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Review of Ceftazidime-Avibactam, Meropenem-Vaborbactam, and Imipenem/Cilastatin-Relebactam to Target *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacterales

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Abstract

Objective: To provide a review of 3 novel antimicrobial agents—ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/cilastatin-relebactam—regarding treatment of *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales (KPC). **Data Sources:** A literature search of PubMed and OVID (MEDLINE) was performed up to March 2020 using the following search terms: *Vabomere, meropenem-vaborbactam, vaborbactam, RPX7009, Klebsiella pneumoniae carbapenemase, KPC, carbapenem-resistant Enterobacteriaceae, CRE, relebactam, imipenem-relebactam, MK-7655, ceftazidime-avibactam*. Abstracts from conferences, article bibliographies, and product information were also reviewed. **Study Selection and Data Extraction:** Articles were first screened by English language, then title, then abstract, and finally by review of the full article. Fifty-five clinical and preclinical studies were included. **Data Synthesis:** These 3 novel β-lactam/β-lactamase inhibitor combinations have shown considerable improvement in safety and efficacy as compared with traditional polymyxin-based combination therapy for the treatment of KPC infections. While meropenem-vaborbactam has not shown improved activity against *Pseudomonas aeruginosa*, it has shown decreased rates of resistance to KPC versus ceftazidime-avibactam. **Conclusions:** With increasing incidence of KPC infections on a global scale, pharmacists should be aware of the notable similarities and differences between these 3 agents, and the current data supporting their use. Pharmacists may want to consider meropenem-vaborbactam over ceftazidime-avibactam for KPC infections due to decreased likelihood of resistance.

Keywords

CRE, carbapenemase-producing Enterobacterales, KPC, *Klebsiella pneumoniae* carbapenemase, ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam

Introduction

Infection due to multidrug-resistant Gram-negative bacteria is an increasing problem throughout the world today, with prevalence ranging from 10% to 50% in hospitals throughout the United States and many other countries.[1,2] Possible explanations include the overuse of existing antimicrobial agents, lack of appropriate antimicrobial stewardship, and an increase in the degree of facility size and interconnectedness.[1,3] β-Lactams represent the most widely used class of antibacterial agents, and resistance from many common Gram-negative organisms is largely mediated by production of β-lactamases.[4] Mechanisms of β-lactamase expression may occur via induction of chromosomally linked AmpC or constitutional production of extended-spectrum β-lactamases (ESBLs), for both of which a carbapenem may be considered for treatment.[5,6]

Particularly troublesome are organisms that produce β-lactamase enzymes capable of even hydrolyzing carbapenems.[7] In general, these infections are associated with prolonged length of hospital stay and mortality ranging from 20% to 50%, with an estimated 1100 deaths in 2017.[7,8] In addition to

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AmpC or ESBL enzymes, carbapenem resistance in Gram-negative bacteria can also be caused by carbapenemases, efflux pumps, and porin loss. These numerous mechanisms of carbapenem resistance have led to multiple acronyms such as carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant organisms (CRO), carbapenemase-producing Enterobacterales (CPE), and carbapenemase-producing organisms (CPO). CRE and CRO are imprecise terms that include a variety of mechanisms of resistance, while CPE and CPO primarily encompass organisms with carbapenamases. These distinctions are clinically important as many of the new agents only have activity against certain types of carbapenemases, as discussed in this review.

