Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections

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This article provides a comprehensive review of currently available treatment options for infections due to carbapenem-resistant Enterobacteriaceae (CRE). Antimicrobial resistance in Gram-negative bacteria is an emerging and serious global public health threat. Carbapenems have been used as the “last-line” treatment for infections caused by resistant Enterobacteriaceae, including those producing extended spectrum β-lactamases. However, Enterobacteriaceae that produce carbapenemases, which are enzymes that deactivate carbapenems and most other β-lactam antibiotics, have emerged and are increasingly being reported worldwide. Despite this increasing burden, the most optimal treatment for CRE infections is largely unknown. For the few remaining available treatment options, there are limited efficacy data to support their role in therapy. Nevertheless, current treatment options include the use of older agents, such as polymyxins, fosfomycin, and aminoglycosides, which have been rarely used due to efficacy and/or toxicity concerns. Optimization of dosing regimens and combination therapy are additional treatment strategies being explored. Carbapenem-resistant Enterobacteriaceae infections are associated with poor outcomes and high mortality. Continued research is critically needed to determine the most appropriate treatment.

Keywords: carbapenemases; carbapenem-resistant Enterobacteriaceae; carbapenems; resistant infections; treatment.

Antimicrobial resistance is globally recognized as one of the greatest threats to public health. Of particular concern are infections caused by resistant Gram-negative bacilli, which are increasingly being reported worldwide. The escalating burden of Gram-negative antimicrobial resistance is largely due to β-lactamases, which are enzymes that bind and deactivate β-lactam antibiotics, rendering them ineffective. For years, carbapenems have been used successfully to treat infections due to resistant Enterobacteriaceae, such as Escherichia coli and Klebsiella pneumoniae, including those producing extended spectrum β-lactamases ([ESBLs] a subset of β-lactamase enzymes that confer broad resistance to penicillins, cephalosporins, and the monobactam aztreonam).

However, recently Enterobacteriaceae-producing carbapenemases (known as carbapenem-resistant Enterobacteriaceae [CRE]) have emerged, which confer broad resistance to most β-lactam antibiotics including “last-line” carbapenems. Carbapenem resistance can also be conferred when porin deficiencies, which allow decreased entry of the β-lactam into the cell membrane, are combined with ESBLs [1]. The prevalence of CRE infections has increased over the last decade, especially in healthcare settings, and as such CRE have been recognized by the US Centers for Disease Control and Prevention as an urgent public health threat [2, 3]. The Centers for Disease Control and Prevention estimates that more than 9000 healthcare-associated infections are caused by the 2 most common type of CRE, carbapenem-resistant Klebsiella species and Escherichia species, each year in the United States [3]. Carbapenem-resistant Enterobacteriaceae can cause a number of
serious infection types (such as intra-abdominal infections, pneumonia, urinary tract infections, and device-associated infections) or asymptomatic colonization [4–6]. Each year approximately 600 deaths result from CRE infections [3]. Infections caused by CRE are extremely concerning, because CRE mortality rates are high and range from 18% to 48% depending on therapy [7]. This result may be due to delayed time to active therapy, pharmacologic limitations of available treatment options, and the fact that patients with CRE infections tend to be critically ill.

At this time, there are a limited selection of treatment options for CRE infections. Clinicians have been forced to re-evaluate the use of agents, which have been historically rarely used due to efficacy and/or toxicity concerns, such as polymyxins, fosfomycin, and aminoglycosides. Additional CRE treatment strategies include optimization of dosing regimens and combination therapy. This review will focus on the current treatment options for CRE infections.

OVERVIEW OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE TREATMENT

There are numerous different types of carbapenemase enzymes, each conferring varying spectrums of resistance. An overview of the carbapenemase enzyme commonly found in Enterobacteriaceae types with the greatest clinical importance can be found in Table 1. In general, the presence of a carbapenemase confers broad resistance to most β-lactam antibiotics including penicillins, cephalosporins, and the monobactam aztreonam (excluding metallo-β-lactamases [MBLs] and oxacillinases [OXAs]) [1]. In vitro activity of carbapenems in the setting of one of these enzymes is variable, and the exact role of carbapenems in infectious due to these organisms is controversial. To further complicate treatment, CRE often exhibit resistance to structurally unrelated antimicrobial classes such as aminoglycosides and fluoroquinolones [11]. However, aminoglycoside susceptibility can vary as a function of K. pneumoniae carbapenemase (KPC) strain type and coexisting aminoglycoside modifying enzymes, which are not tested in a traditional clinical laboratory. The emergence of resistance during therapy is another emerging concern [12, 13].

Despite their increasing burden, the most optimal treatment for CRE infections is largely unknown. At this time, there are no published data from randomized controlled trials assessing antimicrobial treatment options for CRE infections. Although this information is important, in the United States at this time there may not be a sufficient number of patients with serious CRE infections to conduct such a trial. Therefore, much of the existing evidence is from reviews of case reports, case series, and small retrospective studies, which have a number of inherent limitations [14, 15]. A potential CRE treatment algorithm and overview of current treatment options can be found in Tables 2 and 3, respectively.

| Ambler Class (Active Site) | Example Enzymes | Host Organisms | Enzyme Substrates | Inhibition by Currently Available β-Lactamase Inhibitors (Clavulanic Acid, Tazobactam, and Sulbactam) | Region Most Found In | Mainly Found in | Minimal Hydrolysis |
|---------------------------|-----------------|----------------|------------------|-----------------------------------------------------------------------------------------------|---------------------|-----------------|------------------|
| A (serine) | KPC-2 to 22 | Mainly found in Klebsiella pneumoniae have been identified in other Enterobacteriaceae and nonfermenters | Yes | Yes | Yes | Yes | Yes | Yes |
| B (Zinc binding thiol) | NDM-1 | Enterobacteriaceae and nonfermenters | Yes | Yes | Weak Activity | No | No | Weak Activity |
| D (serine) | OXA-48 | Enterobacteriaceae other than K. pneumoniae | Yes | Yes | No | Minimal Hydrolysis | No | No |

Abbreviations: KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.

