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 ß-lactamases. However, *Enterobacteriaceae* that produce carbapenemases, which are enzymes that deactivate carbapenems and most other ß-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 ß-lactamases, which are enzymes that bind and deactivate ß-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 ß-lactamases ([ESBLs] a subset of ß-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 ß-lactam antibiotics including "last-line" carbapenems. Carbapenem resistance can also be conferred when porin deficiencies, which allow decreased entry of the ß-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

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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 ß-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 overviews of current treatment options can be found in Tables 2 and 3, respectively.

Table 1. Overview of Carbapenemase Enzyme Types in *Enterobacteriaceae*

Ambler Class (Active Site)	Example Enzymes	Host Organisms	Enzyme Substrates					Inhibition by Currently Available β-Lactamase Inhibitors (Clavulanic Acid, Tazobactam, and Sulbactam)	Region Mostly Found In
			Penicillins	Narrow Spectrum Cephalosporins	Extended Spectrum Cephalosporins	Aztreonam	Carbapenems		
A (serine)	KPC-2 to 22	Mainly found in *Klebsiella pneumoniae* (have been identified in other *Enterobacteriaceae* and nonfermenters)	Yes	Yes	Yes	Yes	Yes	Variable[a]	United States and worldwide
B (Zinc binding thiol –"MBLs")	NMD-1 IMP-I VIM-1	*Enterobacteriaceae* and nonfermenters	Yes	Yes	Yes	No	Yes	No	Southern Asia
D (serine)	OXA-48	*Enterobacteriaceae* (other types of OXA carbapenemases mainly found in *Acinetobacter* spp.)	Yes	Yes	Weak Activity[b]	No	Minimal Hydrolysis[b]	No	Southern Europe

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

[a] Some KPC enzyme types, such as KPC-2, can hydrolyze clavulanic acid, tazobactam, and sulbactam. However, this ability to hydrolyze these β-Lactamase Inhibitors is uncommon in Class A enzymes [8, 9].

[b] OXA-48 is weakly active against extended spectrum cephalosporins and hydrolyzes carbapenems only minimally [10].

Table 2. Potential Treatment Algorithm for Carbapenem-Resistant KPC-Producing *Klebsiella pneumoniae

Infection Source	Empiric Treatment: Core Drugs	Empiric Treatment: Possible Adjunct Drugs	Antimicrobial Susceptibility Directed Treatment Considerations
Bloodstream	• High-dose meropenem or doripenem • And polymyxin B	• Aminoglycoside • Tigecycline • Fosfomycin • Rifampin	Meropenem/doripenem: • MIC ≤16 μg/mL continue high-dose meropenem/ doripenem • MIC >16 μg/mL consider alternative in vitro active antimicrobial[a] Polymyxin B/colistin: • MIC ≤ 2 μg/mL continue polymyxin B/colistin[b,c] • MIC >2 μg/mL consider alternative in vitro active antimicrobial If both meropenem/doripenem MIC (>16 μg/mL) and polymyxin B/colistin MIC (>2 μg/mL), then consider a high-dose tigecycline-based regimen or a dual dual carbapenem-based regimen[d,e] If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen[e] Tigecycline: • MIC ≤1 μg/mL consider tigecycline[d] • MIC >1 μg/mL consider alternative in vitro active antimicrobial Fosfomycin[f]: • MIC ≤32 μg/mL consider fosfomycin • MIC >32 μg/mL consider alternative in vitro active antimicrobial Amioglycoside: • MIC ≤2 μg/mL (Gentamicin/ Tobramycin) or ≤4 μg/mL (Amikacin) consider aminoglycoside • MIC >2 (Gentamicin/ Tobramycin) or >4 μg/mL (Amikacin) consider alternative in vitro active antimicrobial
Lung	• High-dose meropenem or doripenem • And polymyxin B	• Tigecycline • Aminoglycoside • Fosfomycin • Rifampin	
Gastrointestinal/ biliary tract	• High-dose meropenem or doripenem • And polymyxin B • And high-dose tigecycline	• Fosfomycin • Rifampin	
Urine	• High-dose meropenem or doripenem • And fosfomycin[g] • Or aminoglycoside[g]	• Colistin • Aminoglycoside	

Abbreviations: CRE, carbapenem-resistant enterobacteriaceae; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; OXA, oxacillinase.

