Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations

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Clinical Infectious Diseases

Invesitive infections due to carbapenem-resistant Enterobacteriaceae (CRE) are associated with mortality rates between 20% and 50% and frequently impact the most vulnerable patient populations [1, 2]. The emergence and expansion of infections due to CRE is concerning due to the lack of traditional “first line” treatment options. As a result, clinicians often must rely on toxic and/or pharmacokinetically suboptimal therapeutic options, often in combination.

Fortunately, 2 novel β-lactamase inhibitor combinations, ceftazidime/avibactam and meropenem/vaborbactam, have become available to combat CRE. This review will compare these agents with regard to in vitro activity as a function of mechanism of carbapenem resistance in CRE, comparative clinical data, and the propensity of these agents to select for resistance. Formulary and clinical considerations will be discussed. As the worldwide emergence of CRE has been driven by carbapenemase production, and since the activity of these therapies are driven by carbapenemase inhibition, this manuscript will focus on the role of these agents against carbapenemase-producing Enterobacteriaceae. Additionally, while this review will focus on formulary considerations surrounding CRE, ceftazidime/avibactam also has activity against β-lactam–resistant Pseudomonas aeruginosa (Table 1) and therefore will also have a role for this pathogen at most institutions.

EPIDEMIOLOGY OF CRE

In 2001, the initial report of Klebsiella pneumoniae carbapenemase (KPC)–producing K. pneumoniae was reported in North Carolina [3]. While this was an isolated event, an epidemic of KPCs in the New York City area and the Northeast coast was well under way by 2005, followed by spread of KPC-producing isolates worldwide [4].

The 2 other major carbapenemases of clinical concern in Enterobacteriaceae are OXA-48–like and New Delhi metallobetalactamase (NDM-1) [5]. While KPC remains the predominant mechanism in many countries including the United States, OXA-48 and NDM-1 predominate in other regions. For example, data from 2015 suggest that rates of OXA-48–like-producing CRE approach those of KPC producers in Europe [5]. In certain countries, such as Belgium, France, and Spain, OXA-48–like enzymes are more prevalent than KPCs [5]. Similarly, in parts of Southeast Asia and India [4, 6], as well as in some European countries [5], NDM-1 is the most frequently identified carbapenemase.

Understanding the local epidemiology of CRE is essential for assessing the therapeutic roles of the new agents. This is because both the lability of the parent drug to hydrolysis and the inhibitory properties of the β-lactamase inhibitor will differ as a function of type of carbapenemase present.
4 mg/L of avibactam decreased the MIC\textsubscript{50/90} of ceftazidime from 256/512 mg/L to 0.25/0.5 mg/L. As previously mentioned, avibactam does not have the ability to restore the activity of ceftazidime against MBL-producing strains, including NDM-1.

### IN VITRO ACTIVITY OF MEROPENEM-VABORBACTAM AGAINST CRE

Meropenem-vaborbactam displayed excellent in vitro activity against 991 KPC-producing Enterobacteriaceae from across the globe. Susceptibility was seen in 99% of isolates with MIC\textsubscript{50} and MIC\textsubscript{90} values of 0.06/8 and 1/8 mg/mL, respectively [12]. Of note, ceftazidime/avibactam was also tested against this collection of enzymes and, although susceptibility rates were similar (98%), MIC ranges were higher with MIC\textsubscript{50} and MIC\textsubscript{90} values of 1/4 and 4/4 mg/mL, respectively. MIC distributions of meropenem/vaborbactam were similar in isolates producing KPC-2 and KPC-3. Like ceftazidime/avibactam, meropenem/vaborbactam MICs are higher when mutations to OmpK35 and/or OmpK36 porins are present [13].

Vaborbactam does not restore the activity of meropenem in the presence of either OXA-48 or MBLs (including NDM-1, Verona Integron Metallobetalactamase [VIM]-type, or IMP type [active on imipenem]). Earlier studies demonstrated an inability of vaborbactam to potentiate biapenem, a carbapenem, against 24 NDM-1–producing, 21 IMP-producing, 25 VIM-producing, and 25 OXA-48–producing Enterobacteriaceae [14].

