, ceftazidime/avibactam inhibits the ESBL/AmpC enzymes, thereby enabling aztreonam to become active because it is inherently stable against MBLs.
- D. Aztreonam is typically hydrolyzed by the AmpC β -lactamase of *S. maltophilia*, whereas ceftazidime becomes inactive as a result of efflux pumps. In combination, however, avibactam inhibits the AmpC enzyme, thereby restoring the activity of aztreonam.
15. You receive notification of a prescriber ordering plazomicin for a patient with a UTI. On reviewing the patient's case, you note that plazomicin was chosen because of an NDM-positive urinary isolate of *K. pneumoniae* and that susceptibility to plazomicin is unavailable. Which one of the following points is best to share with this colleague regarding why plazomicin may not be the best choice in this scenario?
- A. MBLs also have crossover ability to hydrolyze aminoglycosides, including plazomicin.
- B. Isolates expressing MBLs often coexpress ribosomal methyltransferases, conferring plazomicin resistance.
- C. MBL-producing CRE often coexpress efflux pumps that decrease intracellular plazomicin concentrations, conferring resistance.
- D. Isolates expressing MBLs often have thickened cell walls that decrease the entry of plazomicin into the cell, diminishing its ability to reach its target site.