Carbapenem-resistant Enterobacteriaceae Infections: A Review of Epidemiology and Treatment Options

Julie Harting[1,2]*

Introduction

In 2013, the Centers for Disease Control (CDC) issued antimicrobial resistance guidance ranking carbapenem-resistant Enterobacteriaceae (CRE), *Neisseria gonorrhea*, and *Clostridium difficile* as the three most urgent resistance threats in the United States [1]. CRE are defined as pathogens testing resistant to the following carbapenem antimicrobials (imipenem, meropenem, doripenem, or ertapenem) or are documented to produce a carbapenemase [2]. In the 2013 CDC report, an estimated 9,300 inpatient cases were predicted annually, and as of December 2017, CRE isolates have now been reported in all 50 states [3]. Enterobacteriaceae cause roughly 27.2% of healthcare-associated infections (HAIs) in acute care settings, with *Klebsiella pneumoniae* and *E. coli* as the predominant species [4]. Carbapenems are useful last line treatment options in multidrug-resistant gram-negative infections. Therefore, CRE are truly a healthcare threat.

Classification of Carbapenemases

The most common mechanism of carbapenem resistance is production of carbapenemases, beta-lactamase enzymes conferring one of several mechanisms of carbapenem resistance. It is important to note that not all carbapenemases are the same and can be classified using either molecular structure (Ambler classification) or functional activity (Bush-Jacoby-Medeiros classification) [5]. Ambler classes A, B, and D comprise the majority of carbapenemases and hydrolyze beta-lactams using either a serine or zinc complex that cleaves the beta-lactam ring and inactivates the antimicrobial. Among multidrug-resistant gram-negative bacteria species, Enterobacteriaceae, *Pseudomonas aeruginosa,* and *Acinetobacter baumanii* are all carbapenemase-producing organisms (CPOs).

In the United States, Class A enzymes including the *Klebsiella pneumoniae* carbapenemase (KPC) are widespread and now considered endemic. KPCs have been documented in several Enterobacteriaceae species including *Klebsiella pneumoniae, E. coli, Citrobacter sp., Enterobacter sp., and Serratia marcescens* [6]. Using isolates from 2011 – 2015, a 96% prevalence of the KPC enzyme among all carbapenemases in the United States was reported, and the KPC enzyme was most commonly acquired by *Klebsiella pneumoniae* [7]. Luckily, several new combination beta-lactams utilizing novel beta-lactamase inhibitors have been FDA approved in the United States to combat Class A carbapenemases, notably ceftazidime-avibactam and meropenem-vaborbactam.

Class B enzymes, or metallo-beta-lactamases (MBLs), are more globally distributed outside of the Unites States. They are characterized by the New Delhi metallo-beta-lactamase (NDM) endemic to India, Verona integrin-encoded metallo-beta-lactamase (VIM) found in Europe, and imipenemase metallo-beta-lactamase (IMP) in Asia and Australia [8]. These carbapenemases are very difficult to treat, as antimicrobial options are limited. To date in the United States, only older antimicrobials such as polymyxins, aminoglycosides, or glycylcosides are available.

As noted above, Class C enzymes, commonly known as cephalosporinases, do not confer carbapenem resistance are not discussed in this article. Lastly, Class D enzymes are caused by a variety of oxacillinase beta-lactamases (OXA) and are endemic in northern Africa, eastern Europe, and India. An example is the oxacillinase (OXA) enzyme subtype.

CRE Laboratory Detection

Accurate laboratory detection of carbapenemases is essential to optimize patient care and facilitate timely infection control prevention measures. In the United States, CRE isolates are reportable to state health departments, with further tracking by the CDC. Laboratories have faced challenges with accurately identifying isolates. Some isolates tested susceptible to carbapenems, however, carbapenem MICs were elevated. In addition, some automated susceptibility testing systems failed to detect low-level carbapenem resistance. In 2010, the Clinical and

Correspondence To: Julie Harting, Pharm.D.
Work Address: 2100 Gardiner Ln., Louisville, KY 40205
Work Email: jharting@sullivan.edu

Laboratory Standards Institute (CLSI) lowered the carbapenem breakpoints in an effort to facilitate detection and reporting of carbapenem-resistant isolates. The US Food and Drug Administration (FDA) shortly followed by updating medication package inserts. With the current guidance, supplemental testing outside of automated susceptibility testing instruments (AST) is no longer recommended. Institutions using older ASTs should update their equipment according to the newer breakpoints. Humphries R, et al. validated the accuracy of newer breakpoints to detect carbapenem-resistant isolates by comparing to polymerase chain reaction (PCR) assay for a variety of carbapenemase genes. Results indicated that few PCR-proven carbapenemase-producing isolates were reported as susceptible; <1% for ertapenem and imipenem, whereas 2.9% for meropenem [6]. Aside from AST, inaccuracies with the modified Hodge test have led to development of more reliable supplementary testing methodologies including the Carba-NP and carbapenem inactivation method. CLSI updates their testing recommendations annually, so please refer to that reference for the most up-to-date information.

