ABSTRACT
Antimicrobial resistance has been identified by the World Health Organization as “one of the three greatest threats to human health.” Gram negative bacteria in particular drive this alarming trend. Carbapenem-resistant Enterobacteriaceae (CRE) such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* species are of particular importance as they are associated with poor clinical outcomes and are common causes for a variety of infections including bacteremia, urinary tract infection, intra-abdominal infections and pneumonia. CRE are difficult to treat as carbapenem resistance is often accompanied by resistance to additional drug classes. For example, CRE may be extensively drug resistant or even pandrug resistant. Unfortunately, CRE infections have increased over the past 15 y while new and effective antibiotics have not kept pace. Recently, however, new agents have become available to help treat CRE infection, and several more are under development. This article reviews the efficacy, safety, and pharmacokinetic issues around 4 emerging agents to treat CRE – ceftazidime-avibactam, fosfomycin, tigecycline, and minocycline. In addition, an overview of agents in the antibiotic pipeline – meropenem-vaborbactam, imipenem-relebactam, plazomicin, and eravacycline is provided. More established agents, such as those in the polymyxin class and aminoglycoside class (other than the pipeline agent plazomicin), are not addressed here.

KEYWORDS
carbapenem-resistant Enterobacteriaceae; ceftazidime-avibactam; fosfomycin; minocycline; tigecycline

Introduction
Gram negative bacteria are a common cause of human disease including intra-abdominal infections, urinary tract infections, pneumonia, and bacteremia. The Enterobacteriaceae family of Gram negative bacteria, which includes species such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* species, among others, is of particular concern for several reasons. First, these pathogens are common. Enterobacteriaceae have been shown to cause 84–87% of urinary tract infections,1,2 42–61%,3,4 of biliary tract infections, and 72–89% of Gram negative bacteremia.5,6 Second, they are associated with increasing antibiotic resistance. Studies from community hospitals and tertiary medical centers have demonstrated that multiple antibiotic-resistant phenotypes of Enterobacteriaceae, including resistance to broad-spectrum cephalosporins (via extended-spectrum β-lactamase [ESBL] production)7-10 and carbapenem resistance,11-15 are increasing. Third, infections due to Enterobacteriaceae are associated with poor outcomes. This is particularly the case with antibiotic resistant phenotypes, as drug resistance has been associated with increased mortality,16 hospital readmissions,17 and cost.18

Carbapenem-resistant Enterobacteriaceae (CRE) are a particular threat to global health as carbapenems are often considered drugs of “last resort” in the management of antibiotic-resistant Gram negative infections. Consequently, the Centers for Disease Control and Prevention (CDC) has labeled the CRE threat as “urgent” – the highest hazard level.19 Rates of CRE continue to increase globally,11-15 and invasive infections due to CRE are associated with mortality ranging from 24–70%, depending on the patient population and treatment variables.20

The focus of this review is the role of emerging agents in treating CRE. Antibiotic options for treating CRE are limited, and depend on the source and severity of the infection, the antibiotic susceptibility profile of the bacterium, and the side effect profiles of the agents being considered. The mainstays of CRE therapy have traditionally been antibiotics from either the polymyxin (e.g., colistin or polymyxin B) or aminoglycoside (e.g., amikacin, tobramycin, gentamicin) classes. However, use of these agents has been complicated by issues of efficacy, pharmacokinetics, and toxicity. Additionally, carbapenems are being increasingly considered when the carbapenem
minimum inhibitory concentrations (MICs) are ≤ 8 mg/mL as part of combination therapy. However, the exact role of carbapenems in the treatment of CRE remains controversial, and newer, emerging carbapenemases such as NDM-1 often display high level carbapenem-resistance. Recently, agents from additional drug classes have demonstrated in vitro activity in treating CRE infections. These include a cephalosporin in combination with a novel β-lactamase inhibitor (ceftazidime-avibactam), a phosphonic (fosfomycin), a glycylcycline (tigecycline), and a tetracycline (minocycline). Here we will review the clinical efficacy and safety data supporting the use of these 3 newer agents in treating CRE. In addition, we will discuss several drugs in the antibiotic pipeline which show promise, primarily from in vitro perspectives, in treating CRE infections, though have not yet been approved by the US Food and Drug Administration (FDA).