### CLINICAL EVIDENCE FOR THE TREATMENT OF CRE INFECTIONS

Although clinical experience for the management of CRE infections is scarce for both agents and comparative data between the 2 are lacking, a few small reports comparing the efficacy of these agents to alternatives are reported. Shields and colleagues retrospectively assessed outcomes in patients with bacteremia due to KPC producers treated with ceftazidime/avibactam (n = 13), carbapenem plus aminoglycoside combination therapy (n = 25), carbapenem plus colistin combination therapy (n = 30), and “other” regimens (n = 41) [15]. Ceftazidime/avibactam-based therapy increased clinical success (11/13 [85%]) over carbapenem plus aminoglycoside combinations (12/25 [48%], P = .04), carbapenem plus colistin combinations (12/30 [40%, P = .009], and “other” regimens (15/41 [37%], P = .004). Similarly, ceftazidime/avibactam was associated with increased 90-day survival (12/13 [92%]) compared with combination therapy (14/25 [56%], P = .03 and 19/30 [63%], P = .07) and “other” regimens (20/41 [49%], P = .008). Furthermore, acute kidney injury was lower in patients receiving ceftazidime/avibactam (2/11 [18%]) than in those receiving aminoglycoside (8/18 [44%], P = .01) or colistin (13/23 [57%], P = .01) combinations.

Similarly, in an observational study, van Duin and colleagues assessed outcomes of patients treated with ceftazidime/avibactam (n = 38) and colistin-based regimens (n = 99) for CRE
infections, of which nearly 70% were either bacteremia or pneumonia [16]. In this study, 94% of colistin patients and 63% of ceftazidime/avibactam patients (P < .001) received additional agents with in vitro activity against CRE. Mortality occurred in 3 of 38 (8%) ceftazidime/avibactam patients compared with 33 of 99 (33%) colistin patients. After inverse probability of treatment weighting, therapy with ceftazidime/avibactam was associated with a decrease in mortality of 23% (95% confidence interval [CI], 9%–35%, P = .001).

The efficacy and safety of meropenem/vaborbactam vs best available therapy (BAT) for treatment of CRE infection was assessed in a small phase 3 randomized open-label (The Targeting Antibiotic Non-Susceptible Gram-Negative Organisms [TANGO II]) trial. Patients were randomized 2:1 to receive either meropenem/vaborbactam monotherapy (n = 28) or BAT (n = 15) [17]. BAT included any of the following agents as monotherapy or part of combination therapy: polymyxins, carbapenems, aminoglycosides, or tigecycline. BAT patients were also allowed to receive ceftazidime/avibactam monotherapy if it was available at the study hospital. Most patients had either bacteremia (47%) or complicated urinary tract infection (35%). Clinical cure at the test-of-cure visit was significantly higher in patients who received meropenem/vaborbactam (18/28 [64.3%] vs 5/15 [33.3%]; absolute difference of 31.0 [95% CI, 1.2–60.7]). The 28-day mortality was 5 of 28 (17.9%) with meropenem/vaborbactam vs 5 of 15 (33.3%) with BAT (absolute difference of –15.5% [95% CI, –42.3% to 12.3%]).

Although data are limited and direct comparisons between ceftazidime/avibactam and meropenem/vaborbactam cannot be made, preliminary evidence supports the superiority of both agents over traditional CRE therapies.

**PROPENSITY FOR RESISTANCE SELECTION IN KPC**

Humphries and colleagues reported on ceftazidime/avibactam resistance driven by porin mutations in combination with enhanced expression of KPC in patients unexposed to ceftazidime/avibactam [18, 19]. More concerning have been the reports of resistance developing while on therapy. This resistance has been caused by mutations in the omega loop of the KPC enzyme leading to enhanced ceftazidime hydrolysis that cannot completely be inhibited by avibactam. Concern regarding selection for this mechanism of resistance was first described in serial passage studies by Livermore et al [20]. In this laboratory-based study assessing the selection of mutants with ceftazidime exposures at 2–16 times the MIC in the presence of 4 mg/L of avibactam, the authors demonstrated the selection of resistant mutants at frequencies of $10^4$ to $10^9$. Thirteen of the mutants and their parent isolates were sequenced. Ten of these isolates had an alteration within or in the immediate proximity of the omega loop of the KPC enzyme.