CRE Infections

The 2013 CDC Urgent Threat Report identified the following patients at high risk for antibiotic resistant infections; immunocompromised patients (cancer chemotherapy, organ and bone marrow transplant, rheumatoid arthritis), dialysis patients, and complex surgical patients [1]. Closer examination of CRE infection literature confirms that dialysis and renal replacement therapy are indeed identifiable risk factors. Other risk factors include intensive care unit (ICU) admission, receipt of antimicrobials in the previous 90 days, cumulative antimicrobial exposures in the current admission, healthcare facility exposure/transfer, and poor functional status [9,10,11].

The impact of CRE infection on clinical outcomes is daunting. Using data from the Consortium on Resistance Against Carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE) study, a prospective, multicenter, observational cohort, Hauck et al. evaluated clinical outcomes in 260 CRE *Klebsiella pneumoniae* patients with bloodstream infection (BSI), pneumonia, and urinary tract infection (UTI) compared to those with CRE colonization and no active infection. A two-fold increase in excess mortality was observed in patients with BSI and pneumonia (27% versus 12%), but not with UTI [12]. Other studies have described CRE BSI mortality rates between 40-70% [9]. A recent BSI study demonstrated that when carbapenem resistance was caused by a carbapenemase enzyme versus another resistance mechanism (ie, outer membrane porin changes), outcomes were worse. Authors suggest that carbapenemase-mediated resistance may be more virulent, although specific virulence factors were not elucidated [13]. An international, multicenter, retrospective study including 256 cases of CRE infection described overall 28-day mortality rates of 28.1%. A disparity was observed among severities of infection; 17.3% mortality with cUTI and pyelonephritis, but up to 44% with severe infections particularly with the following comorbidities were present; renal failure, sepsis, and immune-deficiency [14]. The mortality data discussed in this section was analyzed prior to the clinical use of newer agents that will be discussed below.

Also using data from CRACKLE, Eilertson et al. compared clinical outcomes in CRE-infected patients with healthy renal function versus those with renal replacement therapy (RRT). RRT patients are known from previous studies to have increased

risk of mortality and infectious complications caused by multidrug-resistant pathogens including sepsis and pneumonia. In this study, those infected with CRE had worse outcomes than non-CRE RRT patients; 31% 28-day in hospital mortality [15]. Satlin et al. describe mortality rates of 40% in solid organ transplant and 65% of hematologic malignancy patients. Due to the potential for devastating patient outcomes in an immunocompromised population, the authors emphasize the importance of active surveillance and antimicrobial stewardship to aid in prevention of infection in these patients [16].

CRE Outbreaks

CRE isolates are a major focus of infection control programs since carbapenemases, especially KPCs, can be shared via mobile plasmids resulting in healthcare-associated institution outbreaks. It is important to implement effective infection control measures including contact isolation precautions, hand hygiene, surveillance, patient isolation, and environmental cleaning in patients with active or prior CRE infections [17]. In 2011, Detroit Medical Center reported an outbreak of colistin-resistant NDM-producing *Klebsiella pneumoniae* involving three institutions caused by patient-to-patient transmission [18]. A rural Kentucky hospital reported a CRE outbreak occurring in 2016 from the emergency room to a specific hospital ward. During a 4-month period, the facility detected 23 CRE cases including both KPC and NDM1 carbapenemases. Through a CDC investigation, two observations were made; first, CRE isolates can be spread from urban to rural healthcare settings, and second, environmental cleaning carts (or any equipment moving throughout the facility) can be modes of transmission [19]. Outbreaks have been reported throughout the United States involving duodenoscopes or ventilators, invasive devices such as urinary catheters, hospital room sinks and bedrails, and have been spread across healthcare networks involving acute care and long-term acute care (LTAC) facilities [20,21].

CRE Treatment Options

CRE isolates are resistant to almost all beta-lactams leaving few, and unfortunately older, drug classes with adequate activity. Specifically, these older treatment options include aminoglycosides, polymyxins, a glycylcycline, and fosfomycin [22]. **Table 1** provides dosing regimens and compares advantages and disadvantages of these older agents. It is important to note that polymyxin B and colistin (polymyxin E) are not identical in their adverse effect or pharmacokinetic profiles. At the time of publication, CLSI does not provide interpretive criteria for polymyxins for Enterobacteriaceae, and susceptibility testing for *Pseudomonas aeruginosa* is no longer recommended via Etest gradient diffusion or disk diffusion due to unreliable results [23]. Colistin methanesulfonate (CMS), a prodrug, requires renal elimination then hydrolysis for conversion to its active metabolite, colistin. This step is greatly impacted by renal dysfunction leading to high inter- and intra-patient variability in the serum concentrations of active drug. In patients with healthy renal function, 80% of CMS is eliminated in the urine before metabolism to the active drug even occurs, leaving subtherapeutic serum concentrations for non-urinary tract infections [24]. Polymyxin B is not impacted by this metabolic process and should be considered as the polymyxin of choice for systemic treatment of non-urinary tract infections. With regards to adverse effects, polymyxin B has also been shown to be less nephrotoxic to renal tubular cells [25]. A meta-analysis comparing differences in mortality and adverse effects between the two agents found no difference