**Ceftazidime-avibactam**

Avibactam, a novel β-lactamase inhibitor, was approved for use in combination with the third generation cephalosporin ceftazidime for treating complicated urinary tract and complicated intra-abdominal infections on February 25, 2015 (Table 1). Avibactam inhibits a wide range of β-lactamases including Ambler class A, class C, and some class D enzymes (Table 2). These enzymes decrease the activity of β-lactam antibiotics in some strains of drug-resistant Enterobacteriaceae species and *Pseudomonas aeruginosa*. Relative to other β-lactamase inhibitors, avibactam has both greater potency and activity against a broader range of β-lactamases. These properties are thought to stem from multiple factors including the ability of the avibactam-β-lactamase complex to withstand hydrolysis, reversibility of the complex through deacylation, the relatively smaller molecular size of avibactam, and effective interaction of avibactam with important catalytic residues close to the active sites of β-lactamases. In the United States, the majority of carbapenem resistance in Enterobacteriaceae arises through acquisition of plasmid-encoded *Klebsiella pneumoniae* carbapenemases (KPC), which are class A enzymes. As avibactam effectively inhibits this enzyme, it restores the activity of ceftazidime against KPC-producing Enterobacteriaceae. This activity has been demonstrated

### Table 1. Newer and re-emerging older agents in the treatment of infections caused by carbapenem-resistant Enterobacteriaceae.

| FDA-approved agents | Drug class | Mechanisms of resistance |
|---------------------|------------|--------------------------|
| Ceftazidime-avibactam | 3rd generation cephalosporin-β-lactamase inhibitor | Class B β-lactamases (e.g., NDM-1, IMP-1)102,103 |
| Fosfomycin | Phosphonic acid derivative | Some class D β-lactamases (e.g., OXA-23)102 |
| Tigecycline | Glycylcycline | Glutathione-S-transferases (e.g., FosA) or bacillithiol-S-transferases (e.g., FosB) inactivate drug104 |
| Minocycline | Tetracycline | Modification of fosfomycin target MurA104 |

### Table 2. Ambler classification of β-lactamases.

| Ambler Class | β-Lactamases | Active Site | Examples | Substrates |
|--------------|--------------|-------------|----------|------------|
| A | Penicillinas | Serine | TEM, SHV, CTX-M | Penicillins, 3rd generation cephalosporins |
| | KPC | All β-lactams |
| B | Metallo-β-lactamases | Zinc | IMP, VIM, NDM | All β-lactams, except monobactams |
| C | Cephalosporinas | Serine | AmpC | Cephemycins, 3rd generation cephalosporins |
| D | Oxicillinas | Serine | OXA | All β-lactams, though class D enzymes have highly variable spectra of activity |
through in vitro studies as 98% of CRE isolates containing either KPC or OXA-48 (class D) carbapenemases were susceptible to ceftazidime-avibactam.\textsuperscript{30} This susceptibility persisted even in the presence of co-produced extended-spectrum \(\beta\)-lactamases (ESBLs) and/or AmpC \(\beta\)-lactamases.\textsuperscript{30} Avibactam does not improve the activity of ceftazidime against metallo-\(\beta\)-lactamases such as the New Delhi metallo-\(\beta\)-lactamase (e.g., NDM-1), however.\textsuperscript{30}

Initial clinical efficacy data for ceftazidime-avibactam came primarily from two phase 2 trials.\textsuperscript{31,32} First, Vazquez et al. compared the efficacy of ceftazidime-avibactam 0.5-0.125 g every 8 hours to imipenem-cilastin 0.5 g every 6 hours in 135 hospitalized adults with complicated urinary tract infections in a prospective, investigator-blinded, randomized trial.\textsuperscript{32} Of note, this dose is lower than the currently recommended dose of 2-0.5 g every 8 hours. In the microbiologically evaluable population, a favorable microbiological response was achieved in 70.4% of patients receiving ceftazidime-avibactam and 71.4% receiving imipenem-cilastin (observed difference \(-1.1\% [95\% confidence interval: \(-27.2\%, 25\%\)],\). There was no difference in efficacy between the 2 groups when patients were stratified by pyelonephritis versus other complicated urinary tract infections. Notably, a favorable response was observed in 6/7 (85\%) patients with ceftazidime-resistant and ceftazidime-avibactam-susceptible pathogens receiving ceftazidime-avibactam. Second, Lucasti et al. compared the efficacy of ceftazidime-avibactam 2-0.5 g in combination with metronidazole 500 mg (to treat anaerobic bacteria) every 8 hours to meropenem 1 g in combination with placebo every 8 hours to treat 203 hospitalized patients with complicated intra-abdominal infections in a prospective, double-blinded, randomized trial.\textsuperscript{31} The primary efficacy endpoint was clinical response in the microbiologically evaluable patients, and this was achieved in 91.2\% (62/68) of patients who received ceftazidime-avibactam plus metronidazole and 93.4\% (71/76) who received meropenem (observed difference \(-2.2\% [95\% confidence interval: \(-20.4\%, 12.2\%\)]). Based on the phase 2 clinical trial data, ceftazidime-avibactam (with or without metronidazole) demonstrated similar efficacy to carbapenems in treating complicated urinary tract infections and complicated intra-abdominal infections.