Beta-lactamases are commonly included in 4 groups under the Ambler Classification scheme, based on amino acid sequences and phenotypic properties of the enzymes. These 4 groups are the following: Ambler Class A (serine carbapenemases such as *Klebsiella pneumoniae* carbapenemase [KPC], IMI, and SME), Ambler Class B (metallo-β-lactamases [MBL] such as IMP, VIM, and NDM-1 that break down carbapenems), Ambler Class C (cephalosporinases such as AmpC), and Ambler Class D (oxacillinases [OXA], which are only weakly active against carbapenems).[9] The most common carbapenemases produced by CPE are MBL, OXA-48/-232, and KPC.[10,11] Carbapenemases vary by geography, with KPC being common in the United States and MBL being more prevalent in India.[9] Recently, the rapid spread of KPC has made it the most common cause of CPE in the United States, as well as a substantial challenge on a global scale. Serious KPC infections (eg, bacteremia) have been associated with suboptimal therapy and 30-day mortality rates approaching 50%.[12-14]

Historical use of polymyxin- and aminoglycoside-based therapies for KPC infections are associated with a high incidence of ototoxicity, neurotoxicity, and nephrotoxicity (approaching 60%), which often limit adequate dosing of these agents.[15] Fortunately, novel β-lactam treatment options have shown efficacy in clinical trials and offer a better safety profile versus these traditional therapies—this article provides a review of 3 of these agents: ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/cilastatin-relebactam.

Methods

A literature search was conducted up to March 2020, utilizing PubMed and OVID (MEDLINE) databases. Search terms included "Vabomere," "meropenem-vaborbactam," "vaborbactam," "RPX7009," "*Klebsiella pneumoniae* carbapenemase," "KPC," "carbapenem-resistant Enterobacteriaceae," "CRE," "relebactam," "imipenem-relebactam," "MK-7655," and "ceftazidime-avibactam." Relevant articles were also identified in the ID Week Annual Abstracts from 2012 to 2019. The reference sections of identified articles were also reviewed. Articles were first screened by English language, then title, then abstract, and finally by review of the full article.

Ceftazidime-Avibactam

Avibactam is a diazabicyclooctane non-β-lactam inhibitor that has activity against Ambler class A, C, and some D carbapenemases. Avibactam restores ceftazidime's activity against KPC-producing CPE and currently has the most Food and Drug Administration (FDA)-approved indications of the 3 agents: complicated intraabdominal infections (cIAI), hospital- or ventilator-associated pneumonia (HAP/VAP), and complicated urinary tract infections (cUTI), including pyelonephritis.[16] Ceftazidime-avibactam's in vitro activity was examined in 513 isolates that were nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam (n = 628) from 2013 to 2016 at 94 medical centers in the United States.[17] Results demonstrated susceptibility of the majority (71.8%) of CPE isolates.

Ceftazidime-avibactam was also evaluated for safety and efficacy in 7 Phase III trials for cIAI in combination with metronidazole,[18,19] cUTI,[20] HAP/VAP,[21] and a pathogen-directed trial of cUTI and cIAI caused by Enterobacteriaceae resistant to ceftazidime.[22] It was compared with meropenem,[18,19,21] doripenem,[20] or otherwise best available therapy (BAT) with 96% receiving carbapenem therapy.[22] All trials met noninferiority for the primary endpoint of clinical cure at test of cure visits. No differences were found in adverse effects between comparator agents, with the most common being gastrointestinal upset.

Ceftazidime-avibactam has likewise been compared with polymyxin-based therapies for treatment against CPE infections in 4 studies with more than 10 ceftazidime-avibactam patients. A single-center study[23] examined outcomes of clinical success, 30-day survival, and 90-day survival with ceftazidime-avibactam versus other regimens for KPC bacteremia (n = 109). Patients received a variety of therapies: ceftazidime-avibactam (n = 13), carbapenem and aminoglycoside therapy (n = 25), carbapenem and colistin therapy (n = 30), and other regimens (n = 41). The ceftazidime-avibactam group was shown to have improved 90-day survival ($P = .04$) and clinical success ($P = .02$), but no difference was seen in 30-day survival when compared with the other treatment groups ($P = .10$). Acute kidney injury rates were significantly higher in patients whose regimen included aminoglycosides or colistin as compared with those that did not (42% vs 5%, $P = .002$).