*Some KPC enzymes, such as KPC-2, can hydrolyze carbapenems but are not inhibited by β-Lactamase Inhibitors.
*OXA-48 is weakly active against extended spectrum cephalosporins and hydrolyzes carbapenems only minimally.
CARBAPENEMS

Pharmacokinetic data suggest that \( T > \text{minimum inhibitory concentration (MIC)} \) targets can be achieved using high-dose prolonged-infusion carbapenems when carbapenem MICs are relatively low (<4 \( \mu \)g/mL) or even moderately elevated (8–16 \( \mu \)g/mL) \([16–20]\). Monte Carlo dosing simulations demonstrated that, high-dose meropenem (6000 mg/day) administered by prolonged (over 4 hours)/continuous infusion had a high probability of target attainment (PTA) up to an MIC of 8–16 \( \mu \)g/mL. In another study, the PTA for an MIC of 4 \( \mu \)g/mL increased with prolonged-infusion (over 3 hours) compared with traditional-infusion (over 30 minutes); the PTA for prolonged-infusions were 100% (2000 mg q8h) compared with 69% for traditional-infusion; 93% (1000 mg q8h) compared with 69% for traditional-infusion (1000 mg q8h) \([17]\). At an MIC of 8 \( \mu \)g/mL, only
| Drug               | Bacterial Effect and Mechanism of Action                                                                 | Most Predictive PK/PD Index for Antibacterial Effect | Route and Traditional Dosing | Route and Alternative Dosing* (High and/or Prolonged Infusion) for CRE Infections | Toxicity                                                                 | Clinical Pearls                                                                                     |
|-------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------|------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Carbapenems*      | Bactericidal (time dependent); cell wall inhibition (by inhibition of cell wall cross-linking)           | 40%–50% fTime > MICc                            | IV: 1000 mg IV q8h<sub>REN</sub> | IV: 2000 mg q8h over 4 h<sub>REN</sub>                                          | Local phlebitis/thrombophlebitis (1%), hypersensitivity reactions (rash-3%), headache (2%–8%), gastrointestinal effects (1%–8%), hematological changes (<6%), seizures (1%). | Closely monitor for allergic reactions and adverse drug effects, in particular the development of seizures, in patients receiving high-dose carbapenems. |
| Meropenem<sup>b</sup> | Bactericidal (time dependent); cell wall inhibition (by inhibition of cell wall cross-linking)           | 40%–50% fTime > MICc                            | IV: 500 mg IV q8h<sub>REN</sub> | IV: 1000–2000 mg q8h over 4 h<sub>REN</sub>                                      | Headache (3%–16%), gastrointestinal effects (4%–12%), local phlebitis (2%–8%), hypersensitivity reactions (rash 2%–7%), hematological changes (<1%), increased hepatic enzymes (2%–7%), seizures (<1%). | Dual-carbapenem combination treatment may be an effective option for infections caused by pandrug-resistant CRE. Closely monitor for allergic reactions and adverse drug effects, in particular the development of seizures, in patients receiving dual-carbapenem therapy. |
| Doripenem<sup>b</sup> | Bactericidal (time dependent); cell wall inhibition (by inhibition of cell wall cross-linking)           | 40%–50% fTime > MICc                            | IV: 1000 mg IV q24h<sub>REN</sub> |                                                                                 | Gastrointestinal effects (2%–12%), local phlebitis/thrombo-phlebitis (2%), headache (4%–7%), hypersensitivity reactions (rash-1-3%), hematologic reactions (1%–7%), increased liver enzymes (7%–9%), fever (2%–5%), seizures (<1%). |                                                                                                 |
| Ertapenem<sup>b</sup> | Bactericidal (time dependent); cell wall inhibition (by inhibition of cell wall cross-linking)           | 40%–50% fTime > MICc                            | IV: 1000 mg IV q24h<sub>REN</sub> |                                                                                 |                                                                                                               |                                                                                                 |
| Polymyxins        |                                                                                                        |                                                  |                              |                                                                                 |                                                                                                               |                                                                                                 |
| Colistin<sup>b</sup> | Bactericidal<sup>d</sup> (concentration dependent); disrupt cell membrane permeability (by charge alteration) | fAUC:MIC 60                                    | See Table 5                   | See Table 5                                                                     | Nephrotoxicity (<50%–60%), neurotoxicity                           | Recent literature suggests that nephrotoxicity rates may be higher with colistin compared with polymyxin B. |
| Polymyxin B<sup>b</sup> | Bactericidal<sup>d</sup> (concentration dependent); disrupt cell membrane permeability (by charge alteration) | fAUC:MIC 60                                    | See Table 5                   | See Table 5                                                                     | Nephrotoxicity (20%–40%), neurotoxicity                           | Higher doses of both colistin and polymyxin B may be associated with a higher risk of nephrotoxicity. Colistin preferred over polymyxin B for the treatment of UTIs due to renal clearance of CMS. On-treatment resistance development is a concern for both colistin and polymyxin B, consider using combination therapy for serious infections. |

<sup>a</sup> Renal adjustment for prolonged infusion required. 
<sup>b</sup> Data from the literature. 
<sup>c</sup> Times greater than MIC for bactericidal effect. 
<sup>d</sup> Concentration-dependent activity. 