*CRE infections are complicated and associated with high mortality; always consult a local infectious diseases expert in the management of serious CRE infections and always base treatment on antimicrobial susceptibility results. If the pathogen is suspected to be a MBL or OXA-48, aztreonam may be a preferred empiric core drug. If aztreonam MIC ≤8 μg/mL, consider continuing aztreonam at a dose of 6 to 8 g/day split into 3–4 doses that are given as 3–4 hours infusion. For patients who are critically ill or with deep-seated infections, consider empiric and antibiogram-directed combination therapy with 3 drugs. There are limited clinical data supporting the use of aminoglycosides, rifampin, and fosfomycin. If any of these drugs have in vitro activity and are selected for use (especially for infections outside the urinary tract for aminoglycosides and fosfomycin), consider use in combination with 2 other in vitro active drugs due the potential for the emergence of on-treatment resistance.

[a] Pharmacokinetic data have found that high-dosed, prolonged infusion meropenem has a high probability of target attainment up to an MIC of 16 μg/mL. However, mortality may be higher with meropenem MICs ≥8 μg/mL. Strongly consider combination therapy with moderately elevated (≥4 μg/mL) to elevated (≥8–16 μg/mL) meropenem MICs.

[b] May be difficult to achieve adequate plasma concentrations of polymyxin B/colistin with a polymyxin B/colistin MIC of 1–2 μg/mL.

[c] There are several challenges associated with polymyxin B/colistin MIC testing (see refs. [77, 78] for more information).

[d] High-dose tigecycline should always be considered if a tigecycline-based regimen is used. If tigecycline is used as an adjunct drug, consider the tigecycline MIC and risks and benefits of using high dosing vs traditional dosing.

[e] Dual carbapenem-based regimen should include high-dose meropenem or high-dose doripenem and ertapenem 1 gm daily, and it may be most effective in combination with a third drug.

[f] Oral fosfomycin should not be used for management of infections outside the urinary tract. Intravenous fosfomycin is not available in the United States. See text and Table 3 for more information on fosfomycin treatment.

[g] Urinary tract infections in noncritically ill patients may be successfully treated with monotherapy with in vitro active fosfomycin or an aminoglycoside. However, combination therapy may still be warranted due to the potential for the emergence of resistance. In critically ill patients, strongly consider combination therapy.

CARBAPENEMS

Pharmacokinetic data suggest that T > minimum inhibitory concentration (MIC) targets can be achieved using high-dose prolonged-infusion carbapenems when carbapenem MICs are relatively low (<4 μg/mL) or even moderately elevated (8–16 μg/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 μg/mL [16]. In another study, the PTA for an MIC of 4 μg/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) and 93% (1000 mg q8h) compared with 69% for traditional-infusion (1000 mg q8h) [17]. At an MIC of 8 μg/mL, only

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[a] (High and/or Prolonged Infusion) for CRE Infections	Toxicity	Clinical Pearls
Carbapenems*						
Meropenem[b]	Bactericidal (time dependent); cell wall inhibition (by inhibition of cell wall cross-linking)	40%–50% fTime > MIC[c]	IV: 1000 mg IV q8h[REN]	IV: 2000 mg q8h over 4 h[REN]	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.
Doripenem[b]	Bactericidal (time dependent); cell wall inhibition (by inhibition of cell wall cross-linking)	40%–50% fTime > MIC[c]	IV: 500 mg q8h [REN]	IV: 1000–2000 mg q8h over 4 h[REN]	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%).	
Ertapenem[b]	Bactericidal (time dependent); cell wall inhibition (by inhibition of cell wall cross-linking)	40%–50% fTime > MIC[c]	IV: 1000 mg q24h[REN]		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%).	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.
Polymyxins						
Colistin[b]	Bactericidal[d] (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[b]	Bactericidal[d] (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.

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
Aminoglycosides						
Gentamicin[b]	Bactericidal (concentration dependent); protein synthesis inhibition (at 30S ribosomal subunit)	fCmax:MIC ≥ 10	IV: 5 mg/kg daily dose[REN]	IV: 7–10 mg/kg[REN,e]	Nephrotoxicity, ototoxicity	To optimize therapy and minimize the risk of toxicity, daily administration and limiting therapy to the shortest possible course is preferred.
Tobramycin[b]	Bactericidal (concentration dependent); protein synthesis inhibition (at 30S ribosomal subunit)	fCmax:MIC ≥ 10	IV: 5 mg/kg daily dose[REN]	IV: 7–10 mg/kg[REN,e]	Nephrotoxicity, ototoxicity	Therapy should be individualized through serum drug level monitoring when microbiological data become available.
Amikacin[b]	Bactericidal (concentration dependent); protein synthesis inhibition (at 30S ribosomal subunit)	fCmax:MIC ≥ 10	IV: 10 mg/kg[REN]	IV: 15 mg/kg[REN,f]	Nephrotoxicity, ototoxicity	Aminoglycoside therapy may be most appropriate as a component of combination therapy for CRE infections, especially UTIs.
Glycylcyclines						
Tigecycline[b]	Bacteriostatic; protein synthesis inhibition (at 30S ribosomal subunit)	fAUC:MIC 1	IV: 100 mg loading dose, then 50 mg q12h[HEP]	IV: 200 mg loading dose, then 100 mg q12-24h[HEP]	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% fTime > MIC	PO: 3 g once[g]	PO: 3 g every 2–3 d IV: 1 to 16 g daily divided in doses every 6 to 12 h[REN]	PO: Gastrointestinal effects (1%–10%), headache (4%–10%), vaginitis (6%–8%) IV: Hypokalemia (26%), local pain (4%), heart failure (3%)[i]	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.