In a multicenter retrospective study,[24] ceftazidime-avibactam (n = 41) was compared with other therapy (n = 36) for adult mechanically ventilated patients with CPE infection in multi-organ failure with a primary outcome of organ failure improvement on day 10 and 28-day mortality. Other

therapies consisted of combination therapy (97%), with colistin (86%) and tigecycline (72%) being the most common agents. Ceftazidime-avibactam had improved organ failure scores at day 10 (−2.38 ± 0.89 vs 1.2 ± 0.72, $P = .003$) and improved 28-day survival (85.4% vs 61.1%, $P = .035$). Ceftazidime-avibactam regimens were likewise an independent predictor of survival (odds ratio = 5.575, 95% confidence interval [CI] = 1.469-21.169).

Additionally, a multicenter, prospective, observational study[25] examined ceftazidime-avibactam for the treatment of CPE infections from multiple sources (n = 137), as compared with colistin monotherapy with a primary outcome of 30-day mortality after adjustment of inverse probability for treatment weighting. Secondary outcomes of efficacy, safety, and benefit/risk were assessed using the desirability of outcome rankings (DOOR). The DOOR outcomes for the benefit/risk were hospital death, alive in hospital or discharge not to home with renal failure, alive in hospital or discharged home, no incident renal failure, or discharged home. Bacteremia (n = 63, 49.6%) and pneumonia (n = 30, 21.8%) were the most common indications. Ceftazidime-avibactam was shown to have decreased 30-day mortality (9% vs 32%, $P = .001$) and an improved benefit/risk ratio (64%, 95% CI = 53% to 75%).

The compassionate use of ceftazidime-avibactam in Italy (n = 138) for KPC producing *Klebsiella pneumoniae* infections has also been described.[26] Bacteremic patients (n = 104) were compared with a matched control group (based on Pitt bacteremia scores and time from bacteremia to initiation of salvage therapy) treated with other agents, with a primary outcome of 30-day mortality. The median time to ceftazidime-avibactam therapy was 7 days after first-line treatment. Thirty-day mortality was lower in the ceftazidime-avibactam bacteremia group (36.5% vs 55.8%, $P = .005$). Three patients (2.2%) developed resistance while on ceftazidime-avibactam therapy. Twelve (8.7%) patients experienced treatment relapses after ceftazidime-avibactam was stopped (median of 23 days); all of these cases were cured after retreatment with ceftazidime-avibactam plus gentamicin.

Ceftazidime-avibactam was examined for a primary outcome of clinical failure in a retrospective multicenter study[27] of patients with CPE (n = 117) and *Pseudomonas* (n = 63) infections. The most common sites of infection were the following: respiratory (37.4%), intraabdominal (18.7%), and urine (19.7%). Approximately 10% of patients had bacteremia. Resistance developed in 1/62 patients on therapy. In a multivariate logistic regression model for clinical failure, primary bacteremia, or respiratory tract infection were associated with increased risk for clinical failure (odds ratio = 2.270, 95% CI = 1.115-4.620).

Ceftazidime-avibactam's microbiological failure was also investigated in a retrospective, single-center study[28] of 37 patients who received at least 3 days of ceftazidime-avibactam for CPE. Microbiological failure was defined as isolation of CPE following a week of treatment. Ten patients developed microbiological failure, most commonly seen as recurrent infections within 30 days (n = 5) or 90 days (n = 4). Resistance developed in 3/10 patients after a median of 15 days of therapy. Development of resistance has also been reported in single-patient case studies.[29,30] Additional information about the studies of ceftazidime-avibactam against CPE infections can be found in Table 1.

Ceftazidime-avibactam has been shown to be superior to colistin-based therapy in terms of mortality and acute kidney injury for the treatment of CPE and KPC infections.[23,25,26] Some studies have shown resistance development,[28,31] and increased rates of failure in patients with respiratory infection[27,31] or on renal replacement therapy.[31] In a pharmacoeconomic model,[32] ceftazidime-avibactam was found to be cost effective when compared with colistin-based therapies for CPE. With less nephrotoxicity and mortality, ceftazidime-avibactam was more cost effective in 99% of models with US$150 000 per quality adjusted life year.