Table 1 Older Agents for Treatment of CRE

Antimicrobial	Recommended Dosing for CRE Infections	Advantages	Disadvantages
Colistin [1,2,3,4,5] (Polymyxin E)	• Dosed in milligrams versus international units (14) at CMS • Weight-based and fixed dose regimens have been evaluated (see reference 5) • Loading dose is recommended • Requires dosage adjustment in renal impairment	• Extensive evidence for use in cUTI • Adjunctive inhalation route for HAP/VAP	• Pharmacokinetic disadvantages compared to polymyxin B. Should only be used for urinary tract infections • Combination therapy required • Optimal dosing uncertain • Emergence of resistance • Nephrotoxicity • Lack of activity against *Proteus sp.* and *Serratia marcescens* • Unreliable antimicrobial susceptibility testing
Polymyxin B [2,5]	• Weight-based dose regimens (mg/kg and 14/kg) (see reference 5) • Loading dose is reccommended	• Extensive evidence for use in BSI, PNA, and sepsis • Adjunctive inhalation route for HAP/VAP	• Combination therapy required • Optimal dosing uncertain • Avoid use in urinary tract infections • Emergence of resistance • Nephrotoxicity • Lack of activity against *Proteus sp.* and *Serratia marcescens* • Unreliable antimicrobial susceptibility testing
Tigecycline [6]	100-200 mg IV x1, then either 50 mg IV q12h or 100 mg IV q24h	• Stable against many beta-lactamases	• Bacteriostatic activity • Black Box Warning for all-cause mortality (2013) • Increasing antimicrobial resistance • Dose-dependent adverse effects (mostly GI-related) • Pharmacokinetic limitations (inadequate serum concentrations for treatment of BSI) • Lack of activity against *Pseudomonas aeruginosa*
Fosfomycin trometamol [7]	3 g oral single-dose versus every 48h x3 doses (UTI only)	• Excellent urine penetration • Bactericidal against CRE • Generally well-tolerated	• Only available orally for treatment of lower UTI in the United States • Development of resistance with monotherapy
Gentamicin, Amikacin [3]	G: 7 mg/kg/day IV A: 15 mg/kg/day IV	• Bactericidal activity • Most efficacious option for cUTI • Extended interval dosing • Inhalation route for HAP/VAP	• Nephrotoxicity, ototoxicity • Combination therapy required, unless cUTI

Definitions: BSI: bloodstream infections, cUTI: complicated urinary tract infections, PNA: pneumonia, HAP: hospital-acquired pneumonia, VAP: ventilator-associated pneumonia

1. Dosed using colistimethate sodium, the prodrug and manufactured formulation in the United States.
2. Polymyxins have identical antimicrobial spectrum against gram-negative pathogens, including lack activity against Proteus sp. and Serratia marcescens.
3. IDSA HAP/VAP Guidelines support use, but European HAP/VAP guidelines disagree citing inadequate pulmonary delivery via nebulization and lack of evidence. Inhalation can be used for active infection in combination with a systemic agent, or as prophylaxis in cystic fibrosis patients. Kidd JM, et al. Novel pharmacotherapy for the treatment of hospital-acquired and ventilator-associated pneumonia caused by resistant gram-negative bacteria. Exp Opin Pharmacother 2018;19(4):397-408
4. Liu YY, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2016;16(2):161-68
5. Tsuji BT, et al. International Consensus Guidelines for the Optional Use of the Polymyxins: Endorsed by ACCP, ESCMID, IDSA, ISAP, SCCM, and SIDP. Pharmacotherapy. 2019 Jan; 39(1):10-39.
6. Antimicrobial resistance of tigecycline to Pseudomonas aeruginosa represents a classwide lack in antimicrobial spectrum among all tetracyclines
7. Karageorgopolous D, et al. Emergence of resistance to fosfomycin used as adjunct therapy in KPC Klebsiella pneumoniae bacteremia: report of three cases. J Antimicrob Chemother. 2012;67(11):2777-9

in clinical outcomes, but an increase in nephrotoxicity with colistin [26]. Future studies are needed to determine whether pharmacokinetic differences truly translate to undesirable patient clinical outcomes.

Alexander E, et al performed an international, multicenter CRE review using isolates from 2013-2014 and found overall antimicrobial resistance rates of greater than 80% to penicillins, cephalosporins, aztreonam, fluoroquinolones (FQs), and trimethoprim/sulfamethoxazole (TMP/SMX). The same CRE isolate review found antimicrobial resistance rates of 80% to tobramycin, 57.8% to amikacin, 43.1% to gentamicin, 37% to tigecycline, 26.4% to polymyxins [14]. The isolates in this study reflect an international summary of antimicrobial resistance and may not predict regional antimicrobial resistance trends. Antimicrobial stewardship programs (ASPs) have a profound effect on local institution resistance patterns by closely monitoring antimicrobial utilization. Luckily, newer beta-lactam agents and an aminoglycoside have been FDA approved in the United States to combat these highly resistant pathogens.