**Table 3. Principal Characteristics of Currently Available Drugs With Activity Against Carbapenem-Resistant Enterobacteriaceae**
| Drug | Bacterial Effect and Mechanism of Action | Most Predictive PK/PD Index for Antibacterial Effect | Route and Traditional Dosing | Route and Alternative Dosing (High and/or Prolonged Infusion) for CRE Infections | Toxicity | Clinical Pearls |
|------|-----------------------------------------|--------------------------------------------------|-----------------------------|--------------------------------------------------------------------------------|---------|----------------|
| **Aminoglycosides** | | | | | | |
| Gentamicin<sup>b</sup> | Bactericidal (concentration dependent); protein synthesis inhibition (at 30S ribosomal subunit) | fCmax:MIC ≥ 10 | IV: 5 mg/kg daily dose<sup>REN</sup> | IV: 7–10 mg/kg<sup>REN,a</sup> | Nephrotoxicity, ototoxicity | To optimize therapy and minimize the risk of toxicity, daily administration and limiting therapy to the shortest possible course is preferred. |
| Tobramycin<sup>b</sup> | Bactericidal (concentration dependent); protein synthesis inhibition (at 30S ribosomal subunit) | fCmax:MIC ≥ 10 | IV: 5 mg/kg daily dose<sup>REN</sup> | IV: 7–10 mg/kg<sup>REN,a</sup> | Nephrotoxicity, ototoxicity | Therapy should be individualized through serum drug level monitoring when microbiological data become available. |
| Amikacin<sup>b</sup> | Bactericidal (concentration dependent); protein synthesis inhibition (at 30S ribosomal subunit) | fCmax:MIC ≥ 10 | IV: 10 mg/kg<sup>REN</sup> | IV: 15 mg/kg<sup>REN,b</sup> | Nephrotoxicity, ototoxicity | Aminoglycoside therapy may be most appropriate as a component of combination therapy for CRE infections, especially UTIs. |
| **Glycylcyclines** | | | | | | |
| Tigecycline<sup>b</sup> | Bacteriostatic; protein synthesis inhibition (at 30S ribosomal subunit) | fAUC:MIC 1 | IV: 100 mg loading dose, then 50 mg q12h<sup>HEP</sup> | IV: 200 mg loading dose, then 100 mg q12-24h<sup>HEP</sup> | Nausea (26%), vomiting (18%), diarrhea (12%) | Accumulates in the intracellular and tissue compartments rapidly after IV infusion. Not recommended as monotherapy for treating bacteremia because peak serum concentration (approximately 1 µg/mL) is similar to the MIC of many resistant Gram-negative organisms. Should not be used for UTIs due to poor urine drug concentrations (only 22% is excreted in the urine as the active drug). At higher doses, gastrointestinal effects may be more severe and are usually dose-limiting. |
Table 3 continued.

| Drug                        | Bacterial Effect and Mechanism of Action                                                                 | Most Predictive PK/PD Index for Antibacterial Effect | Route and Traditional Dosing | Route and Alternative Dosing\(^a\) (High and/or Prolonged Infusion) for CRE Infections | Toxicity                                                                 | Clinical Pearls                                                                 |
|-----------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| **Phosphonic Acid Derivatives** |                                                                                                        |                                                     |                               |                                                                                 |                                                                           |                                                                                |
| Fosfomycin\(^b\)             | Bactericidal (time dependent vs concentration-dependent activity unclear, appears to have concentration-dependent killing against *E coli*), cell wall inhibition (by inhibition of synthesis of cell wall peptidoglycan) | 60%–70% \(\text{fTime > MIC}\) \(\text{PO: 3 g once}^g\)  | \(\text{IV: 3 g every 2–3 d divided in doses every 6 to 12 h}^\text{REN}\) | \(\text{PO: Gastrointestinal effects (1%–10%), headache (4%–10%), vaginitis (6%–8%), local pain (4%), heart failure (3%)}\) | Oral fosfomycin should not be used for the management of CRE infections outside the urinary tract. Fosfomycin (intravenous and oral formulations) achieves high enough concentrations in the lungs, bones, heart valves, and cerebrospinal fluid to interfere with pathogen growth, but optimal dosing for these sites has not been determined. Very limited clinical data on use in CRE infections. Fosfomycin therapy may be most appropriate as a component of combination therapy for CRE infections. |

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Abbreviations: **AUC**, area under the curve; **C\(\text{max}\)**, maximal concentration; **CMS**, colistimethate; **CRE**, carbapenem-resistant *Enterobacteriaceae*; *E coli*, *Escherichia coli*; \(\text{f}\), free drug; **HEP**, hepatic dose adjustment necessary; **IV**, intravenous; **MIC**, minimum inhibitory concentration; **PK/PD**, pharmacokinetic/pharmacodynamic; **PO**, oral; **REN**, renal dose adjustment necessary; **UTI**, urinary tract infection.

\(^a\) The safety and efficacy of alternative (high or prolonged) infusion dosing is largely unknown. It is important to weight the risks and benefits of alternative dosing, which may be necessary to treat serious CRE infections.

\(^b\) Strongly consider use in combination for empiric therapy to reduce the risk of potentially inappropriate therapy and targeted therapy due to the potential for on-treatment resistance, especially in critically ill patients.

\(^c\) Higher T > MIC targets (as least 75% T > MIC) may be more appropriate in patients who are critically ill or who have immunocompromising conditions to increase the chance of clinical response.