Meropenem-Vaborbactam

Vaborbactam, formerly RPX-7009, is a novel β-lactamase inhibitor with a unique structure based on a cyclic boronic acid pharmacophore.[33] It has demonstrated considerable inhibitory activity against ESBL, AmpC, and serine carbapenemases (including KPC), but has not been shown to inhibit Ambler Class B or Class D carbapenemases.[34-36] Vaborbactam, when co-formulated with the carbapenem meropenem, is currently FDA-approved for the treatment of patients 18 years of age and older with cUTI (including pyelonephritis), caused by *Escherichia coli, Klebsiella pneumoniae*, or *Enterobacter cloacae*.[33,37]

In preclinical studies, vaborbactam was shown to restore meropenem activity against KPC-producing CPE, including isolates that were also resistant to ertapenem.[11,36,38,39] It also significantly increased bacterial killing when combined with meropenem versus untreated controls, meropenem alone, or meropenem in combination with other antibacterial agents.[38,40-45] An in vitro study[46] separately demonstrated MIC lowering in 99 cUTI-derived CPE and ESBL isolates by meropenem-vaborbactam versus meropenem alone. Similarly, it has also shown nondiminished activity in pulmonary surfactant.[47-49] Pharmacokinetics of vaborbactam are conveniently similar to those of meropenem.[37]

Clinical studies have been similarly promising, and a summary can be found in Table 1. The Targeting Antibiotic Non-susceptible Gram-Negative Organisms study (TANGO I)[50] was a multicenter, international, Phase III, randomized, double-blind, double-dummy, active-control trial that investigated the efficacy and safety of meropenem-vaborbactam versus piperacillin-tazobactam in patients with cUTI (including pyelonephritis). Meropenem-vaborbactam achieved noninferiority to piperacillin-tazobactam (98.4% vs 94%, 95% CI = 0.7-9.1) for the primary endpoint of

Table 1. Summary of Clinical Literature of BL/BLI for Treatment of CPE Infections.

Study	BL/BLI	Comparator regimens	Site of infection	ICU; immunosuppression	Outcome
Wunderink et al 2018[51]	Meropenem-vaborbactam (n = 32)	BAT[a] (n = 15)	• Bacteremia (n = 22, 47%) • cUTI/AP (n = 16, 34%) • HAP/VAP (n = 5, 11%) • cIAI (n = 4, 9%)	n = 8 (17%); n = 19 (40%)	*28-day all-cause mortality*: 16% (5/32) vs 33% (5/15) (P = .20) *Test of cure on follow-up (7 days after end of therapy)*: 59% (19/32) vs 27% (4/15) (P = .02) *End-of-therapy cure (day 7-14)*: 66% (21/32) vs 33% (5/15) (P = .03)
Ackley et al 2020[31]	Meropenem-vaborbactam (n = 26)	Ceftazidime-avibactam (n = 105)	• Bacteremia (n = 53; 40%) • Respiratory site (n = 40; 30%) • Soft tissue (n = 20; 15%)	n = 75 (57%); n = 16 (12%)	*Clinical success*: 69.2% vs 61.9% (P = .49) *30-day mortality*: 11.5% vs 19.1% (P = .57)
Shields et al 2017[23]	Ceftazidime-avibactam (n = 13)	Carbapenem plus aminoglycoside (n = 25) Carbapenem plus colistin (n = 30) other (n = 41)[b]	• Bacteremia (n = 100%)	n = 56 (54%); n = 54 (52%)	*30-day survival*: 92% (12/13) vs 69% (66/96)[c] (P = .10)
van Duin et al 2018[25]	Ceftazidime-avibactam (n = 38)	Colistin (n = 99)	• Bacteremia (n = 63, 46%) • Pneumonia (n = 30, 22%) • UTI (n = 19, 14%) • Wound (n = 14, 10%) • Other (n = 11, 8%)	n = 81 (59%); n = 25 (18%)	*30-day mortality*: 9% vs 32% (P = .001)
Tumbarello et al 2019[26]	Ceftazidime-avibactam (n = 104)	Double carbapenem (n = 29) Fosfomycin plus aminoglycoside (n = 24) Others (n = 51)[d]	• Bacteremia (n = 208, 100%)	n = 66 (32%); Not reported[e]	*30-day mortality*: 36.5% vs 55.8% (P = .005)
Tsolaki et al 2020[24]	Ceftazidime-avibactam (n = 41)	Other (n = 36)[f]	• Bacteremia (n = 50; 64%) • VAP (n = 20; 26%)	n = 77 (100%); not reported	*28-day survival*: 85.4% vs 61.1% *SOFA score improvement on day 10*: −2.38 ± 0.89 vs 1.20 ± 0.72 (P = .003)
Kaye et al 2018[56]	Imipenem/cilastatin-relebactam (n = 28)	Imipemen/cilastatin plus colistin (n = 13)	• HAP/VAP (n = 12, 29%) • cUTI (n = 21, 51%) • cIAI (8, 20%)	Unknown (APACHE II score >15 = 29%)	*Favorable overall response*[g]: adjusted difference = −7.3% (90% CI = −27.5 to 21.4)