Recently, a larger phase 3 trial addressed the efficacy of ceftazidime-avibactam in treating complicated intra-abdominal infections.\textsuperscript{33} Mazuski et al. evaluated the efficacy of ceftazidime-avibactam 2-0.5 g along with metronidazole 500 mg every 8 hours compared to meropenem 1 g and placebo every 8 hours to treat 1066 patients with complicated intra-abdominal infections in 2 identical, prospective, double-blinded, randomized trials (RECLAIM 1 and RECLAIM 2). The primary endpoint was clinical cure at 28-35 d after randomization in the microbiologically modified intention to treat population. Ceftazidime-avibactam plus metronidazole was non-inferior to meropenem in the microbiologically modified intention to treat population with clinical cure rates of 81.6\% vs. 85.1\%, respectively (between group difference [i.e., ceftazidime-avibactam plus metronidazole versus meropenem], \(-3.5\% [95\% confidence interval: \(-8.64, 1.58\)]). In patients with ceftazidime-resistant infections, the clinical cure rate of ceftazidime-avibactam plus metronidazole (83.0\%) was comparable to that with meropenem (85.9\%) and similar to the ceftazidime-avibactam’s efficacy against ceftazidime-susceptible infections (82.0\%). Importantly, in patients with moderate renal impairment (creatinine clearance >30 to \(\leq 50\)) there was a decreased response with ceftazidime-avibactam plus metronidazole in both the microbiologically modified intention to treat (clinical cure with ceftazidime-avibactam + metronidazole: 14/31 [45\%]; clinical cure with meropenem: 26/35 [74\%]; between-group difference \(-29.1\% [95\% Confidence interval: \(-50.05, -5.36\)]\) and modified intention to treat (20/41 [48\%]; 32/43 [74\%]; \(-25.6\% [94.53, -4.78\%]\) populations. This numerical difference was also seen in the clinically evaluable population (18/25 [72\%]; 22/25 [88\%]; \(-16.0\% [38.23, 6.87]\); however it failed to reach statistical significance due to an extremely small sample size. It is however worth mentioning that subsequent pharmacokinetic/pharmacodynamic (PK/PD) modeling suggested that the renal dose adjustment performed in this study was too severe of a reduction and could potentially have lead to suboptimal exposures in patients in this clearance category. In fact, due to the findings from the clinical study, the package insert dose recommendation accounted for this finding with a revised, PK/PD-driven dose adjustment for patients with moderate and severe renal function.\textsuperscript{34} The time above a threshold concentration was determined to be the parameter that best predicts efficacy in in vitro and in vivo models. This modification in dose adjustment may allow for better attainment of optimal ceftazidime-avibactam plasma levels in patients with moderate and severe renal dysfunction than was noted in the phase 3 study.

Finally, Carmeli Y et al. recently published an international, randomized, open-label, phase 3 clinical trial (REPRISE) that addressed the efficacy of ceftazidime-avibactam (2-0.5 g IV every 8 hours) vs. best available therapy in treating complicated urinary tract infection or complicated intra-abdominal infection due to ceftazidime-resistant Enterobacteriaceae or \(P.\) aeruginosa. Patient infections due to Enterobacteriaceae accounted for 85\% (\(n = 283\)) of the total 333 enrolled patients.\textsuperscript{35} Notably, 163 of 168 (97\%) in the best available therapy group received a carbapenem. The proportion of patients...
with clinical cure at the test-of-cure visit was similar in those treated with ceftazidime-avibactam (91% [95% confidence interval: 85.6%, 94.7%]) versus best available therapy (91% [85.9%, 95.0%]). This study provides support for the use of ceftazidime-avibactam in treating drug-resistant Gram negative infections, though does not address the specific issue of efficacy in CRE. In addition, as the majority of study patients with Enterobacteriaceae infections had a complicated urinary tract infection (93% [263/283]), this study does not address the efficacy of ceftazidime-avibactam in treating invasive Gram negative infections in general and invasive CRE infections in particular.