Abbreviations: AUC, area under the curve; C_{max}, maximal concentration; CMS, colistimethate; CRE, carbapenem-resistant *Enterobacteriaceae*; *E coli*, *Escherichia coli*; 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.

* Imipenem not generally used for the treatment of CRE infections, because use in high-doses or in prolonged infusions is limited due to higher risk for seizures and poor stability at room temperature.

[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 *f*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 *f*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 ≤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 ≤ 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 (%)	Mortality If In vitro Active Therapy, n (%)	Combination Therapy (CT) vs Monotherapy (MT) Mortality (In vitro Active Therapy), n (%)			Mortality Select Treatment Regimens (In vitro Active Therapy), n (%)			Predictors of Mortality in Multivariate Analysis	Predictors of Survival in Multivariate Analysis
							CT	MT	*P* Value	Drug	CT[a]	MT[b]		
Zarkotou (2011)	Greece	53	KPC-2 (n = 53); enzyme coproduction SHV-12 (n = 46) CTX-M-15 (n = 4)	Line related, 12 (22.6%) Respiratory tract, 7 (13.2%) Urinary tract, 6 (11.3%) Skin or soft tissue, 4 (7.5%) CNS, 1 (1.9%) Source not detected, 23 (43.4%)	Crude mortality: 28 (52.8%)	Infection mortality: 7 of 35 (20.0%)	0/20 (0%)	7/15 (46.7%)	.001	Carb Col Tig Amg	0/4 (0%) 0/14 (0%) 0/17 (0%) 0/8 (0%)	1/1 (100%) 4/7 (66.7%) 2/5 ((40.0%) 0/2 (0%)	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, 0.05; 95% CI, .003–.74; *P* = .030).
Qureshi (2012)	United States	41	KPC-2 (n = 21), KPC-3 (n = 20)	Line related, 13 (31.7%) Respiratory tract (pneumonia), 10 (24.4%) Urinary tract, 7 (17.1%) Source not detected, 6 (14.6%)	Crude 28 d mortality; 16 (39.0%)	Crude 28 d mortality; 13 of 34 (38.2%)	2/15 (13.3%)	11/19 (57.8%)	.01	Carb Col Tig Amg	2/9 (22.2%) 1/7 (14.3%) 0/6 (0%) 0/3 (0%)	2/4 (50.0%) 4/7 (57.1%) 4/5 (80.0%) 0/1 (0%)	None	Definitive combination therapy (OR, 0.07; 95% CI, .009–.71; *P* = .02).
Tumbarello (2012)	Italy	125	KPC-2 (n = 27), KPC-3 (n = 98)	Line related, 13 (10.4%) Respiratory tract, 28 (22.4%) Urinary tract, 17 (13.6%) Other, 5 (4.0%) Source not detected, 75 (60.0%)	Crude 30 d mortality; 52 (41.6%)	Same as overall mortality	27/79 (34.1%)	25/46 (54.3%)	.02	Carb Col Tig Amg	7–14/37 (18.9–37.8%)[c] 9–20/51 (17.6–39.2%)[c] 16- 21/61 (26.2–34.4%)[c] 18/32 (56.3%)	. . . 11/22 (50.0%) 10/19 (52.6%) 4/5 (80.0%)	Presentation with septic shock (OR, 7.17; 95% CI, 1.65–31.03; *P* = .008), Inadequate empiric therapy (OR, 4.17; 95% CI, 1.61–10.76; *P* = .003), APACHE II score (OR, 1.04; 95% CI, 1.02–1.07; *P* < .001).	Combination of tigecycline, colistin, and meropenem (OR, 0.11; 95% CI, .02–.69; *P* = .009;).
Daikos (2014)	Greece	205	KPC-2 (n = 163, 36 coproduced VIM-1), VIM-1 (n = 42)	Line related, 22 (10.7%) Respiratory tract, 43 (21.0%) Abdomen, 29 (14.1%) Genitourinary tract, 19 (9.3%) Skin or soft tissues, 6 (2.9%)CNS, 3 (1.5%) Source not detected, 83 (40.5%)	Crude 28 d mortality; 82 (40.0%)	Crude 28 d mortality; 60 of 175 (34.3%)	28/103 (27.2%)	32/72 (44.4%)	.018	Carb Col Tig Amg	6/31 (19.4%)% 16/56 (28.6%)[d] 19/67 (28.4%)[d] 18/57 (31.6%)[d]	7/12 (58.3%) 12/22 (54.5%) 11/27 (40.7%) 2/9 (22.2%)	Ultimately fatal disease (HR, 3.25; 95% CI, 1.51–7.03; *P* = .003), Rapidly fatal underlying disease (HR, 4.20; 95% CI, 2.19–8.08; *P* < .001), Septic shock (HR, 2.15; 95% CI, 1.16–3.96; *P* = .015).	Combination therapy (HR mortality MT vs CT 2.08; 95% CI, 1.23–3.51; *P* = .006), mostly due to the effectiveness of carbapenem-containing regimens.