The most common mutation was a tyrosine for aspartic acid substitution at amino acid position 179 (D179Y) [20]. Similarly, in 2015, Winkler et al demonstrated that substitution at position 179 of the KPC-2 enzyme to alanine, glycine, or asparagine led to enhanced ceftazidime hydrolysis (increase in MIC from 64 mg/L to >512 mg/L) that could not be completely overcome by addition of 4 mg/L of avibactam (MIC = 32–64 mg/L) [21].

Unfortunately, this mechanism of resistance has now been described in multiple clinical reports. Shields and colleagues reported their experience with ceftazidime/avibactam treatment for KPC infections [22]. Ten of 37 patients treated had microbiological failure and in 3 of the 10 instances of failure, resistance developed to ceftazidime/avibactam after 10–19 days of therapy (baseline MICs were 2/4–4/4 mg/L and subsequent MICs ranged from 32/4 to >256/4) [22]. There were 7 ceftazidime/avibactam-resistant isolates recovered from these 3 patients, all producing variations of the KPC enzyme. The most common substitution, displayed in 5 of the 7 isolates, was D179Y, the same variant described previously by Livermore et al [20]. Interestingly, these KPC variants lost their carbapenemase activity and meropenem susceptibility was restored [23]. Regrettably, this reversion in meropenem susceptibility appears unsustainable. In an in vitro serial passage study with meropenem on these isolates, meropenem resistance was restored due largely to selection of mutations to the OmpK36 porin [24]. Importantly, the mechanism of carbapenem resistance was unknown in some experiments and, in others, restoration of the original KPC enzyme in combination with porin mutations was demonstrated [24].

In the TANGO II study, 4 patients received ceftazidime/avibactam therapy and one patient developed resistance. The ceftazidime/avibactam MIC increased from 0.5/4 to >256/4 during therapy, and this isolate demonstrated a D179Y substitution in the KPC enzyme [25]. A third report of resistance development was described in a patient receiving 12 days of ceftazidime/avibactam for an intra-abdominal infection due to a KPC producer [26]. The original isolate had a ceftazidime/avibactam MIC of 3/4 mg/L; however, the subsequent isolate had an MIC of >256/4, and the D179Y mutation was demonstrated. Consistent with the above reports, the subsequent isolate displayed a significantly decreased MIC to meropenem (from 128 mg/L to 2 mg/L). However, after a change in therapy to polymyxin B plus meropenem, resistance to both ceftazidime/avibactam (MIC = 12/4 mg/L) and meropenem (MIC ≥128 mg/L) were demonstrated in a recovered isolate [26]. Similar to the serial passage studies, this occurred as a result of reversion to the parent KPC-2 enzyme, albeit with enhanced expression, in combination with mutations to OmpK35 and OmpK36.

Moving forward, it will be important to determine if carbapenem/β-lactamase inhibitor combinations such as meropenem/vaborbactam and imipenem/relebactam offer a potential solution to ceftazidime/avibactam resistance in these variants. Although the variants initially demonstrate carbapenem susceptibility the utility of carbapenems appears limited. As the
emergence of meropenem resistance after meropenem exposure in both in vitro [24] and in vivo reports [26] has been associated with reversion to the parent KPC enzyme, it will be interesting to see if addition of a KPC inhibitor such as vaborbactam or relebactam preserves carbapenem activity in this setting and makes resistance selection more difficult.