In the phase 2/3 clinical trials described above, the overall rate of adverse events was similar in the experimental and control arms. In RECLAIM 1/RECLAIM 2, for example, adverse events were described in 45.9% of the ceftazidime-avibactam plus metronidazole patients and 42.9% of the meropenem patients. Serious adverse events were noted in 7.9% receiving ceftazidime-avibactam plus metronidazole and 7.6% receiving meropenem. The incidence of therapy discontinuation due to adverse events was low in the ceftazidime-avibactam plus metronidazole (2.6%) and meropenem (1.3%) arms. The most common side effects in the ceftazidime-avibactam plus metronidazole arm included gastrointestinal symptoms such as diarrhea (7.6%), nausea (6.8%), and vomiting (4.5%). There was one case of Clostridium difficile enterocolitis in each treatment group (<1%).

The FDA has approved ceftazidime-avibactam for treatment of complicated urinary tract infections and complicated intra-abdominal infections. Additional trials to evaluate its efficacy in other infections (e.g., nosocomial pneumonia) are ongoing. Pneumonia is a potential indication as a study in healthy volunteers noted the area under the concentration-time curve for ceftazidime and avibactam in epithelial lining fluid was 31-35% of the corresponding values for plasma, and pulmonary surfactant has not been observed to adversely affect the in vitro activity of ceftazidime-avibactam. Overall, the primary niche for ceftazidime-avibactam in treating CRE infections is that caused by bacteria producing class A (e.g., KPC) or class D (e.g., OXA-48) carbapenemases. We emphasize, however, that clinical efficacy data in patients with CRE infections are lacking at the time of this publication and therefore is an area that requires further study.

**Fosfomycin**

Fosfomycin is a phosphonic acid derivative (cis-1,2-eposypropyl-phosphonic acid) that exerts bactericidal antimicrobial activity against susceptible pathogens by blocking the early stage of bacterial cell wall synthesis. Specifically, fosfomycin binds to and inhibits the cytoplasmic enzyme uridine diphosphate N-acetylgalactosamine (UDP-GlcNAc) enolpyruvyl transferase (MurA), which is responsible for production of a metabolic intermediate (UDP-N-acetylenolpyruvylglucosamine) in the synthesis of the peptidoglycan layer of the bacterial cell membrane. Fosfomycin has broad spectrum activity and may be effective against both Gram positive (e.g., Staphylococcus aureus, Enterococcus species, Streptococcus pneumoniae) and Gram negative bacteria (e.g., Enterobacteriaceae, Pseudomonas aeruginosa). The susceptibility of CRE isolates to fosfomycin varies by geography. Vardakas et al. recently published a systematic review of studies assessing the in vitro susceptibility of clinical isolates to fosfomycin. In studies that examined carbapenem-resistant K. pneumoniae (n = 12), susceptibility to fosfomycin varied from 39.2% to 100% (frequency 73.5% [95% confidence interval: 66.4%, 81.4%]). There was variability in the MIC breakpoints for these studies, however, as 10 studies referenced the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint (≤64 mg/L) and 2 studies utilized the European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoint (≤32 mg/L). Decreased susceptibility to fosfomycin was particularly notable in the 2 studies from China, where only 39% and 42%, respectively, of the carbapenem-resistant K. pneumoniae were fosfomycin-susceptible. This resistance was driven by plasmid-mediated spread of gene fosA3, which codes for a glutathione-S-transferase which inactivates the drug. In most studies, however, the MIC50 and MIC90 for CRE were 16–32 μg/mL and 64–128 μg/mL, respectively.

There are limited data on the clinical efficacy of fosfomycin in treating patients with CRE infections. Oral fosfomycin is useful for treating urinary tract infections due to susceptible pathogens as a single 3-gram dose produces peak urine concentrations in excess of 4000 μg/mL, and concentrations above the MIC persist for up to 72 hours. Case reports have demonstrated success in using fosfomycin to treat urinary tract infections caused by KPC- and NDM-producing Enterobacteriaceae. In addition, fosfomycin in combination with colistin effectively treated 2 cases of CRE urinary tract infections that were complicated by bacteremia. In the United States, only the oral formulation of fosfomycin has been approved by the FDA. A single case of successful IV fosfomycin therapy in the United States to treat CRE bacteremia has been reported in the literature, however. The safety and efficacy of the intravenous formulation in treating complicated urinary...
tract infections in the United States is currently being investigated in a phase 3 clinical trial. In Europe, however, an intravenous fosfomycin formulation is also available. A small study from Europe (n = 11) evaluated the efficacy of IV fosfomycin in combination with other agents (e.g., colistin, gentamicin, piperacillin-tazobactam) to treat nosocomial carbapenem-resistant K. pneumoniae infections in critically ill patients. These hospital-acquired infections included ventilator-associated pneumonia, bacteremia, urinary tract infections, and wound infections. All patients with normal renal function were treated with a dosage of 4 g via a central venous catheter 4 times daily. The daily dose was adjusted to 2 g administered 4 times daily in patients who were elderly or had impaired renal function. The all-cause hospital mortality in this study was 2/11 (18%), which is significantly less than what is typically observed in patient cohorts with invasive CRE infections (~50%). A potential pitfall with fosfomycin use, however, is the development of resistance during treatment. This has been described in patients with CRE infections, and therefore caution should be taken before giving fosfomycin as monotherapy for invasive infections.