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.

Table 5. Comparison of Colistin vs Polymyxin B*

		Colistin		Polymyxin B	
Form administered		Prodrug (CMS)		Active drug	
Best pharmacodynamics predictor of activity		fAUC/MIC		fAUC/MIC	
Dosing units		United States – mg CBA Europe – International Units		International Units	
Dosing equivalents		30 mg CBA = 80 mg CMS = 1 million International Units CMS		10 000 International Units = 1 mg	
Loading dose[a]		5 mg CBA/kg[b,c,d] (loading dose required)		20 000–25 000 International Units (2–2.5 mg)/kg[e] (loading dose recommended)	
Time until maintenance dose[a]		12 to 24 h		12 h	
Maintenance dose[a]	Not on renal replacement therapy[b,f]	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[b,g]	Non-HD day = 75 mgCBA 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			
	CrCl >70 mL/min	q8–12h			
	Intermittent HD	q12h			
	Continuous renal replacement	q8h			
Renal dose adjustment		Yes		No[h]	
Maximum approved dose (caution in using doses greater than maximum approved dosages)		300 mg CBA		2 million International Units (200 mg)	

Abbreviations: AUC, area under the curve; CBA, colistin base activity; CMS, colistimethate; CrCl, creatinine clearance; $C_{ss,avg}$, average plasma steady state concentration; f, free drug; HD, hemodialysis; MIC, minimum inhibitory concentration.

* For more information on colistin and polymyxin B MIC testing, see ref. [78].

[a] 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].

[b] Assuming a target colistin $C_{ss,avg}$ 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^2. In these situations, authors suggested that it may be best to use CMS/colistin in combination with other active agents.

[c] Use the lower of ideal or actual body weight (kg).

[d] Not to exceed 300 mg.

[e] Dose on actual body weight.

[f] 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^2 unless a low $C_{ss,avg}$ can be recommended. Colistin may be best used as a part of combination therapy for patients with good renal function.

[g] 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.

[h] 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 polmyxin 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 *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 *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]; $P = .006$) [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 carbapemase-producing *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 *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 prodrug 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 ($P = .011$) [36]. In a retrospective study of 76 patients with Gram-negative bacteremia, the median colistin dose was higher in patients who achieved microbiological

Table 6. Drug in Late Stage (Phase 3) Clinical Development With Activity Against Carbapenem-Resistant *Enterobacteriaceae*

Drug	Class	Stage of Development	Carbapenemase Spectrum	Phase III Studies	Proposed Dose
Ceftazidime-avibactam	Cephalosporin-β-lactamase inhibitor	Phase 3	Activity against KPCs and OXA-48 (not active against MBLs)	• Ceftazidime-avibactam + metronidazole vs meropenem for cIAI • Ceftazidime-avibactam + metronidazole vs meropenem for NP • Ceftazidime-avibactam vs doripenem for cUTI	IV: 2000 mg (ceftazidime)/500 mg (avibactam) q8h
Ceftaroline-avibactam	Cephalosporin-β-lactamase inhibitor	Entering Phase 3	Active against KPCs and OXA-48 (not active against MBLs)	• Ceftaroline- avibactam vs doripenem for cUTI (Phase II study, proposed Phase III studies not yet available)	IV: 600 mg (ceftaroline)/600 mg (avibactam) q8h
Plazomicin	Aminoglycoside	Phase 3	Active against most KPCs (not active against many NDMs)	• Plazomicin vs colistin when combined with a second antibiotic (either meropenem or tigecycline) for CRE BSI or NP	IV: 10–15 mg/kg q24h
Eravacycline	Tetracycline	Phase 3	Active against KPCs	• Eravacycline vs ertapenem for cIAI • Eravacycline vs levofloxacin for cUTI	IV: 1.0 mg/kg q12h or 1.5 mg/kg q24h PO: 200–250 mg q12h