Abbreviations: BL/BLI, β-lactam/β-lactamase; CPE, carbapenemase-producing enterobacterales; ICU, intensive care unit; BAT, best available therapy; cUTI, complicated urinary tract infection; HAP/VAP, hospital-/ventilator-acquired pneumonia; cIAI, complicated intraabdominal infection; CI, confidence interval.

[a]BAT = ertapenem, meropenem, imipenem, tigecycline, amikacin, gentamicin, tobramycin, colistin, and polymyxin B alone or in combination, or ceftazidime-avibactam monotherapy.

[b]Other regimens included monotherapy (n = 29) or combination therapy (n = 12). Monotherapy consisted of an aminoglycoside (n = 11), carbapenem (n = 8), tigecycline (n = 4), colistin (n = 4), and ciprofloxacin (n = 2). Combination regimens were colistin + tigecycline (n = 3), aminoglycoside + tigecycline (n = 2), and 1 each of aminoglycoside + cefepime, aminglycoside + colistin + tigecycline, colistin + aztreonam, colistin + cefepime, colistin + ciprofloxacin, carbapenem + doxycycline, and carbapenem + tigecycline.

[c]All other regimens.

[d]Gentamicin monotherapy (n = 14), gentamicin + meropenem (n = 11), colistin + fosfomycin (n = 10), colistin (n = 9), and others (n = 7).

[e]Neutropenia and solid organ transplant reported as n = 15 (10.9%) and n = 35 (25.4%), respectively.

[f]Only 1 patient received monotherapy. Combination antibiotics received by the other patients included: colistin (n = 31), tigecycline (n = 26), aminoglycosides (n = 11), fosfomycin (n = 6), and trimethoprim/sulfamethazole (n = 3).

[g]Favorable overall response defined as: HAP/VAP survival through day 28; cIAI clinical response at day 28; cUTI composite clinical and microbiological response 5 to 9 days after end of therapy.