\(^d\) The ideal \(\text{AUC/MIC}\) target for bactericidal activity for the polymyxins has not yet been defined due to strain variability. In the largest population pharmacokinetic study to date, a \(\text{AUC/MIC}\) of 60 for formed colistin was generally associated with an effect somewhere between stasis and 1-log kill against 3 strains each of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in murine thigh and lung infection models [79, 80].

\(^e\) For organisms with an MIC \(\leq 0.5\) mg/L, a 5 mg/kg daily dose of gentamicin or tobramycin was associated with the highest probability of response and the lowest probability of nephrotoxicity. At an MIC 1 or 2 µg/mL, daily doses of 7 mg/kg may be necessary. In this study, even at an MIC of 4.0 µg/mL, a 10 mg/kg dose was associated with an 80% probability of response with a negligible risk of toxicity [81].

\(^f\) At an MIC \(\leq 4.0\) µg/mL 15 mg/kg once daily may be appropriate, but at an MIC of 8 or 16 higher doses may be needed [29].

\(^g\) In the United States, only oral fosfomycin is approved by the Food and Drug Administration as a single 3 gram dose for the treatment of uncomplicated urinary tract infections. In Europe, IV formulations are available. Outside the United States, IV fosfomycin has been used for a wide range of infections including bacteremia, osteomyelitis, and meningitis at daily doses of 1–16 g divided in 3 or 4 doses.

\(^h\) Intravenous doses of 16 g divided in 2 doses have been reported to achieve pharmacokinetic targets against pathogens up to an MIC of 35. For the treatment of isolates with higher MICs, higher doses of up to 20 g per day, administered by prolonged or continuous infusion, may be considered. However, there are little data on the safety of higher-dose regimens [34, 82, 83].

\(^i\) Hypokalemia may be associated with rapid infusions over 30 minutes, heart failure may be due to the high salt concentration of the IV formulation [84].
Table 4. Summary of Studies Assessing Treatment and Outcomes for Bloodstream Infections Caused by KPC-Producing *Klebsiella pneumoniae*

| First Author (Publication Year) | Study Origin | N | Enzyme Type | Source of Bacteremia, n (%) | Overall Mortality, n (%) | Combination Therapy (CT) vs Monotherapy (MT) | Mortality Select Treatment Regimens (In vitro Active Therapy), n (%) | Predictors of Mortality in Multivariate Analysis |
|--------------------------------|--------------|---|-------------|-----------------------------|--------------------------|---------------------------------------------|------------------------------------------------|----------------------------------------------|
| Zarkotou (2011) | Greece | 53 | KPC-2 (n = 53); enzyme coproduction | Line related, 12 (22.6%); | 29/56 (20.4%); | 0/20 (0%); 7/15 (46.7%); | 1/1 (100%); APACHE II score (OR, 1.26; 95% CI, 1.04–1.53; P = .021), Age (OR, 1.21; 95% CI, 1.02–1.44; P = .029). | Appropriate antimicrobial therapy (OR, 0.07; 95% CI, 0.05–0.09; P = .003). | 
| Qureshi (2012) | United States | 41 | KPC-2 (n = 21), KPC-3 (n = 20) | Line related, 13 (31.7%); | 28/67 (41.2%); | 11/19 (57.8%); | 2/5 (40.0%); | None | 
| Tumbarello (2012) | Italy | 125 | KPC-2 (n = 27), KPC-3 (n = 98) | Line related, 13 (10.4%); | 28 (22.4%); | 27/79 (34.1%); | 1/7 (14.3%); | Definitive combination therapy (OR, 0.07; 95% CI, 0.09–0.71; P = .02). | 
| Daikos (2014) | Greece | 205 | KPC-2 (n = 163, 36 coproduced VIM-1), VIM-1 (n = 42) | Line related, 22 (10.7%); | 28/103 (27.2%); | 28/103 (27.2%); | 7/12 (58.3%); | Combination therapy (HR, 1.21; 95% CI, 1.02–1.40; P = .006). | 

Abbreviations: Amg, aminoglycoside; Carb, carbapenem; CI, confidence interval; CNS, central nervous system; Col, colistin; HR, hazard ratio; MT, monotherapy; OR, odds ratio; Tig, tigecycline; KPC, *Klebsiella pneumoniae* carbapenemase.

*a* Mortality data provided for combination therapy including drug of interest.

*b* Mortality data provided for monotherapy therapy with drug of interest only.

*c* Mortality range determined based on data provided in referenced study. Actual mortality rate for drug of interest not included in referenced study. For more information see referenced study.