Abbreviations: BSI, bloodstream infection; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant enterobacteriaceae; cUTI, complicated urinary tract infection; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NP, nosocomial pneumonia; OXA, oxacillinase; IV, intravenous; PO, oral.

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], .23–.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 q6 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 active 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 infections 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 received 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 carbapenem 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, colistin, tigecycline combination was associated with a significant reduction in mortality, even in patients who received inappropriate empiric therapy then this combination as definitive therapy. In the most recent and largest cohort study to date, combination 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 ceftazidime-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. Ceftazidime-avibactam received a priority review based on Phase II data, and it should be reserved for patients with limited or no alternative treatment options [72].

Ceftazidime-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-lactamases (such as NDM-1) [73, 74]. In 2 Phase II trials, efficacy and safety rates were similar for ceftazidime-avibactam versus comparator drugs for the treatment of cIAI and cUTI [75, 76]. For cIAI, favorable clinical response rates were observed for ceftazidime-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, favorable 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 antibiotics, there is a risk for serious hypersensitivity [72]. Phase III trails are underway assessing ceftazidime-avibactam for the treatment of cIAI, cUTI, and nosocomial pneumonia, and results will likely be available in late 2015 [72].

CONCLUSIONS

The burden of antimicrobial resistance among Gram-negative pathogens, particularly carbapenem-resistant *Enterobacteriaceae*, is increasing rapidly worldwide. Treatment options for serious CRE infections remain extremely limited at this time. Optimization of dosing of currently available agents and combination therapy may be the most appropriate treatment strategies 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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References

1. Nordmann P, Dortet L, Poirel L. Carbapenem resistance in *Enterobacteriaceae*: here is the storm! Trends Mol Med **2012**; 18:263–72.
2. Centers for Disease Control and Prevention. Vital signs: carbapenem-resistant *Enterobacteriaceae*. MMWR Morb Mortal Wkly Rep **2013**; 62:165–70.
3. Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2013. Atlanta: CDC, **2013**. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed 26 November 2014.
4. Hossain A, Ferraro MJ, Pino RM, et al. Plasmid-mediated carbapenem-hydrolyzing enzyme KPC-2 in an Enterobacter sp. Antimicrob Agents Chemother **2004**; 48:4438–40.
5. Peleg AY, Franklin C, Bell JM, Spelman DW. Dissemination of the metallo-beta-lactamase gene blaIMP-4 among gram-negative pathogens in a clinical setting in Australia. Clin Infect Dis **2005**; 41:1549–56.
6. Leavitt A, Navon-Venezia S, Chmelnitsky I, Schwaber MJ, Carmeli Y. Emergence of KPC-2 and KPC-3 in carbapenem-resistnt *Klebsiella* pneumoniae strains in an Israeli hospital. Antimicrob Agents Chemother **2007**; 51:3026–9.
7. Akova M, Daikos GL, Tzouvelekis L, Carmeli Y. Interventional strategies and current clinical experience with carbapenemase-producing Gram-negative bacteria. Clin Microbiol Infect **2012**; 18:439–48.