Fosfomycin is generally well-tolerated. Side effects are often transient and self-limited, and can involve diarrhea (24%), pruritis (20%), abdominal pain (4%), back pain (4%), or rarely transaminitis. Other common but minor adverse effects include rash, headache, and vaginitis. The intravenous formulation may be associated with sodium overload and hypokalemia as every gram of intravenous fosfomycin contains 0.32 g of sodium and the drug increases potassium urinary excretion in the distal part of the renal tubules.

In the United States, only the oral formulation of fosfomycin is currently available for use. Given that the serum concentration following administration of the oral formulation does not reach that following administration of the intravenous formulation, oral fosfomycin monotherapy should only be used to treat cystitis. Intravenous fosfomycin, however, has been shown to penetrate well into multiple tissues including lung, bone, soft tissue, blood, heart valves, bladder wall, and the central nervous system. Thus it is an attractive therapy to treat serious CRE infections at these sites, though efficacy data in using fosfomycin to treat CRE infections is quite limited, particularly as monotherapy. In addition, the optimum dosing regimen for CRE infections at these sites is not clear. These issues, coupled with the observation that resistance to fosfomycin may develop while on therapy, raise concerns for using fosfomycin as monotherapy to treat serious CRE infections. It may be prudent to use fosfomycin in combination with other antibiotics for serious CRE infections until data become available demonstrating the efficacy of fosfomycin monotherapy.

**Tigecycline**

Tigecycline is the first member of the glyyclcycline class of antibiotics. As a tetracycline derivative, it binds with high affinity to bacterial ribosomes, though is unaffected by the typical mechanisms that drive bacterial resistance to tetracyclines (Table 1). It was approved by the FDA in 2005, and is labeled for treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia in adults. As tigecycline does not appear to interact with specific carbapenemases, it has activity against some strains of CRE that produce class A (e.g., KPC), B (e.g., NDM-1), or D (e.g., OXA-48) enzymes. *In vitro* assays with CRE isolates from the United Kingdom (n = 81) suggest that there is significant variability in susceptibility to tigecycline, and this is true even in bacteria that possess similar mechanisms of resistance. However, *in vitro* assays with a larger collection of CRE isolates (n = 280) from throughout Europe demonstrated excellent (88-96%) susceptibility to tigecycline. Thus, it is important to consider local antimicrobial resistance patterns when prescribing tigecycline as an empiric agent.

The FDA issued a black box warning for tigecycline in 2010 due to an observed increase in mortality in a meta-analysis of 13 phase 3 and phase 4 trials. The pooled mortality rate of 4% (150/3788) in patients treated with tigecycline and 3% (110/3646) in patients treated with the comparator antibiotics resulted in an adjusted risk difference of 0.6%. The indications for which reviewed studies were performed included community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, diabetic foot infections, complicated intra-abdominal infections, and complicated skin and soft tissue infections. The findings of increased mortality were primarily driven by HABP/VABP studies. In addition, multiple studies evaluating patients with KPC-producing Enterobacteriaceae bloodstream infections demonstrated increased mortality in patients treated with tigecycline monotherapy. However, there are data suggesting that tigecycline may be effective when used in combination with other antibiotics. For example, Tumbarello et al. performed a retrospective study of 125 patients with KPC-producing *K. pneumoniae* bloodstream infections, and demonstrated that combination therapy with tigecycline, colistin, and meropenem was independently protective against mortality (Odds ratio 0.11 [95% Confidence interval: 0.02, 0.69]).
relative to other antibiotic combinations. Further, a systematic review and meta-analysis of 26 trials addressing the efficacy of tigecycline in treating CRE infections showed a significant improvement in 30-day mortality in the tigecycline combination therapy group relative to the control group (Odds ratio 0.59 [95% confidence interval: 0.39, 0.88]). The control group received combination therapy without tigecycline. Similarly, tigecycline mono-therapy was associated with increased 30-day mortality relative to tigecycline combination therapy (Odds ratio 1.83 [95% confidence interval: 1.07, 3.12]). Though no randomized clinical trial assessing the efficacy of tigecycline in treating CRE has yet been performed, these data suggest that combination therapy which includes tigecycline is at least not inferior to other antimicrobial regimens when treating serious CRE infections. These data also suggest that tigecycline-based combination therapy is more effective than tigecycline monotherapy in treating CRE infections.