*d* Mortality range determined based on data provided in referenced study. Drug of interest was not included in mortality calculations for this table if listed as a possible (“or”) component of combination regimen, additionally unknown if drug of interest was included in category listed as “other combinations” in referenced study. For more information see referenced study.
| Form administered | Colistin | Polymyxin B |
|--------------------|----------|-------------|
| Best pharmacodynamics predictor of activity | fAUC/MIC | fAUC/MIC |
| Dosing units | United States – mg CBA | International Units |
| Dosing equivalents | 30 mg CBA = 60 mg CMS = 1 million International Units CMS | 10 000 International Units = 1 mg |
| Loading dose | 5 mg CBA/kg<sup>b,c,d</sup> (loading dose required) | 20 000–25 000 International Units (2–2.5 mg/kg<sup>e</sup>) (loading dose recommended) |
| Time until maintenance dose | 12 to 24 h | 12 h |
| Maintenance dose<sup>a</sup> | | |
| | CrCl (mL/min) | Daily dose (mg CBA) | MIC < 1 µg/mL | 25 000 International Units (2.5 mg/kg per day) |
| | 0 | 75 | | |
| | 10 | 112.5 | | |
| | 20 | 150 | | |
| | 30 | 187.5 | | |
| | 40 | 225 | | |
| | 50 | 262.5 | | |
| | 60 | 300 | | |
| | 70 | 337.5 | | |
| | Intermittent HD<sup>b,g</sup> | Non-HD day = 75 mg CBA per day HD day = 97.5 mg CBA per day | MIC 1–2 µg/mL | 30 000 International Units (3 mg/kg per day) |
| | Continuous renal replacement | Dose recommended by Garonzik et al [31] much greater than maximum approved dose, see article for more information. | MIC ≥ 4 µg/mL | Consider combination therapy as 30 000 International Units (3 mg/kg per day unlikely to reach targets |
| Dosage intervals | CrCl <10 mL/min | q12h | q12h |
| | CrCl 10–70 mL/min | q8–12h | q8–12h |
| | CrCl >70 mL/min | q12h | q12h |
| | Continuous renal replacement | q8h | q8h |
| Renal dose adjustment | Yes | No<sup>h</sup> |
| Maximum approved dose (caution in using doses greater than maximum approved doses) | 300 mg CBA | 2 million International Units (200 mg) |

Abbreviations: AUC, area under the curve; CBA, colistin base activity; CMS, colistimethate; CrCl, creatinine clearance; C<sub>ss,avg</sub>, average plasma steady state concentration; f, free drug; HD, hemodialysis; MIC, minimum inhibitory concentration.

<sup>a</sup> The ideal dosages of colistin and polymyxin B are largely unknown, especially in the case of renal failure, renal replacement therapy, and critical illness, because the first dosage recommendations were made before consistent pharmacokinetic data were available.

Loading and maintenance doses and dosing interval in table based on the largest pharmacokinetic studies to date, which developed the first scientifically based dosing suggestions for colistin and polymyxin B [31, 32].

<sup>b</sup> Assuming a target colistin C<sub>ss,avg</sub> of 2.5 µg/mL. However, note this target should be based on MIC, site, and severity of infection. At a daily dose of CMS at or close to the maximum product-recommended dose (300 mg), it is very difficult to achieve adequate plasma concentrations of colistin with CMS monotherapy, especially if treating an infection due to an organism with an MIC >0.5 µg/mL or in a patient with a creatinine clearance of >70 mL/min/1.73 m<sup>2</sup>. In these situations, authors suggested that it may be best to use CMS/colistin in combination with other active agents.

<sup>c</sup> Use the lower of ideal or actual body weight (kg).

<sup>d</sup> Not to exceed 300 mg.

<sup>e</sup> Dose on actual body weight.

<sup>f</sup> Caution should be used when dosing beyond maximum recommended dose of 300 mg. Garonzik et al [31] dosing not recommended for patients with CrCl >70 mL/min/1.73 m<sup>2</sup> unless a low C<sub>ss,avg</sub> can be recommended. Colistin may be best used as a part of combination therapy for patients with good renal function.

<sup>g</sup> On non-HD days give 37.5 mg q12h, and on HD days give an additional 30% of daily maintenance dose after HD, thus dose 1 = 37.5 mg and dose 2 = 60 mg.

<sup>h</sup> Preliminary data suggest that the dose of polymyxin B need not be renally adjusted even in patients on hemodialysis; however, package insert dosing recommendations for polymyxin B include vague renal dosing recommendations that have been followed in all of the polymyxin B literature to date, and, therefore, the efficacy and safety of nonrenally adjusted polymyxin B remains unclear [85–87].
high-dose prolonged-infusion meropenem had a high PTA (85%).

Although pharmacokinetic data appears favorable, there are only limited clinical data assessing the efficacy of carbapenem monotherapy in the treatment of CRE infections. In a study that compiled data from several studies, in 44 patients treated with carbapenem monotherapy for infections due to carbapenemase-producing \textit{K pneumoniae}, treatment efficacy varied based on MIC [20]. The efficacy ranged from 69% (MIC ≤ 4 µg/mL), 60% (MIC 8 µg/mL), to only 29% (MIC > 8 µg/mL). Treatment efficacy when the MIC was ≤4 µg/mL was similar to that observed in 22 patients with noncarbapenemase-producing \textit{K pneumoniae} infections (73%). The lowest mortality rate was observed in patients who received carbapenem-containing-combination treatment (MIC ≤ 4 µg/mL). The mortality rate was lower for patients who received carbapenem-containing regimens compared with noncarbapenem regimens (12% [3 of 26] vs 41% [46 of 112]; \(P = 0.006\)) [20]. In a recent review, the mortality rate associated with carbapenem monotherapy was unacceptably high (40.1%) [15]. For patients with serious infections and/or who are critically ill, adding another active agent may increase the probability of clinical response.