8. Papp-Wallace KM, Bethel CR, Distler AM, Kasuboski C, Taracila M, Bonomo RA. Antimicrob Agents Chemother. Inhibitor resistance in the KPC-2 beta-lactamase, a preeminent property of this class A beta-lactamase. **2010**; 54:890–7.
9. Temkin E, Adler A, Lerner A, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: biology, epidemiology, and management. Ann N Y Acad Sci. **2014**; 1323:22–42.
10. Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: the phantom menace. J Antimicrob Chemother. **2012**; 67:1597–606.
11. Bratu S, Tolaney P, Karumudi U, et al. Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents. J Antimicrob Chemother **2005**; 56:128–32.
12. Lee J, Patel G, Huprikar S, et al. Decreased susceptibility to polymyxin B during treatment for carbapenem-resistant *Klebsiella pneumoniae* infection. J Clin Microbiol **2009**; 47:1611–2.
13. Anthony KB, Fishman NO, Linkin DR, et al. Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. Clin Infect Dis **2008**; 46:567–70.
14. Paul M, Carmeli Y, Durante-Mangoni E, et al. Combination therapy for carbapenem-resistant Gram-negative bacteria. J Antimicrob Chemother **2014**; 69:2305–9.
15. Tzouvelekis LS, Markogiannakis A, Piperaki E, et al. Treating infections caused by carbapenemase-producing *Enterobacteriaceae*. Clin Microbiol Infect **2014**; 20:862–72.
16. Roberts JA, Kirkpatrick CM, Roberts MS, et al. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother **2009**; 64:142–50.
17. Kuti JL, Dandekar PK, Nightingale CH, Nicolau DP. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. J Clin Pharmacol **2003**; 43:1116–23.
18. Bulik CC, Nicolau DP. In vivo efficacy of simulated human dosing regimens of prolonged-infusion doripenem against carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2010**; 54:4112–5.
19. Li C, Kuti JL, Nightingale CH, Nicolau DP. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. J Clin Pharmacol **2006**; 46:1171–8.
20. Daikos GL, Markogiannakis A. Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems? Clin Microbiol Infect **2011**; 17:1135–41.
21. Qureshi ZA, Paterson DL, Potoski BA, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother **2012**; 56:2108–13.
22. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. Clin Infect Dis **2012**; 55:943–50.
23. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother **2014**; 58:2322–8.
24. Sbrana F, Malacarne P, Viaggi B, et al. Carbapenem-sparing antibiotic regimens for infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* in intensive care unit. Clin Infect Dis **2013**; 56:697–700.
25. Giamarellou H, Galani L, Baziaka F, Karaiskos I. Effectiveness of a double-carbapenem regimen for infections in humans due to carbapenemase-producing pandrug-resistant *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2013**; 57:2388–90.
26. Ceccarelli G, Falcone M, Giordano A, et al. Successful ertapenem-doripenem combination treatment of bacteremic ventilator-associated pneumonia due to colistin-resistant KPC-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2013**; 57:2900–1.
27. Bulik CC, Nicolau DP. Double-carbapenem therapy for carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2011**; 55:3002–4.
28. Wiskirchen DE, Crandon JL, Nicolau DP. Impact of various conditions on the efficacy of dual carbapenem therapy against KPC-producing *Klebsiella pneumoniae*. Int J Antimicrob Agents **2013**; 41:582–5.
29. Zavascki AP, Bulitta JB, Landersdorfer CB. Combination therapy for carbapenem-resistant Gram-negative bacteria. Expert Rev Anti Infect Ther **2013**; 11:1333–53.
30. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). J Antimicrob Chemother **2011**; 66:2070–4.
31. Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother **2011**; 55:3284–94.
32. Sandri AM, Landersdorfer CB, Jacob J, et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. Clin Infect Dis **2013**; 57:524–31.
33. Bergen PJ, Landersdorfer CB, Zhang J, et al. Pharmacokinetics and pharmacodynamics of 'old' polymyxins: what is new? Diagn Microbiol Infect Dis **2012**; 74:213–23.
34. Petrosillo N, Giannella M, Lewis R, Viale P. Treatment of carbapenem-resistant *Klebsiella pneumoniae*: the state of the art. Expert Rev Anti Infect Ther **2013**; 11:159–77.
35. Vicari G, Bauer SR, Neuner EA, Lam SW. Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia. Clin Infect Dis **2013**; 56:398–404.
36. Falagas ME, Rafailidis PI, Ioannidou E, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. Int J Antimicrob Agents **2010**; 35:194–9.
37. Elias LS, Konzen D, Krebs JM, Zavascki AP. The impact of polymyxin B dosage on in-hospital mortality of patients treated with this antibiotic. J Antimicrob Chemother **2010**; 65:2231–7.
38. Akajagbor DS, Wilson SL, Shere-Wolfe KD, et al. Higher incidence of acute kidney injury with intravenous colistimethate sodium compared with polymyxin B in critically ill patients at a tertiary care medical center. Clin Infect Dis **2013**; 57:1300–3.
39. Phe K, Lee Y, McDaneld PM, et al. In vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. Antimicrob Agents Chemother **2014**; 58:2740–6.
40. Pogue JM, Lee J, Marchaim D, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. Clin Infect Dis **2011**; 53:879–84.
41. Marchaim D, Chopra T, Pogue JM, et al. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. Antimicrob Agents Chemother **2011**; 55:593–9.
42. Antoniadou A, Kontopidou F, Poulakou G, et al. Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multiclonal cluster. J Antimicrob Chemother **2007**; 59:786–90.
43. Lynch JP 3rd, Clark NM, Zhanel GG. Evolution of antimicrobial resistance among *Enterobacteriaceae* (focus on extended spectrum beta-lactamases and carbapenemases). Expert Opin Pharmacother **2013**; 14:199–210.
44. Hirsch EB, Tam VH. Detection and treatment options for *Klebsiella pneumoniae* carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. J Antimicrob Chemother **2010**; 65:1119–25.
45. Balkan II, Aygun G, Aydin S, et al. Blood stream infections due to OXA-48-like carbapenemase-producing *Enterobacteriaceae*: treatment and survival. Int J Infect Dis **2014**; 26C: 51–6.