Treatment strategies utilizing these older agents is complex, and ongoing research regarding novel combination therapies has helped to optimize therapies. Combinations utilizing polymyxins, tigecycline, or aminoglycosides with or without a carbapenem have been described with mixed results. The polymyxins, aminoglycosides (except for treatment UTI), and intravenous fosfomycin should always be used in combination to prevent emergence of antimicrobial resistance. In a 2014 review of 20 studies using older agents to treat CRE infections, mortality rates were lower when combination therapy was utilized compared to monotherapy (27.4% vs. 38.7%; p < 0.001, respectively). In addition, combination regimens containing carbapenems resulted in the lowest mortality rates (18.8%) [27].

Other studies have found conflicting evidence regarding combination therapies with older agents. A 2014 meta-analysis of 692 patients described mortality rates for tigecycline-colistin and carbapenem-colistin regimens of 64% and 67%. Due to lack of statistically significant benefit of combination therapy in all infection types, authors concluded that it may only be beneficial in severely ill patients with severe infections [28]. Another review of 661 KPC infection episodes in Italy illustrated that only those patients with high-risk infection (defined as non-UTI) or a meropenem MIC ≤8 mg/L. benefited from combination therapy [29]. In a recent randomized, controlled trial of 406 patients with pneumonia or bacteremia, Paul M et al evaluated colistin alone versus colistin plus meropenem for carbapenem-resistant gram-negative infections [30]. Although the majority of infections in this study were caused by *Acinetobacter baumanii* instead of CRE isolates, combination therapy was not superior to monotherapy and resulted in an increase in adverse effects, most notably diarrhea.

Knowing whether an isolate is interpreted as intermediate or resistant to carbapenems is clinically relevant. Use of prolonged infusions and combination therapy can be implemented to overcome intermediate resistance and improve clinical outcomes. Trained antimicrobial stewardship experts (physicians and pharmacists) are valuable resources for antimicrobial selection and dosage optimization. In addition, infectious disease consultation is associated with decreased 30-day readmission, mortality, length of stay, and overall cost, particularly in patients with *Staphylococcus aureus* bacteremia and multidrug-resistant gram-negative infections [31,32,33].

Newer Agents with CRE-Activity

Ceftazidime-avibactam (CAZ-AVI) is an intravenous cephalosporin/beta-lactamase inhibitor combination. Avibactam, a novel non-beta-lactam beta-lactamase inhibitor (NB-BLI) diazabicyclooctane (DBO), is currently commercially available as a combination agent with ceftazidime, and is also being studied in combination with aztreonam and ceftaroline [34]. CAZ-AVI inhibits Class A, C, and some D enzymes, but is inactive against Class B MBLs. It is most clinically useful for its activity against extended-spectrum beta-lactamases (ESBLs) and KPC carbapenemases. In 2015, CAZ-AVI was FDA approved for treatment of complicated urinary tract infections including acute pyelonephritis (cUTI/AP) and complicated intra-abdominal infections (cIAI) in addition to metronidazole. In early 2018, CAZ-AVI also gained FDA approval for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). The pneumonia trial comparator was meropenem 1g IV q8h [35]. CAZ-AVI should be administered 2.5g IV q8h infused over 2 hours, and a renal dosage adjustment is required for patients with a creatinine clearance (CrCl) <50 ml/min. Reported adverse effects from Phase 3 trials are similar to ceftazidime monotherapy.

Although patients infected with CRE-producing strains were excluded from the cUTI, cIAI and pneumonia trials due to lack of CRE activity with the comparator agents, newer clinical experiences describe efficacy and use of combination therapy for CRE infections. Two retrospective studies evaluated clinical success and mortality rates in CRE patients treated with CAZ-AVI. In both studies, *Klebsiella pneumoniae* was the predominant strain. Shields RK, et al. evaluated 30-day clinical success and mortality rates in thirty-seven cases. Fifty percent were diagnosed with HAP or VAP, and 70% were treated with monotherapy [36]. King et al, evaluated end of treatment clinical success and mortality rates in sixty cases [37]. The most common infection types were bacteremia, pneumonia, and UTI, and 55% were treated with monotherapy. Between the two studies, clinical success rates were similar regardless of the timepoint, 59% and 65% respectively. Mortality rates were also similar; in-hospital mortality 32%, and 30- and 90-day mortality, 24% and 38%. CAZ-AVI resistance developed during therapy in both studies. The King study found no statistically significant difference in outcomes between monotherapy and combination therapy.

Other studies have compared CAZ-AVI to alternative agents for treatment of CRE infections. A comparative study between CAZ-AVI-containing regimens and alternative regimens (mostly combinations with carbapenems) in patients with KPC-*Klebsiella pneumoniae* bacteremia demonstrated higher clinical success rates (85% versus 37-48%, P = 0.04). 90-Day mortality rates were lowest among patients receiving CAZ-AVI regimens. Patients receiving combination regimens containing an aminoglycoside or colistin experienced a higher rate of nephrotoxicity [38]. Another comparative study (n = 137 patients), using data from the CRACKLE database, analyzed efficacy, safety, and benefit-risk outcomes between CAZ-AVI- and colistin-containing initial treatment regimens. Patients had a greater probability of a better outcome in all categories with initial treatment with CAZ-AVI versus colistin. Fourteen (37%) patients were treated with monotherapy in the CAZ-AVI arm [39].