Resistance to meropenem/vaborbactam in KPC-producing isolates is mediated by a combination of KPC production and mutations to OmpK35 and OmpK36 [27, 28]. Encouragingly, the likelihood of resistance selection while receiving meropenem/vaborbactam appears to be decreased compared with ceftazidime/avibactam, particularly for isolates that are susceptible (MIC ≤4/8 mg/L). Sun and colleagues performed a serial passage study with meropenem/vaborbactam in 18 KPC-producing strains that coproduced various other β-lactamases, had porin mutations, and demonstrated meropenem/vaborbactam MICs ranging from ≤0.06/8 to 32/8 mg/L. Concentrations of 8 mg/L of meropenem and 8 mg/L of vaborbactam were able to suppress resistance in 14 of the 18 strains, whereas for the other 4 strains (baseline meropenem/vaborbactam MICs of 2, 4, 16, and 32 mg/L) resistance was suppressed at concentrations of 16 mg/L meropenem and 8 mg/L vaborbactam [28]. The meropenem and vaborbactam concentrations chosen for these analyses are clinically relevant and achievable in vivo using labeled dosing (Table 2). Notably, the 4 resistant mutants selected were not KPC-3 variants, but rather resistance was mediated by increased KPC expression and/or further mutations to OmpK35 and OmpK36 [28].

Data from hollow fiber infection models support the low propensity for meropenem/vaborbactam to select for resistance at the labeled dose [27]. When simulating exposures of meropenem/vaborbactam at this dose using phase 1 pharmacokinetic data, resistance was suppressed in all isolates up to MICs of 8/8 mg/L. However, a resistant subpopulation was selected in an isolate with a baseline MIC of 16/8 mg/L. Interestingly, when the exposures of vaborbactam were increased to mimic pharmacokinetic data observed in phase 3 trials as opposed to phase 1 trials (median vaborbactam area under the concentration time curve over 24 hours $[\text{AUC}_{\text{24h}}]$ of 550 mg × h/L as opposed to an $\text{AUC}_{\text{24h}}$ of 320 mg × h/L), suppression was demonstrated in the isolate with the baseline MIC of 16/8 mg/L [27]. These findings are supported by hollow fiber model data suggesting that a free vaborbactam AUC to meropenem/vaborbactam MIC ratio of >24 is the pharmacodynamic parameter associated with resistance suppression [29]. This target should be easily met with labeled dosing at the MIC breakpoint of 4/8 mg/L.

These in vitro data are supported by data from the TANGO II trial. Of 25 patients in this study who received meropenem/vaborbactam monotherapy, 5 patients had subsequent isolates recovered after a mean of 8.5 days of meropenem/vaborbactam. Only one of these isolates had a ≥4-fold increase in meropenem/vaborbactam MIC, and the MIC in that isolate increased from 0.25/8 mg/L to 1/8 mg/L, which remains within the susceptibility range [25].

Taken together, these data suggest the possibility of a lower propensity for resistance development during therapy with meropenem/vaborbactam. It is important to note that ceftazidime/avibactam has been available for >3 years and thus there have been more opportunities for resistance emergence during therapy. Therefore, it remains to be determined whether or not these in vitro and early clinical advantages for meropenem/vaborbactam hold true when real-world use increases.

**CONSIDERATIONS FOR FORMULARY DECISIONS**

Both ceftazidime/avibactam and meropenem/vaborbactam have revolutionized the management of CRE infections, and

### Table 2. Key Pharmacologic Considerations for Ceftazidime/Avibactam and Meropenem/Vaborbactam

<table>
<thead>
<tr>
<th>PK Consideration</th>
<th>Ceftazidime/Avibactam</th>
<th>Meropenem/Vaborbactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (normal renal function)</td>
<td>2.5 g (2 g ceftazidime/500 mg avibactam) every 8 h</td>
<td>4 g (2 g meropenem/2 g vaborbactam) every 8 h</td>
</tr>
<tr>
<td>Infusion length</td>
<td>2 h</td>
<td>3 h</td>
</tr>
<tr>
<td>Renal dose adjustments</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Package insert CrCl calculation recommendation</td>
<td>Cockcroft-Gault</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>Hepatic dose adjustments</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Most common adverse reactions in clinical trials</td>
<td>Nausea, Vomiting, Diarrhea</td>
<td>Headache, Phlebitis/infusion site reactions, Diarrhea</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Probenecid, Valproic acid</td>
<td>Probenecid</td>
</tr>
<tr>
<td>Susceptibility breakpoint, mg/L</td>
<td>8/4</td>
<td>4/8</td>
</tr>
<tr>
<td>Other considerations</td>
<td>3-h infusion, but 4-h stability at room temperature will require structured compounding and administration protocols</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CrCl, creatinine clearance; PK, pharmacokinetic.
clinicians are fortunate to have these “game-changing” therapies. For the management of infections due to KPC producers, treatment with these agents is associated with decreased mortality, improved clinical success, and decreased toxicity compared with older options such as colistin.