overall success, as a composite endpoint of clinical cure and microbial eradication. However, TANGO I did not assess the efficacy of meropenem-vaborbactam for the treatment of CPE. Conversely, TANGO II[51] was a smaller, multicenter, international, Phase III, randomized, prospective, open-label trial that studied the efficacy, safety, and tolerability of meropenem-vaborbactam compared with BAT in patients with severe KPC-producing CPE infections such as bacteremia, cIAI, HAP/VAP, cUTI, and pyelonephritis. In this study, BAT included combinations of the following agents: ertapenem, meropenem, imipenem, tigecycline, amikacin, gentamicin, tobramycin, colistin, polymyxin B, and ceftazidime-avibactam. Treatment with meropenem-vaborbactam resulted in higher rates of clinical cure at the end of therapy (64.3% vs 33.3%, $P = 0.04$), a relative risk reduction in 28-day all-cause mortality of 33.3% ($P = .03$), and demonstrated stability to ESBL, AmpC, and KPC-producing organisms. Although TANGO II had a small sample size for both arms (n = 28 and 15 for meropenem-vaborbactam and BAT, respectively) and only included 10% of patients with creatinine clearance ≤30 mL/min (those requiring continuous renal replacement were excluded), both preclinical and clinical studies reported no serious adverse events with meropenem-vaborbactam. An almost 50% absolute risk reduction ($P < .001$) of the composite endpoint of clinical failure and nephrotoxicity with meropenem-vaborbactam versus BAT was observed. Overall, these characteristics suggest that it carries an enhanced safety profile over aminoglycosides, colistin, and tigecycline.

More recently, a small cohort[52] (n = 19) of critically ill patients with KPC-producing CRE infections found a 63% success rate and 89% 30-day survival rate, largely with meropenem-vaborbactam monotherapy for a median duration of 8 days. Microbiological failure, defined as isolation of the same species posttreatment, occurred in 32% of patients.

Imipenem/Cilastatin-Relebactam

Relebactam, formerly MK-7655, is a non-β-lactam, bicyclic diazabicyclooctane β-lactamase inhibitor that is structurally related to avibactam.[37] Relebactam is primarily renally excreted, with most pharmacokinetic parameters similar to imipenem and not altered by co-administration.[37] In combination with imipenem/cilastatin, it inhibits both Ambler Class A and Class C β-lactamases, and restores imipenem's activity against KPC.[37,53] Similarly, in 1705 European isolates, susceptibility increased from 72.0% to 94.7% in imipenem-susceptible organisms, and from 0% to 81.1% in imipenem-non-susceptible organisms.[54] The combination of imipenem/cilastatin-relebactam is currently FDA-indicated for adult patients with cIAI and cUTI, including pyelonephritis.[55]

RESTORE-IMI 1[56] is a Phase III, double-blinded, multisite, randomized, controlled trial that included 41 adult patients with HAP/VAP, cIAI, or cUTI, not only caused by CPE but also a variety of other carbapenem-resistant Gram negatives as well. The authors demonstrated noninferiority of imipenem/cilastatin-relebactam to imipenem/cilastatin plus colistin for the primary endpoints of mortality and overall clinical cure (Table 1), yet showed an advantage with regard to incidence of renal toxicity. Additional double-blinded, randomized, Phase II clinical trials for imipenem/cilastatin-relebactam have reported noninferiority to imipenem monotherapy for treatment of cIAI and cUTI (including pyelonephritis) with no statistically significant increase in adverse events.[37] Phase III trials are currently underway to assess efficacy for imipenem-resistant bacterial infections, including HAP/VAP.

Comparisons Summary

This article serves to provide a review of the clinical and in vitro studies for ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/cilastatin-relebactam. However, one multicenter retrospective study[31] compared meropenem-vaborbactam (n = 26) with ceftazidime-avibactam (n = 105) for CPE infections with a primary outcome of clinical cure and secondary outcomes of mortality and adverse events. There was no difference in clinical success, 30- or 90-day mortality, or adverse events. Ceftazidime-avibactam patients were more likely to be on combination therapy (61% vs 15%; $P < .01$), most commonly with colistin (19.1%), tigecycline (17.1%), or aminoglycosides (14.3%). The time to drug initiation was longer in the ceftazidime-avibactam group (48.7 hours vs 19.9 hours; $P = .02$) due to rapid diagnostic implementation during the study period. Three of 15 ceftazidime-avibactam patients with recurrence of CPE infections developed resistance to ceftazidime-avibactam; all of these patients originally had respiratory sites of infection and renal replacement therapy. To date, there have been no head-to-head studies comparing meropenem-vaborbactam to imipenem/cilastatin -relebactam.