Table 2 Antimicrobial Pipeline for Treatment of CRE infections

Antimicrobial	Drug Class	Indications	Notes
Cefiderocol (CFDC)[1,2,3]	Siderophore cephalosporin	Phase 3 RCT cUTI/AP • CFDC 2 g IV every 8 hr vs. imipenem/cilastatin 1 g IV every 8 hr • DOT 7-14 days Phase 3 RCT HABP/VABP • CFDC 2 g IV every 8 hr vs. meropenem 2 g IV every 8h plus linezolid 600 mg IV every 12 hr • DOT 7-14 days Phase 3 RCT HABP/VABP, BSI/Sepsis, cUTI • CFDC 2 g IV every 8 hr vs. best available therapy for CRE DOT 7-14 days	• Active against all carbapenemases including Class B MBLs • Adverse effects similar to other cephalosporins • Excellent activity against *Acinetobacter sp.*
Imipenem/cilastatin-relebactam (IMI-REL) [4,5]	Carbapenem + NB-BLI DBO	Phase 3 RCT cUTI, cIAI, or HABP/VABP • IMI-REL 500-250 mg IV every 6 hr vs. imipenem/cilastatin 500 mg IV every 6 hr plus colistin IV every 8-12 hr • DOT 5-21 days (cUTI/cIAI) or 7-21 days (HABP/VABP) Phase 3 RCT HABP/VABP • IMI-REL 500-250 mg IV every 6 hr vs. piperacillin/tazobactam 4.5 g IV every 6 hr • DOT 7-14 days	• Active against Class A, C, and D carbapenemases • Inactive against Class B MBLs
Aztreonam-avibactam (ATM-AVI) [6]	Monobactam + NB-BLI DBO	Phase 3 RCT cIAI, HABP/VABP • ATM-AVI 6.5/2.1 g loading dose, then 6/2 g daily divided every 8 hr +/- metronidazole 500 mg IV every 8 hr vs. meropenem 1-2 g IV every 8h +/- colistin IV every 8-12 hr	• Active against Class A, C and D carbapenemases • Inactive against Class B MBLs
Fosfomycin for injection [7,8]	Epoxide antimicrobial	Phase 2/3 RCT cUTI/AP • Fosfomycin 6 g IV every 8 hr vs. piperacillin/tazobactam 4.5 g IV every 6 hr • DOT 7 days, 14 days if bacteremia	• Active against Class A, C and D carbapenemases • Variable activity against Class B MBLs • Intravenous formulation available in many countries • Dose optimization studies are ongoing for use in the United States • Combination therapy required

Definitions: RCT: randomized controlled trial, BSI: bloodstream infections, cUTI: complicated urinary tract infections, AP: acute pyelonephritis, HABP: hospital-acquired bacterial pneumonia, VABP: ventilator-associated bacterial pneumonia, NB-BLI DBO: non-beta-lactam beta-lactamase inhibitor diazabicyclooctane, cIAI: complicated intra-abdominal infection, DOT: duration of therapy

1. Ito A, et al. In Vitro antibacterial properties of cefiderocol, a novel siderophore cephalosporin, against gram-negative bacteria. Antimicrob Agent Chemother 2018;62(1):e01454-17
2. Portsmouth S, et al. Clinical response of cefiderocol compared with imipenem/cilastatin in the treatment of adults with complicated urinary tract infections with or without pyelonephritis or acute uncomplicated pyelonephritis: results from a multicenter, double-blind, randomized study (APEKS-cUTI). Open Forum Infect Dis 2017;4(Suppl 1):S537
3. Clinical study of S-649266 for the treatment of nosocomial pneumonia caused by gram-negative pathogens (APEKS-NP) [Internet] Identifier NCT03032380 Bethesda MD: National Library of Medicine [cited 2018 May 14]
4. Zhanel G, et al. Imipenem-relebactam and meropenem-vaborbactam: Two novel carbapenem-beta-lactamase inhibitor combinations. Drugs 2018 Jan;78(1):65-98
5. Kidd JM, et al. Novel pharmacotherapy for the treatment of hospital-acquired and ventilator-associated pneumonia caused by resistant gram-negative bacteria. Expert Opinion on Pharmacotherapy 2018;19(4):397-408
6. A study to determine the efficacy, safety and tolerability of aztreonam-avibactam (ATM/AVI) +/- metronidazole versus meropenem +/- colistin for the treatment of serious infections due to gram-negative bacteria. [Internet] Identifier NCT03329092 Bethesda MD: National Library of Medicine [cited 2018 May 14]
7. Kaye K, et al. Intravenous fosfomycin (ZTI-01) for the treatment of complicated urinary tract infections including acute pyelonephritis: results from a multicenter, randomized, double-blind Phase 2/3 study in hospitalized adults (ZEUS). Open Forum Infect Dis 2017;4(Suppl1):S528. #1845
8. Karageorgopoulos DE, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in gram-negative pathogens. J Antimicrob Chemother 2012;67(2):255-68

Meropenem-vaborbactam (MVB) is an intravenous carbapenem/ beta-lactamase inhibitor combination. Vaborbactam is the first non-beta-lactam boronic acid inhibitor with activity against Class A and C beta-lactamases, and is inactive against Class B MBLs. Similar to CAZ-AVI, MVB is also most clinically useful for its activity against ESBLs and KPC carbapenemases [40]. In 2017, MVB was FDA approved for treatment of cUTI/AP (TANGO-1 trial). The comparator was piperacillin-tazobactam, and patients could be switched to oral levofloxacin to complete treatment. Few CRE infections were included in this trial [41]. MVB 2g/2g IV should be administered every 8 hours infused over 3 hours, and a renal dosage adjustment is required for patients with a creatinine clearance (CrCl) <50 ml/min. Reported adverse effects from Phase 3 trials are similar to meropenem monotherapy.