In addition, several retrospective studies have observed lower rates of mortality with carbapenem-based combination therapy compared with noncarbapenem combination therapy [20–23]. The efficacy of carbapenem combination therapy also appears to be MIC dependent. In a large multicenter study where high-dose prolonged-infusion meropenem was used (2000 mg administered over ≥3 hours q8h), mortality rates stratified by MIC were as follows: 13.3% (2 of 15) for ≤4 µg/mL, 25.0% (1 of 4) for 8 µg/mL, and 35.3% (6 of 17) for ≥16 µg/mL [22]. In a large cohort study (see Table 4), the mortality rate associated with carbapenem-containing-combination therapy for carbapenemase-producing \textit{K pneumoniae} bacteremia increased from 19.4% (6 of 31, MIC ≤ 8 µg/mL) to 35.5% (11 of 31, MIC > 8 µg/mL) [23]. In a review of 20 clinical studies, carbapenem-containing regimens were associated with lower mortality than noncarbapenem-containing regimens (18.8% vs 30.7%) [15]. Although these findings are encouraging, it is important to note that not all reports have focused on carbapenem-containing regimens. A retrospective study conducted from a 10-bed intensive care unit (ICU) showed success in 24 of 26 (92%) patients with KPC infections (16 ventilator-associated pneumonias [VAP], 7 bloodstream infections, 2 urinary tract infections [UTIs], 1 peritonitis) with the use of carbapenem-sparing-combination therapy regimens [24].

Dual-carbapenem combination treatment may be an effective option for infections caused by pandrug-resistant CRE; however, data are limited to selected case reports [25, 26]. Experimental data have shown that the KPC enzyme may have increased affinity for ertapenem than other carbapenems; therefore, when given together, KPC preferentially deactivates ertapenem, which hinders degradation and improves the activity of the concomitant carbapenem [27, 28]. In case reports, ertapenem plus either doripenem or meropenem has been used successfully to treat select pandrug-resistant and colistin-resistant KPC-producing \textit{K pneumoniae} infections (bacteremia, VAP, and UTI). Dual-carbapenem combination treatment is a promising option, which may be most effective in combination with a third drug [29].

Polymyxins

Colistin (polymyxin E) and polymyxin B are considered to be the most active in vitro agents against CRE [30]. Polymyxin B and colistin differ by a single amino acid. A comparison of the 2 drugs can be found in Table 5. There are several potential advantages to the use of polymyxin B over colistin, many of which stem from the fact that colistin is administered as the inactive prodrug colistimethate (CMS). Only a small fraction of CMS is converted to colistin and this conversion is slow, with maximum concentrations occurring ≥7 hours after administration [31]. Because the conversion of CMS to colistin is slow and inefficient in patients with normal renal function, the majority of CMS is cleared before conversion to colistin. Therefore, despite being dosed at a lower milligram per kilogram per day dose, polymyxin B can achieve higher peak serum concentrations, which are achieved much more rapidly than with colistin [31, 32].

Renal dose adjustments are necessary for colistin and CMS but are not required polymyxin B [29]. The reason for this is that there is minimal renal clearance of colistin, but the produrg CMS is predominately cleared renally [29]. As with colistin, polymyxin B undergoes extensive renal tubular reabsorption and is eliminated by mostly nonrenal clearance. More importantly, however, polymyxin B package insert dosing recommendations include vague renal dosing adjustments that have been followed in all of the polymyxin B literature to date. The efficacy and safety of nonrenally adjusted polymyxin B remains unclear. The renal clearance of CMS allows an advantage over polymyxin B that a higher concentration of active drug in the urine is reached, which would make colistin and CMS a viable UTI treatment alternative [29, 33]. Despite the potential advantages of polymyxin B use, the majority of clinical data to date for CRE infections has focused on the use of colistin.

The ideal dosages of colistin and polymyxin B are largely unknown, especially in the case of renal failure, renal replacement therapy, and critical illness [34]. Scientifically based dosing recommendations can be found in Table 5 [31, 32]. For serious infections caused by resistant Gram-negative pathogens, high total daily doses of colistin appear to be important to maximize treatment efficacy [31, 35]. In a retrospective study of 258 patients treated with CMS, 21.7% of patients on the highest total daily dose (9 million IU/day) died compared with 27.8% and 38.6% patients on lower doses of 6 and 3 million IU/day, respectively (\(P = 0.011\)) [36]. In a retrospective study of 76 patients with Gram-negative bacteremia, the median colistin dose was higher in patients who achieved microbiological
success (2.9 vs 1.5 mg/kg per day; \(P = .011\)) and 7-day survival (2.7 vs 1.5 mg/kg per day; \(P = .007\)) [35]. Another retrospective study found similar results with polymyxin B treatment [37].

Historically, neurotoxicity was an important concern with the use of polymyxins; however, with current formulations, this side effect is reported less frequently. Patients discussed in the recent literature are more critically ill, ventilated, and sedated, which might significantly limit the ability to detect neurotoxicity, which is primarily manifested as paresthesias and ataxia. However, nephrotoxicity remains a concern because it continues to occur in ≥40% patients treated with polymyxins [38]. Although nephrotoxicity has been reported with both colistin and polymyxin B use, recent evidence suggests that nephrotoxicity rates might be higher with colistin use than polymyxin B (50%–60% vs 20%–40%) [38, 39]. The use of colistin and polymyxin B at higher doses, which may be necessary for CRE infections, may be associated with a higher risk of nephrotoxicity [35, 37]. The better outcomes associated with high-dose colistin may come at the cost of worsening renal function [35]. In a retrospective study, a colistin dose of ≥5 mg/kg of ideal body weight/day was independently predictive of the development of renal insufficiency [40]. For polymyxin B, a retrospective cohort study of 276 patients demonstrated that high doses (≥200 mg/day) were independently associated with lower mortality (adjusted odds ratio [OR], 0.43; 95% confidence interval [CI], 0.23–0.79) [37]. However, the use of ≥200 mg/day was associated with a significantly higher risk of severe renal impairment (adjusted OR, 4.51; 95% CI, 1.58–12.90; \(P = .005\)). Even when controlling for the development of moderate to severe renal dysfunction, multivariate analyses showed that doses ≥200 mg/day were still associated with decreases in mortality.