Though tigecycline has been approved by the FDA for treatment of skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia in adults, its in vitro activity and the lack of effective alternatives for treatment of highly-resistant CRE drive its use in other clinical settings. For example, a systematic review of trials evaluating tigecycline for CRE infection therapy revealed that bacteremia, urinary tract infection, and nosocomial pneumonia were the most common types of CRE infection treated with tigecycline. Thus the majority of tigecycline use in CRE infections appears to be off-label. One concern with off-label use is that sub-optimal drug concentrations at each of these anatomic sites (blood, urine, lungs). In these cases, there are limited evidence to suggest that higher tigecycline dosing may produce better outcomes. In a randomized controlled trial that assessed the efficacy of 2 tigecycline dosing regimens (150 and 200 mg daily) compared to imipenem-cilastatin in treating hospital-acquired pneumonia, clinical cure in the 200 mg daily tigecycline group (17/20, 85.0%) was higher than in the 150 mg daily tigecycline group (16/23, 69.6%) and the imipenem-cilastin group (18/24, 75%). Similarly, the Ni et al. meta-analysis revealed that in 2 pooled studies the ICU mortality associated with CRE infections was higher with standard tigecycline dosing relative to the higher dose (Odds ratio 12.48 [95% confidence interval: 2.06, 75.43]). Further investigation is needed to better establish the efficacy of high-dose tigecycline, however.

The most common side effects of tigecycline therapy include nausea, vomiting, and diarrhea. While the drug is generally well-tolerated, these adverse effects were noted to occur more frequently with use of high-dose tigecycline (200 mg daily). Importantly, clinical isolates of E. coli and K. pneumoniae have demonstrated increased tigecycline MIC after tigecycline therapy. Clinicians using tigecycline must therefore be mindful for the development of tigecycline resistance while on therapy.

The FDA issued a black box warning for tigecycline given increased mortality associated with its use. Nevertheless, in treating CRE infections there are data to suggest that combination therapy with tigecycline is as effective as other antibiotic options, though well-controlled clinical trial data are lacking. For treatment of CRE infections, tigecycline has often been used in combination with one or more of the following: polymyxins, aminoglycosides, carbapenems and rifampin. Until convincing data become available demonstrating the efficacy of tigecycline monotherapy, tigecycline should not be used as monotherapy for treatment of invasive CRE infections, such as bacteremia and pneumonia.

Minocycline

Minocycline is a tetracycline antibiotic that was originally approved by the FDA in 1970s. Recently, it has received renewed attention given its potential utility in the fight against drug-resistant Gram negative bacteria as well as its new intravenous formulation which allows administration in a more tolerable fluid load (Table 1). For example, several studies described the successful use of minocycline in treating carbapenem-resistant Acinetobacter baumannii infections. Given these initial successes, IV minocycline was evaluated as a potential alternative to tigecycline or doxycycline in treating carbapenem-resistant A. baumannii and carbapenem-resistant K. pneumoniae. In vitro assays demonstrated that 78% of carbapenem-resistant A. baumannii were susceptible to minocycline, though only 12% (7/59) of carbapenem-resistant K. pneumoniae isolates were susceptible. While high rates of CRE resistance to minocycline may limit its use as an empiric agent, it may still serve as effective adjunct therapy in susceptible isolates. Pogue et al. describes three cases of carbapenem-resistant and minocycline-susceptible K. pneumoniae bloodstream infections treated with minocycline combination therapy. In all 3 cases, minocycline was used empirically as part of a combination therapy with 1-2 additional antibiotics (colistin, meropenem, tobramycin, or amikacin). Microbiological cure was achieved in all patients, and clinical cure was achieved in 67% (2/3). Additional data are needed to understand the effectiveness of minocycline therapy in treating susceptible CRE isolates.