The TANGO-2 trial is a Phase 3 study including patients with CRE infection (59.7%). Patients with cUTI/pyelonephritis, cIAI, bacteremia, nosocomial pneumonia were included, and the comparator was "best available therapy" (BAT), meaning one of the older anti-CRE agents discussed above as monotherapy or in combination. Recognizing that CRE patients have multiple comorbidities and are different than typical study populations for these types of infections, study investigators performed a retrospective review of patients with CRE infections in order to better define study design enrollment criteria [14]. Authors estimate that only 22% of the TANGO-2 study population would have met enrollment using traditional criteria. As a result of the study, it is unique that the TANGO-2 study allowed immunocompromised patients, and those with severe sepsis and renal insufficiency needing dialysis, although these types of patients did not comprise the majority of those enrolled. Enrollment in the BAT arm was discontinued early when interim analysis revealed better outcomes in MVB-treated patients; in CRE patients, clinical cure 57.1% versus 26.7%. Despite promising clinical outcomes, minimum inhibitory concentrations (MIC) increased in several MVB-treated isolates [42,43].

Plazomicin (PZM) is an intravenous aminoglycoside antimicrobial with activity against ESBL- and carbapenemase-producing aerobic gram negative rods. It is stable against aminoglycoside modifying enzymes that inactivate gentamicin, tobramycin, and amikacin, and most carbapenemase classes, including some activity against Class B MBLs (except NDM) [44]. There is limited activity against *Stenotrophomonas maltophilia, Acinetobacter baumanii,* and *Pseudomonas aeruginos*a, and future studies are needed to determine clinical utility for these pathogens. In 2018, PZM gained FDA approval for treatment of cUTI/AP (EPIC trial) [45]. The comparator was meropenem 1g IV q8h as a 30 minute infusion, and a switch to an oral agent was allowed at 4 days. PZM was studied using extended interval dosing, 15 mg/kg IV once daily over 30 minutes, and a renal dosage adjustment is required for patients with a creatinine clearance (CrCl) <60 ml/min. Forty percent of Enterobacteriaceae isolates were an ESBL-producing or aminoglycoside non-susceptible strain. Therapeutic drug monitoring of a serum trough concentration (goal ≤3 mg/L) is recommended 30 minutes prior to the second dose.

With regards to adverse effects, in the EPIC study the incidence of nephrotoxicity in the PZM arm, defined as a serum creatinine increase of ≥0.5 mg/dL, was 3.6%. Results from another Phase 2 study comparing PZM to levofloxacin 750 daily for cUTI/AP suggest higher nephrotoxicity when 15 mg/kg was used compared to 10 mg/kg, although the higher dose was selected for Phase 3 trials to optimize pharmacokinetic and pharmacodynamic targets [46]. A Phase 3, open label, Combating Antibiotic-Resistant Enterobacteriaceae (CARE) study evaluated plazomicin versus colistin in combination with meropenem or tigecycline for serious CRE infections (BSI and HABP/VABP). Results include lower 28-day all-cause mortality, higher microbiological response rates, and reduced nephrotoxicity. Authors concluded that plazomicin-based combination therapy had a better efficacy and safety profile compared to colistin-based combination regimens [47,48]. Although classwide warnings for nephrotoxicity, ototoxicity, neuromuscular blockage, and fetal harm were included in product labeling, the incidence of nephrotoxicity appears to be reduced compared to colistin or earlier aminoglycosides, especially when therapeutic drug monitoring is utilized.

In summary, for the two newer beta-lactam agents CAZ-AVI and MVB, safety and efficacy data appear favorable compared to older therapies for CRE infections. It Is concerning that MIC elevations, some conferring resistance to both CAZ-AVI and MVB, were observed. PZM offers a potential expanded CRE spectrum of activity and a better safety and efficacy profile compared to colistin-based combination regimens. Future studies are needed to optimize protection against antimicrobial resistance through combination therapy or optimal dosing.'

Antimicrobial Pipeline

Several agents with novel mechanisms of action are in the antimicrobial development pipeline. **Table 2** lists five agents with Phase 2 and 3 clinical trial data, and likely review for FDA approval in the near future. Both non-CRE and CRE studies were included in the table.