Another concern with the use of polymyxins is on-treatment resistance development. Blood isolates from 1 patient infected with carbapenem-resistant \(K\) \(pneumoniae\) and treated with polymyxin B monotherapy showed a significantly increased polymyxin B MIC in just 5 days (0.75 µg/mL to 1024 µg/mL) [12]. In addition, there have been reports of colistin-resistant, carbapenem-resistant \(K\) \(pneumoniae\) outbreaks [41, 42]. Therefore, polymyxins may be most effective as part of a combination for serious CRE infections [34, 43]. In a recent review that used compiled data on 889 patients with CRE infections (bacteremia, pneumonia, intra-abdominal infections, UTIs, and surgical site infections), the mortality rate for colistin monotherapy was 42.8% [15]. A review of 15 studies which included 55 unique patients found that clinical success was lower for colistin monotherapy compared with colistin combination therapy for treatment of infections caused by KPC producers (14.3% [1 of 7] vs 72.7% [8 of 11]) [44]. In a recent cohort study of 36 patients with blood stream infections due to CRE (all but 2 yielded both OXA-48 and CTX-M ESBLs), colistin-based combination therapy was associated with better 28-day survival than noncolistin regimens (33.3% vs 5.5%; \(P = .018\)) [45].

### Tigecycline

The majority of CRE isolates remain active against tigecycline in vitro; however, resistance to tigecycline is increasing [46–48]. There are only limited clinical data to support use of tigecycline monotherapy for infections caused by CRE that demonstrate in vitro susceptibility [22, 23, 44, 49, 50]. A review which included a small number of patients with carbapenem-resistant \(K\) \(pneumoniae\), found that 71.4% (5 of 7) patients had a favorable
outcome with tigecycline treatment [44]. High mortality rates have been reported with the use of tigecycline monotherapy in the treatment of bloodstream infections due to carbapenem-resistant *K. pneumoniae* in 2 separate cohort studies (see Table 4) [22, 23]. In addition, despite in vitro susceptibility, on-treatment resistance emergence has been described [13, 43].

Tigecycline may be most effective when used at higher doses and/or in combination for serious CRE infections and depending on the source of the infection [43, 51, 52]. However, high-dose tigecycline may only transiently lead to increased plasma concentrations, because higher doses may lead to increased intracellular accumulation and tissue distribution [51]. In 30 complex patients with severe intra-abdominal infections due to KPC-producing *K. pneumoniae*, high-dose tigecycline in combination with colistin was associated with lower mortality compared with approved dose tigecycline plus colistin [53]. In a review that used compiled data on patients with various types of CRE infections, the mortality rate with tigecycline monotherapy was 41.1% [15]. A carbapenem-sparing regimen of tigecycline plus either gentamicin or colistin was effective in 92% (24 of 26) of ICU patients treated for KPC infections [24].

**Fosfomycin**

Limited data have demonstrated that fosfomycin has activity against KPC-producing *K. pneumoniae* and New Delhi metallo-β-lactamase (NDM)-1-producing *Enterobacteriaceae* [54, 55]. Fosfomycin achieves high urinary concentrations for prolonged time periods (after a single 3-gram dose, peak urine concentrations of >4000 µg/mL are obtained and concentrations above the MIC persist for up to 72 hours) [56]. Select case reports have demonstrated success of oral fosfomycin for treating UTIs caused by fosfomycin-susceptible KPC- and NDM-producing *Enterobacteriaceae* [57, 58]. Two patients with OXA-48-producing *K. pneumoniae* UTIs were successfully treated with oral fosfomycin and colistin [59].

In Europe, an intravenous fosfomycin formulation is available. In a small (n = 11) European study, intravenous fosfomycin (2–4 g q 6 h) in combination was associated with good bacteriological and clinical outcomes in all patients for various carbapenem-resistant *K. pneumoniae* infections (bacteremia, VAP, UTI, wound infections) [60]. In a report of 3 cases of KPC-producing *K. pneumoniae* bacteremia, intravenous fosfomycin was used as an adjunct “last-resort” treatment, which initially led to bacteremia control; however, ultimately, all 3 patients failed treatment due to relapse and resistance development [61]. The use of intravenous fosfomycin monotherapy for the treatment of systemic infections may be limited due to the potential for the development of drug resistance during treatment [62].

**Aminoglycosides**

Gentamicin is generally the most active aminoglycoside in vitro against carbapenem-resistant *K. pneumoniae*; however, amikacin can be most active against other CRE [49, 63, 64]. Data on the use of aminoglycosides as monotherapy are limited, and aminoglycosides monotherapy appears to be most efficacious in the treatment of UTIs [15, 44, 65]. In a retrospective cohort study of cases of carbapenem-resistant *K. pneumoniae* bacteriuria, treatment with an in vitro active aminoglycoside was associated with a significantly higher rate of microbiologic clearance compared with either polymyxin B or tigecycline [65]. In multivariate analysis, aminoglycoside treatment was independently associated with microbiologic clearance.

Aminoglycoside therapy may be most appropriate as a component of combination therapy for infections, especially UTIs, caused by CRE [66–68]. In the largest CRE bacteremia cohort study to date, the mortality rate for aminoglycoside monotherapy was 22.2% and that of combination therapy was approximately 30% (see Table 4); however, only a small number of patients (n = 9) were treated with monotherapy compared with over 50 patients treated with aminoglycoside combination therapy [23]. In a review which included 24 cases of aminoglycoside combination therapy (most often with colistin, carbapenems, fluoroquinolones, and tigecycline), all patients who failed aminoglycoside-based combination therapy had bloodstream infections [68]. In a review of 20 clinical studies, the combination of an aminoglycoside and a carbapenem had the lowest mortality rate (11.1%) [15].