Interestingly, in the same analysis, Pogue et al. noted better outcomes in patients who received the maximum dose of 200 mg twice daily (6/7 with clinical cure in
combined CRE and *A. baumannii* groups) relative to those who received 100 mg twice daily (0/2 with clinical cure). One of the benefits of minocycline relative to tigecycline is improved pharmacokinetics as it achieved higher serum concentrations (average max concentration 4.2 vs. 1.6 μg/mL following 200 mg IV dose). Additional benefits of minocycline relative to tigecycline include a favorable side effect profile, an oral option for step-down therapy, and the fact that it has been approved by the FDA for treatment of urinary tract infections.

Minocycline is generally well-tolerated. It should be avoided in pregnant women and in children less than 8 y old due to the possibility of tooth discoloration. Some potential side effects include photosensitivity, lightheadedness, vertigo, gastrointestinal disturbances, and local injection site reactions. However, several studies evaluating minocycline treatment of drug-resistant bacterial infections have noted no drug toxicities or adverse effects.

Though more investigation is needed to establish the efficacy of minocycline in treating CRE infections, preliminary data suggests that it can be useful as part of combination therapy in minocycline-susceptible isolates. In such cases, high dose therapy (200 mg twice daily) should be considered.

**Antibiotic pipeline**

Several potential agents for treatment of CRE infection are in the antibiotic pipeline, though have not yet been approved for general use by the FDA.

**Meropenem-vaborbactam (formerly known as RPX7009)**

Vaborbactam is a novel cyclic boronic acid inhibitor of many class A and class C enzymes. It was designed and synthesized to be a potent inhibitor of serine carbapenemases, and KPC in particular. In vitro data suggests that meropenem-vaborbactam is highly active against KPC-producing Enterobacteriaceae (*K. pneumoniae*: MIC~50~ ⏞️ [meropenem-vaborbactam] = 0.06–4 and 0.03–8 μg/mL; MIC~90~ = 2/4 and 0.5/8 μg/mL). Little effect on *A. baumannii* containing OXA-type carbapenemases was observed. Due to completion of phase 1 clinical trials for a similar agent (biapenem-RPX7009), the meropenem-vaborbactam combination proceeded directly to phase 3 clinical trials. Currently there are ongoing phase 3 clinical trials to evaluate the safety, efficacy, and tolerability of meropenem-vaborbactam in treating patients with complicated urinary tract infections and serious CRE infections.

**Imipenem-relebactam**

Relebactam is a non-β-lactam serine β-lactamase inhibitor, similar to avibactam, that was designed to have inhibitory activity against class A and C β-lactamases. In vitro assays with CRE isolates demonstrated that MICs were significantly lowered when imipenem was tested with relebactam against KPC-producing *K. pneumoniae* (MIC~50~ = 0.25/4 μg/mL; MIC~90~ = 1/4 μg/mL). Compared to imipenem alone, little reduction in imipenem-relebactam MICs were noted in OXA-48-producing *K. pneumoniae* or OXA-23-producing *A. baumannii*, suggesting that that relebactam, unlike avibactam, does not have significant activity against the class D enzymes. Clinical trials have used imipenem-cilastatin combined with relebactam in phase 2 and phase 3 clinical trials. Phase 2 clinical trials investigating the safety, tolerability, and efficacy of imipenem-cilastatin-relebactam in treating complicated urinary tract infections and complicated intra-abdominal infections have been completed. Results of the intra-abdominal infection trial were presented at the Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) and International Congress of Chemotherapy and Infection (ICC) joint meeting in 2015. In this multicenter, double-blind study, 351 patients were randomized to receive imipenem-cilastatin with either relebactam 250 mg, relebactam 125 mg, or placebo. The percentage of microbiologically evaluable patients with favorable clinical response was similar across all treatment groups – 96.3%, 98.8%, and 95.2%, respectively. In addition, phase 3 trials evaluating the efficacy and safety of imipenem-cilastatin-relebactam in treating pneumonia and imipenem-resistant bacterial infections are ongoing.