Ceftazidime/avibactam was the first new antibiotic to come to market for CRE. Real-world data have emerged demonstrating its superiority to polymyxin-based therapy from both efficacy and safety standpoints [15, 16]. Although it remains unclear whether this agent should be administered as monotherapy or combined with other agents (eg, aminoglycosides), ceftazidime/avibactam represents an effective treatment option for KPC producers. However, issues pertaining to the emergence of resistance during therapy are concerning. The similarities in emergence of resistance in preclinical [20, 21] and clinical studies [22, 25, 26] are striking.

The enhanced in vitro potency of meropenem/vaborbactam (MIC$_{50/90}$ of 0.06/1 compared to 1/4) against KPC producers, as well as data suggesting that emergence of resistance is less likely to occur, makes meropenem/vaborbactam, in our opinion, the preferred agent for treatment of KPC-producing CRE. Importantly, it will be crucial to assess whether these advantages translate to improved outcomes.

Furthermore, as resistance to meropenem/vaborbactam develops in clinical isolates, the mechanisms of resistance as well as activity of ceftazidime/avibactam against these meropenem/vaborbactam-resistant isolates will further inform considerations regarding a preferred agent. If one agent were less likely to select for resistance mechanisms that cause resistance to both novel therapies (and other pipeline agents) it would be an important consideration when deciding on a preferred agent. Encouragingly, data suggest that cross-resistance currently remains infrequent [12]. Of 991 KPC isolates tested, only 24 (2%) displayed resistance to either agent. Importantly only 5 (21%) were resistant to both, with 14 of 18 (78%) of ceftazidime/avibactam-resistant isolates being susceptible to meropenem/vaborbactam and 6 of 10 (60%) meropenem/vaborbactam-resistant isolates remaining susceptible to ceftazidime/avibactam [12].

Clinicians will need to pay attention to emerging resistance trends and local susceptibility data to continually assess which agent maintains better activity and is less likely to select for cross-resistance.

Due to avibactam’s unique inhibitory profile against OXA-48-like enzymes and ceftazidime’s stability to hydrolysis by this enzyme, ceftazidime/avibactam is the preferred agent for treatment of OXA-48-producing CRE. Furthermore, avibactam’s broad inhibitory profile also makes it an ideal agent to combine with aztreonam for the management of MBLs. MBLs do not have the ability to hydrolyze aztreonam. However, due to frequent coproduction of other enzymes (eg, ESBLs, OXA-48), MBL-producing Enterobacteriaceae are often resistant to aztreonam. Concomitant administration of avibactam, which can inhibit all non-MBL enzymes present, can restore aztreonam’s activity. This has been demonstrated in vitro where addition of 4 mg/L of avibactam decreased the MIC of aztreonam to ≤0.5 mg/L in 7 aztreonam-resistant MBL producers [30]. Although the aztreonam/avibactam combination antibiotic is currently under development and is unavailable, combining ceftazidime/avibactam with aztreonam is an emerging treatment strategy for MBL producers that has been employed with varying degrees of clinical success [31, 32].

In conclusion, clinicians will likely have a need for both agents for the management of CRE. Ultimately, local CRE epidemiology will drive decisions regarding the preferred agent, based on the most frequent mechanism of carbapenem resistance (KPC vs OXA-48 vs MBL) within an institution. Furthermore, because resistance mechanisms are complex and often multifactorial, we recommend that all CRE pathogens be routinely tested against both ceftazidime/avibactam and meropenem/vaborbactam. While one agent might be preferred for empiric use based on local epidemiology, individualized definitive therapeutic decisions should be based upon characteristics of the patient and pathogen being treated. Moreover, as reports of resistance development while on therapy have emerged, it is critical that repeat susceptibility testing is performed in patients with persistently positive cultures that to ensure that resistance has not developed to the agent utilized.

**Notes**

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**References**