**Combination Therapy**

Combination therapy for CRE infections may decrease mortality compared with monotherapy. It is also an important empiric consideration when a CRE is suspected [21, 22, 34]. Benefits of combination therapy include reduction of initial inappropriate antimicrobial therapy, potential synergistic effects, and suppression of emerging resistance [34]. Because monotherapy options all have significant limitations (pharmacokinetics, toxicity, emergence of resistance), combination therapy can be an attractive option to optimize therapy. However, with combination therapy, there is the potential for an increased risk for the development of *Clostridium difficile* infection, colonization or infection with other resistant bacteria, and adverse effects such as nephrotoxicity [14, 34]. Combination therapy leads to increased antimicrobial pressure and may potentiate the development of antimicrobial resistance. The benefits of combination therapy may outweigh the risks, and many experts recommend combination therapy as opposed to monotherapy for the treatment of severe CRE infections [34, 43].

As previously described, emerging clinical evidence suggests that treatment with combination therapy may be beneficial for serious CRE infections [15, 21–24, 44, 45, 69–71]. In the most comprehensive review to date, which included data on 889 patients with CRE infections, combination therapy with 2 or more in vitro active agents was associated with lower mortality than treatment with a single in vitro active agent (27.4% [121 of 441] vs 38.7% [134 of 346]; *P* < .001) [15]. Monotherapy resulted in
mortality rates that were not significantly different from those in patients treated with inappropriate therapy with no in vitro ac-
tive agents (46.1% [48 of 102]). Another comprehensive review
found similar mortality results (18.3% vs 49.1%) [34]. Several
observational studies have assessed the efficacy of combination
therapy vs monotherapy in the treatment of bloodstream infec-
tions due to carbapenemase-producing K pneumoniae (mostly
KPC producers) [21–23, 69]. A summary of these studies
can be found in Table 4. In the first study, all patients who re-
cieved combination therapy had favorable outcomes, whereas
46.7% patients who received active monotherapy died [69].
The next retrospective cohort study also demonstrated lower
mortality rate with combination treatment (usually a carbape-
nem with colistin or tigecycline) compared with monotherapy
[21]. A larger multicenter retrospective cohort study also found
similar results [22]. It is interesting to note that meropenem, co-
listin, tigecycline combination was associated with a significant
reduction in mortality, even in patients who received inap-
nropriate empiric therapy then this combination as definitive ther-
apy. In the most recent and largest cohort study to date, com-
ination therapy again was associated with lower mortality than
monotherapy (27.2% vs 44.4%) [23]. Combination therapy
was an independent predictor of survival, which was mostly due
to the effectiveness of carbapenem-containing regimens.

Emerging Treatment
An overview of emerging treatment options can be found in
Table 6. The Food and Drug Administration approved ceftazi-
dime-avibactam in February 2015 for the treatment of complicated
intra-abdominal infections (cIAIs) and complicated UTIs (cUTIs)
[72]. It is expected that ceftazidime-avibactam will be available in
the second quarter of 2015. Cefazidime-avibactam received a pri-
ority review based on Phase II data, and it should be reserved for
patients with limited or no alternative treatment options [72].

Cefazidime-avibactam is combination of an established
broad-spectrum cephalosporin (ceftazidime) and a novel β-
lactamase inhibitor (avibactam) with activity against class A,
class C, and some class D β-lactamases [73, 74]. Avibactam
has activity against KPC-type carbapenemases and some OXA
enzymes; however, it has no activity against metallo-β-lactamas-
es (such as NDM-1) [73, 74]. In 2 Phase II trials, efficacy and
safety rates were similar for ceftazidime-avibactam versus com-
parator drugs for the treatment of cIAI and cUTI [75, 76]. For
cIAI, favorable clinical response rates were observed for ceftazid-
ime-avibactam (2000/500 mg IV q8h) plus metronidazole
(500 mg IV q8h) compared with meropenem (1000 mg IV
q8h; 91.2% [62 of 68] vs 93.4% [71 of 76]) [76]. For cUTI, fa-
vorable clinical response rates were observed for ceftazidime-
avibactam (500/125 mg IV q8h) compared with imipenem
(500 mg IV q6 h; 85.7% [24 of 28] vs 80.6% [29 of 36]) [75].
The most common adverse drug reactions (>10%) in trials
were vomiting, nausea, constipation, and anxiety [72]. In a
Phase III trial, clinical cure rates for ceftazidime-avibactam
were lower for patients with a creatinine clearance between 30
and 50 mL/min [72]. In addition, seizures have been reported
with the use of ceftazidime, and, as with other β-lactam antibi-
otics, there is a risk for serious hypersensitivity [72]. Phase III
trials are underway assessing ceftazidime-avibactam for the
treatment of cIAI, cUTI, and nosocomial pneumonia, and re-
results will likely be available in late 2015 [72].

CONCLUSIONS
The burden of antimicrobial resistance among Gram-negative
pathogens, particularly carbapenem-resistant Enterobacteri-
aceae, is increasing rapidly worldwide. Treatment options for se-
rious CRE infections remain extremely limited at this time.
Optimization of dosing of currently available agents and com-
bination therapy may be the most appropriate treatment strat-
egies at this time. However, continued research is desperately
needed, in particular randomized controlled trials, to determine
the most appropriate treatment for serious CRE infections.

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