**Plazomicin**

Plazomicin is a novel aminoglycoside that was synthetically derived from sisomicin. Like other aminoglycosides, it is a bactericidal agent that works primarily through inhibition of protein synthesis. Plazomicin is structurally similar to the traditional aminoglycosides (amikacin, gentamicin, tobramycin), though was modified to resist aminoglycoside-modifying enzymes that are often present in CRE. Plazomicin is not affected by carbapenemase production and has demonstrated good in vitro activity against carbapenem-resistant isolates of *K. pneumoniae*, *E. coli*, and Enterobacter species producing a variety of carbapenemases and ESBLs. Of note, in one study plazomicin was less active versus isolates producing NDM-1 enzymes due the co-existence of ArmA and RmtC 16S rRNA methyltransferases. The presence of 16S rRNA methyltransferase in Enterobacteriaceae, which modifies the ribosomal site that binds plazomicin,
leads to plazomycin resistance. Plazomycin has been demonstrated to be more potent than other aminoglycosides in treating Enterobacteriaceae. For example, in vitro susceptibility data from non-NDM-containing CRE isolates (n = 65) showed that plazomycin MICs ranged from \( \leq 0.5–2 \mu g/mL \), as opposed to 0.25–\( >256 \mu g/mL \) for gentamicin and 1–128 \( \mu g/mL \) for amikacin. None of the aminoglycosides, including plazomycin, had considerable activity against most NDM-containing isolates, however. The safety and efficacy of plazomycin vs. levofloxicin in treating complicated urinary tract infections or acute pyelonephritis was evaluated in a phase 2 trial. Microbiological eradication of the offending pathogen and clinical outcome were similar in the plazomycin- and levofloxicin-treated cohorts. Phase 3 trials evaluating the efficacy of plazomycin in treating complicated urinary tract infections and CRE infections are ongoing. Aminoglycosides are known to potentially cause nephrotoxic and ototoxic effects. A phase 1 study in healthy subjects did not reveal any nephrotoxic or ototoxic effects of plazomycin therapy. In the phase 2 trial, elevations in creatinine were relatively mild, though present in 5.2% of plazomycin-treated patients. Values returned to near baseline by the last follow-up visit in all but one plazomycin patient (1/96, 1%). Adverse events possibly associated with vestibular (mild vertigo, 1 patient) and cochlear function (mild unilateral permanent tinnitus, 1 patient) occurred in the plazomycin 15 mg/kg group. Thus although plazomycin may be associated with nephrotoxicity and neurologic side effects, based on available data, rates appear to be lower relative to other aminoglycosides. Further investigation is needed.

**Eravacycline**

Eravacycline is a novel synthetic fluorocycline that is active against most Gram negative species. In vitro assays have demonstrated that eravacycline is 2- to 4-fold more potent than tigecycline against CRE. A phase 2, randomized, double-blind study was done to evaluate the efficacy and safety of eravacycline compared with ertapenem in patients with complicated intra-abdominal infections. Results of the study have been posted to ClinicalTrials.gov. Clinical cure in the microbiological intent-to-treat population was similar in those treated with eravacycline (86.8%, 191/220) compared to ertapenem (87.6%, 198/226). The most common side effects with eravacycline therapy were nausea (8%) and vomiting (4%). The percentage of patients experiencing serious adverse events with eravacycline (6.3%) was similar to that in the ertapenem group (6.0%). Notably, however, a phase 3 clinical trial of eravacycline administered as an IV to oral transition therapy for the treatment of complicated urinary tract infections did not achieve its primary endpoint of non-inferiority compared to levofloxicin. These data remain unpublished to date and thus further study is needed to establish the role of eravacycline in treating CRE. Eravacycline may have advantages over tigecycline due to its improved in vitro activity against CRE isolates, higher serum levels, and better tolerability, though further investigation is needed.

**Conclusions**

Infections with CRE are associated with high mortality, and are increasing throughout the world. These infections are difficult to treat as carbapenem resistance is often accompanied by resistance to other antibiotic classes. Carbapenem resistance has emerged through multiple mechanisms, which makes drug development challenging. In an increasing number of cases, CRE may be extensively drug resistant or even pandrug resistant. While emerging drugs such as ceftazidime-avibactam, fosfomycin, tigecycline, minocycline, and others in the antibiotic pipeline offer additional therapeutic alternatives with fewer side effects and toxicities than agents such as the polymyxins, important issues still remain. First, there is no clear optimum drug regimen for treating CRE. Additional investigation is needed to firmly establish the efficacy of monotherapy versus combination therapy and the efficacy of specific agents. Second, more study is needed to determine the appropriate dosing regimen for some agents (such as tigecycline), from both clinical efficacy and toxicity perspectives. Third, the best antimicrobial stewardship practices to prevent infection and spread of CRE with regards to utilization of newer as well as older agents, has not yet been determined. Finally, studies need to focus on use of new agents for the treatment of patients with infection due to CRE, as data from these types of studies would reflect “real world” usage of these agents and better inform clinicians regarding dosing, toxicity, and clinical efficacy.
of newer agents in complex patient populations with CRE infection.

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No potential conflicts of interest were disclosed.

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