46. Daikos GL, Markogiannakis A, Souli M, Tzouvelekis LS. Bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae*: a clinical perspective. Expert Rev Anti Infect Ther **2012**; 10:1393–404.
47. Sader HS, Farrell DJ, Flamm RK, Jones RN. Variation in potency and spectrum of tigecycline activity against bacterial strains from U.S. medical centers since its approval for clinical use (2006 to 2012). Antimicrob Agents Chemother **2014**; 58:2274–80.
48. Livermore DM, Warner M, Mushtaq S, et al. What remains against carbapenem-resistant *Enterobacteriaceae*? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. Int J Antimicrob Agents **2011**; 37:415–9.
49. Souli M, Galani I, Antoniadou A, et al. An outbreak of infection due to beta-lactamase *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* in a Greek University Hospital: molecular characterization, epidemiology, and outcomes. Clin Infect Dis **2010**; 50:364–73.
50. Nguyen M, Eschenauer GA, Bryan M, et al. Carbapenem-resistant *Klebsiella pneumoniae* bacteremia: factors correlated with clinical and microbiologic outcomes. Diagn Microbiol Infect Dis **2010**; 67:180–4.
51. Cunha BA. Pharmacokinetic considerations regarding tigecycline for multidrug-resistant (MDR) *Klebsiella pneumoniae* or MDR *Acinetobacter baumannii* urosepsis. J Clin Microbiol **2009**; 47:1613.
52. De Pascale G, Montini L, Pennisi MA, et al. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. Crit Care **2014**; 18:R90.
53. Di Carlo P, Gulotta G, Casuccio A, et al. KPC - 3 *Klebsiella pneumoniae* ST258 clone infection in postoperative abdominal surgery patients in an intensive care setting: analysis of a case series of 30 patients. BMC Anesthesiol **2013**; 13:13.
54. Tuon FF, Rocha JL, Formighieri MS, et al. Fosfomycin susceptibility of isolates with blaKPC-2 from Brazil. J Infect **2013**; 67:247–9.
55. Perry JD, Naqvi SH, Mirza IA, et al. Prevalence of faecal carriage of *Enterobacteriaceae* with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. J Antimicrob Chemother **2011**; 66:2288–94.
56. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? Eur J Clin Microbiol Infect Dis **2010**; 29:127–42.
57. Kitchel B, Sundin DR, Patel JB. Regional dissemination of KPC-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2009**; 53:4511–3.
58. Peirano G, Ahmed-Bentley J, Woodford N, Pitout JD. New Delhi metallo-beta-lactamase from traveler returning to Canada. Emerg Infect Dis **2011**; 17:242–4.
59. Navarro-San Francisco C, Mora-Rillo M, Romero-Gomez MP, et al. Bacteraemia due to OXA-48-carbapenemase-producing *Enterobacteriaceae*: a major clinical challenge. Clin Microbiol Infect **2013**; 19:E72–9.
60. Michalopoulos A, Virtzili S, Rafailidis P, et al. Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation. Clin Microbiol Infect **2010**; 16:184–6.
61. Karageorgopoulos DE, Miriagou V, Tzouvelekis LS, et al. Emergence of resistance to fosfomycin used as adjunct therapy in KPC *Klebsiella pneumoniae* bacteraemia: report of three cases. J Antimicrob Chemother **2012**; 67:2777–9.
62. Falagas ME, Kastoris AC, Kapaskelis AM, Kara georgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, *Enterobacteriaceae* infections: a systematic review. Lancet Infect Dis **2010**; 10:43–50.
63. Livermore DM, Mushtaq S, Warner M, et al. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant *Enterobacteriaceae* isolates. J Antimicrob Chemother **2011**; 66:48–53.
64. Castanheira M, Sader HS, Jones RN. Antimicrobial susceptibility patterns of KPC-producing or CTX-M-producing *Enterobacteriaceae*. Microb Drug Resist **2010**; 16:61–5.
65. Satlin MJ, Kubin CJ, Blumenthal JS, et al. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem-resistant *Klebsiella pneumoniae* from urine. Antimicrob Agents Chemother **2011**; 55:5893–9.