Conclusions

CRE infections are a healthcare and public health threat. Mortality rates are high, and agents with better safety and efficacy profiles plus expanded carbapenemase activity are desperately needed. When using older agents, combination therapy, particularly carbapenem-containing regimens, reduces mortality with severe infections, but may not have as much of a benefit with UTIs. Three newer agents, CAZ-AVI, MVB and PZM, are available and have activity against Class A-producing *Klebsiella pneumoniae*, the predominant CRE pathogen in the United States. In small studies, these agents demonstrate promising these clinical outcome and mortality data compared to older agents. However, further studies are needed to optimize their use (monotherapy versus combination therapy) and prevent emergence of therapy. Infections caused by MBLs remain infrequent in the United States, and treatment options against these strains are sparse. Several antimicrobial agents are in the pipeline to address this need.

References

1. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, April 2013. Available at: http://cdc.gov/drugresistance/treat-report-2013

2. Centers for Disease Control and Prevention. Facility Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE). November 2015. Update CRE Toolkit 2015; www.cdc.gov

3. Centers for Disease Control and Prevention: Tracking CRE. December 2017 data.

4. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al.; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014 Mar;370(13):1198–208.

5. Bush K. The ABCD's of β-lactamase nomenclature. J Infect Chemother. 2013 Aug;19(4):549–59.

6. Humphries RM, Hindler JA, Epson E, Horwich-Scholefield S, Miller LG, Mendez J, et al. Carbapenem-resistant Enterobacteriaceae detection practices in California: what are we missing? Clin Infect Dis. 2018 Mar;66(7):1061–7.

7. Ansari U, Lawsin A, Campbell D, Albrecht V, McAllister G, Bulens S, et al. Molecular Characterization of Carbapenem-Resistant Enterobacteriaceae in the USA, 2011–2015. Open Forum Infect Dis. 2017;4 suppl 1:S179. https://doi.org/10.1093/ofid/ofx163.328.

8. Bonomo RA, Burd EM, Conly J, Limbago BM, Poirel L, Segre JA, et al. Carbapenemase-producing organisms: A global scourge. Clin Infect Dis. 2018 Apr;66(8):1290–7.

9. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother. 2008 Mar;52(3):1028–33.

10. Guh AY, Bulens SN, Mu Y, Jacob JT, Reno J, Scott J, et al. Epidemiology of carbapenem-resistant Enterobacteriaceae in 7 US communities, 2012-2013. JAMA. 2015 Oct;314(14):1479–87.

11. Lodise T, Ye M, Keyloun KR, Zhao Q, Gillard P. Identification of patients at greatest risk for carbapenem resistance in patients with serious hospital-onset infections due to Enterobacteriaceae species. InOpen Forum Infect Dis. 2016; Oct 24 (Vol. 3, No. suppl_1, p. 1794). Oxford University Press.

12. Hauck C, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, et al.; Antibacterial Resistance Leadership Group. Spectrum of excess mortality due to carbapenem-resistant Klebsiella pneumoniae infections. Clin Microbiol Infect. 2016 Jun;22(6):513–9.

13. Tamma PD, Goodman KE, Harris AD, Tekle T, Roberts A, Taiwo A, et al. Comparing the outcomes of patients with carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2017 Feb;64(3):257–64.

14. Alexander EL, Loutit J, Tumbarello M, Wunderink R, Felton T, Daikos G, Fusaro K, White D, Zhang S, Dudley MN. Carbapenem-resistant Enterobacteriaceae infections: results from a retrospective series and implications for the design of prospective clinical trials. InOpen forum infectious diseases 2017 Apr 1 (Vol. 4, No. 2). Oxford University Press.

15. Eilertson B, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, et al.; Antibacterial Resistance Leadership Group. Carbapenem-resistant Enterobacteriaceae infections in patients on renal replacement therapy. Open Forum Infect Dis. 2017 Oct;4(4):ofx216. PMID:29181422

16. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014 May;58(9):1274–83.

17. World Health Organization: Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumanii, and Pseudomonas aeruginosa in healthcare facilities. 2017

18. Marchaim D, Chopra T, Pogue JM, Perez F, Hujer AM, Rudin S, et al. Outbreak of colistin-resistant, carbapenem-resistant Klebsiella pneumoniae in metropolitan Detroit, Michigan. Antimicrob Agents Chemother. 2011 Feb;55(2):593–9.

19. Chae SR, Yaffee AQ, Weng MK, Ham DC, Daniels K, Wilburn AB, Porter KA, Flinchum AH, Boyd S, Shams A, Walters MS. Notes from the Field: Investigation of Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Among Patients at a Community Hospital—Kentucky, 2016. MMWR. Morbidity and mortality weekly report. 2018 Jan 5;66(5152):1410.

20. Ray MJ, Lin MY, Tang AS, Arwady MA, Lavin MA, Runningdeer E, Jovanov D, Trick WE. Regional Spread of an Outbreak of Carbapenem-Resistant Enterobacteriaceae Through an Ego Network of Healthcare Facilities. Clinical Infectious Diseases. 2018 Feb 3:ciy084.

21. Won SY, Munoz-Price LS, Lolans K, Hota B, Weinstein RA, Hayden MK; Centers for Disease Control and Prevention Epicenter Program. Emergence and rapid regional spread of Klebsiella pneumoniae carbapenemase-producing Enterobacteriaceae. Clin Infect Dis. 2011 Sep;53(6):532–40.

22. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev. 2018 Apr 1;31(2):e00079-17.

23. Clinical and Laboratory Standards Institute M100 document. 26th Edition. Accessed December 2018.

24. Nation RL, Velkov T, Li J. Colistin and polymyxin B: peas in a pod, or chalk and cheese? Clin Infect Dis. 2014 Jul;59(1):88–94.

25. Zavascki AP, Nation RL. Nephrotoxicity of polymyxins: is there any difference between colistimethate and polymyxin B? Antimicrob Agents Chemother. 2017 Mar 1;61(3):e02319-16.

26. Vardakas KZ, Falagas ME. Colistin versus polymyxin B for the treatment of patients with multidrug-resistant Gram-negative infections: a systematic review and meta-analysis. Int J Antimicrob Agents. 2017 Feb;49(2):233–8.

27. Tzouvelekis LS, Markogiannakis A, Piperaki E, Souli M, Daikos GL. Treating infections caused by carbapenemase-producing Enterobacteriaceae. Clin Microbiol Infect. 2014 Sep;20(9):862–72.

28. Falagas ME, Lourida P, Poulikakos P, Rafailidis PI, Tansarli GS. Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence. Antimicrob Agents Chemother. 2014;58(2):654–63.

29. Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, et al.; ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva). Infections caused by KPC-producing

Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother. 2015 Jul;70(7):2133–43.

30. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018 Apr;18(4):391–400.

31. Burnham JP, Olsen MA, Stwalley D, Kwon JH, Babcock HM, Kollef MH. Infectious diseases consultation reduces 30-day and 1-year all-cause mortality for multidrug-resistant organism infections. InOpen forum infectious diseases 2018 Mar 15 (Vol. 5, No. 3, p. ofy026). US: Oxford University Press.

32. Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in Staphylococcus aureus bacteremia: results from a large multicenter cohort study. Clin Infect Dis. 2015 May;60(10):1451–61.

33. 33. Butt AA, Al Kaabi N, Khan T, Saifuddin M, Khan M, Krishnanreddy KM, Jasim WH, Sara M, Pitout M, Weber S. Impact of infectious diseases team consultation on antimicrobial use, length of stay and mortality. The American journal of the medical sciences. 2015 Sep 1;350(3):191-4.

34. Zhanel G, et al. Ceftazidime-avibactam: a novel cephalosporin/beta-lactamase inhibitor combination. Drugs 2013;73:-159-77

35. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, Song J, Taylor D, Laud PJ, Stone GG, Chow JW. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. The Lancet Infectious Diseases. 2018 Mar 1;18(3):285-95.

36. Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis. 2016 Dec;63(12):1615–8.

37. King M, Heil E, Kuriakose S, Bias T, Huang V, El-Beyrouty C, et al. Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother. 2017 Jun;61(7):e00449–17.

38. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, Doi Y, Kreiswirth BN, Clancy CJ. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. Antimicrobial agents and chemotherapy. 2017 May 30:AAC-00883.

39. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al.; Antibacterial Resistance Leadership Group. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2018 Jan;66(2):163–71.

40. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M, Lagacé-Wiens PR, Walkty A, Denisuik A, Golden A, Gin AS. Imipenem–relebactam and meropenem–vaborbactam: two novel carbapenem-β-lactamase inhibitor combinations. Drugs. 2018 Jan 1;78(1):65-98.

41. Kaye K, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V, et al. Effect of meropenem-vaborbactam versus piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection. JAMA. 2018;319(8):788–99.

42. Kaye K, et al. Clinical outcomes of serious infections due to carbapenemase-producing Enterobacteriaceae in TANGO-II, a Phase 3, randomized, multinational, open-label trial of meropenem-vaborbactam against best available therapy. ID Week 2017. San Francisco, CA. Abstract 1868.

43. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, Cornely OA, Solomkin J, Bhowmick T, Bishara J, Daikos GL. Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infectious diseases and therapy. 2018 Dec 1;7(4):439-55.

44. Zemdri (plazomicin) [package insert] San Francisco, CA, USA; Achaogen, Inc. June 2018.

45. 45. Golan Y, et al. Improved outcomes at late follow-up with plazomicin compared with meropenem in patients with complicated urinary tract infection, including acute pyelonephritis, in the EPIC study. ID Week 2017 Poster 1859.

46. Connolly LE, Riddle V, Cebrik D, Armstrong ES, Miller LG. A Multicenter, randomized, double-blind, phase 2 study of the efficacy and safety of plazomicin compared with levofloxacin in the treatment of complicated urinary tract infection and acute pyelonephritis. Antimicrob Agents Chemother. 2018 Mar;62(4):e01989–17.

47. McKinnell JA, et al. Improved outcomes with plazomicin compared with colistin in patients with bloodstream infections caused by carbapenem-resistant Enterobacteriaceae: results from the CARE study. ID Week 2017 Poster 1853

48. Pontikis K, et al. Plazomicin is associated with fewer postbaseline infectious complications compared with colistin in patients with serious infections due to carbapenem-resistant Enterobacteriaceae (CRE): Results from the randomized controlled CARE study. ECCMID 2018 Poster P0284