A further comparison of summarized, agent-specific characteristics can be found in Table 2. Ceftazidime-avibactam currently has the most FDA-approved indications of the 3 agents, and is likewise the only one approved in both adult and pediatric populations. While meropenem-vaborbactam may be administered via extended infusion versus imipenem/cilastatin-relabactam's short infusion time, it also has a much higher sodium content per dose than the other 2 formulations. The 3 agents do not differ substantially regarding KPC coverage, dose modification for renal impairment, or common adverse effects.

A survey[57] of infectious diseases pharmacists in the United States (n = 218) in November to December 2018

Table 2. Comparison of BL/BLI Agents.

BL/BLI	FDA-approved indications	FDA-approved populations	Usual dosing	Infusion time	Modifications for organ impairment	Sodium content[a]	Common ADE
Ceftazidime-avibactam[16]	cUTI, acute pyelonepthritis, HAP/VAP, and cIAI (in combination with metronidazole)	Adults, pediatrics (3 months or older)	2.5 g IV q8h	2 hours	Renal	146-596 mg	Diarrhea, nausea, vomiting, rash, and infusion-site reaction
Meropenem-vaborbactam[58]	cUTI	Adults	4 g IV q8h	3 hours	Renal	2500-9000 mg	Headache, diarrhea, and infusion-site reaction
Imipenem/cilastatin-relebactam[55]	cUTI, acute pyelonephritis, and cIAI	Adults	1.25 g IV q6h	30 minutes	Renal	37.5-937.5 mg	Diarrhea, nausea, vomiting, headache, and infusion-site reaction

Abbreviations: BL/BLI, β-lactam/β-lactamase; FDA, Food and Drug Administration; ADE, adverse drug event; cUTI, complicated urinary tract infection; IV, intravenous; HAP/VAP, hospital-/ventilator-acquired pneumonia; cIAI, complicated intraabdominal infection; q6h, every 6 hours; q8h, every 8 hours.
[a]Total sodium content per dose of the final preparation depending on dose, diluent, and final volume desired.

was conducted to determine the availability and formulary status of ceftazidime-avibactam, meropenem-vaborbactam, and plazomicin. Ceftazidime-avibactam and meropenem-vaborbactam were formulary restricted or nonformulary, but available at 84% and 68% of hospitals, respectively. Smaller hospitals (stratified by ≤200, 201-400, and >400 beds) were less likely to have made a formulary decision ($P = .0005$). Ceftazidime-avibactam and meropenem-vaborbactam were positioned as first-line agents for pneumonia (54% and 32%) and bacteremia (58% and 31%), respectively.

Although evaluations of activity against nonfermenting Gram-negative bacilli were beyond the scope of this review, it should be noted that vaborbactam was not shown to restore meropenem's activity against *Pseudomonas aeruginosa*, potentially giving it a disadvantage versus the other 2 agents.[2,33] Conversely, ceftazidime-avibactam's recurrence rates of 8.7% to 13.5%, resistance rates of 2.2% to 8.1%, and increased rates of failure in patients with renal replacement therapy and pneumonia were previously discussed. Although there have been more limited reports of KPC treatment with meropenem-vaborbactam, it has not shown similar issues. Therefore, pharmacists may want to consider meropenem-vaborbactam over ceftazidime-avibactam for KPC infections due to decreased likelihood of resistance.

Nevertheless, these 3 new β-lactam/β-lactamase inhibitor combinations with CPE activity have shown improvement in safety and efficacy as compared with traditional polymyxin-based combination therapy. With increasing incidence of KPC infections on a global scale, pharmacists should be aware of the similarities and differences between these agents, as this may assist with clinical decision-making.

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