66. Benenson S, Navon-Venezia S, Carmeli Y, et al. Carbapenem-resistant *Klebsiella pneumoniae* endocarditis in a young adult. Successful treatment with gentamicin and colistin. Int J Infect Dis **2009**; 13: e295–8.
67. Bratu S, Brooks S, Burney S, et al. Detection and spread of *Escherichia coli* possessing the plasmid-borne carbapenemase KPC-2 in Brooklyn, New York. Clin Infect Dis **2007**; 44:972–5.
68. Lee GC, Burgess DS. Treatment of *Klebsiella pneumoniae* carbapenemase (KPC) infections: a review of published case series and case reports. Ann Clin Microbiol Antimicrob **2012**; 11:32.
69. Zarkotou O, Pournaras S, Tselioti P, et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. Clin Microbiol Infect **2011**; 17:1798–803.
70. Jernigan MG, Press EG, Nguyen MH, et al. The combination of doripenem and colistin is bactericidal and synergistic against colistin-resistant, carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2012**; 56:3395–8.
71. Falagas ME, Lourida P, Poulikakos P, et al. Antibiotic treatment of infections due to carbapenem-resistant enterobacteriaceae: systematic evaluation of the available evidence. Antimicrob Agents Chemother **2014**; 58:654–63.
72. Actavis plc. Actavis Receives U.S. FDA Approval for AVYCAZ™ (CEFTAZIDIME-AVIBACTAM). **2015**. Feb 25, Available at: http://www.prnewswire.com/news-releases/actavis-receives-us-fda-approval-for-avycaz-ceftazidime-avibactam-300041592.html. Accessed 3 March 3 2015.
73. Castanheira M, Farrell SE, Krause KM, et al. Contemporary diversity of beta-lactamases among *Enterobacteriaceae* in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. Antimicrob Agents Chemother **2014**; 58:833–8.
74. Aktas Z, Kayacan C, Oncul O. In vitro activity of avibactam (NXL104) in combination with beta-lactams against Gram-negative bacteria, including OXA-48 beta-lactamase-producing *Klebsiella pneumoniae*. Int J Antimicrob Agents **2012**; 39:86–9.
75. Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin **2012**; 28:1921–31.
76. Lucasti C, Popescu I, Ramesh MK, et al. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial. J Antimicrob Chemother **2013**; 68:1183–92.
77. Sader HS, Rhomberg PR, Flamm RK, Jones RN. Use of a surfactant (polysorbate 80) to improve MIC susceptibility testing results for polymyxin B and colistin. Diagn Microbiol Infect Dis **2012**; 74:412–4.
78. Behera B, Mathur P, Das A, et al. Evaluation of susceptibility testing methods for polymyxin. Int J Infect Dis **2010**; 14:e596–601.
79. Dudhani RV, Turnidge JD, Coulthard K, et al. Elucidation of the pharmacokinetic/pharmacodynamic determinant of colistin activity against *Pseudomonas aeruginosa* in murine thigh and lung infection models. Antimicrob Agents Chemother **2010**; 54:1117–24.
80. Dudhani RV, Turnidge JD, Nation RL, Li J. fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against *Acinetobacter baumannii* in murine thigh and lung infection models. J Antimicrob Chemother **2010**; 65:1984–90.
81. Drusano GL, Louie A. Optimization of aminoglycoside therapy. Antimicrob Agents Chemother **2011**; 55:2528–31.
82. Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. Clin Infect Dis **2008**; 46:1069–77.
83. Roussos N, Karageorgopoulos DE, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. Int J Antimicrob Agents **2009**; 34:506–15.

84. Florent A, Chichmanian RM, Cua E, Pulcini C. Adverse events associated with intravenous fosfomycin. Int J Antimicrob Agents **2011**; 37:82–3.
85. Kwa AL, Abdelraouf K, Low JG, Tam VH. Pharmacokinetics of polymyxin B in a patient with renal insufficiency: a case report. Clin Infect Dis **2011**; 52:1280–1.
86. Zavascki AP. Dose adjustment of polymyxins for renal insufficiency. Antimicrob Agents Chemother **2011**; 55:4940.
87. Sandri AM, Landersdorfer CB, Jacob J, et al. Pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis. J Antimicrob Chemother **2013**; 68:674–7.