Practical Implications of New Antibiotic Agents for the Treatment of Carbapenem-Resistant Enterobacteriaceae

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ABSTRACT

OBJECTIVE: To provide insight into the practical implications of the use of ceftazidime/avibactam and meropenem/vaborbactam for the management of carbapenem-resistant Enterobacteriaceae (CRE) and to identify strategies for overcoming barriers to the use of these agents in clinical practice.

DATA SOURCES: A literature search of PubMed was conducted using the following search terms: ceftazidime/avibactam, meropenem/vaborbactam, carbapenem-resistant Enterobacteriaceae, antimicrobial stewardship, and clinical laboratory standards institute. Abstracts from infectious diseases conferences, article bibliographies, and relevant drug monographs were also reviewed.

STUDY SELECTION/DATA EXTRACTION: Relevant English-language studies were considered.

DATA SYNTHESIS: Studies demonstrating the clinical utility of ceftazidime/avibactam and meropenem/vaborbactam over older agents for CRE were summarized. Laboratory challenges, including lack of widespread technology and delays in usable information, and formulary considerations were discussed. Insight was provided into overcoming these challenges and minimizing barriers using infectious diseases pharmacists, antimicrobial stewardship teams, and infection control teams.

RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE: This review informs clinicians of the potential difficulties of the use of ceftazidime/avibactam and meropenem/vaborbactam in clinical practice and provides tools to overcome these difficulties, thus allowing clinicians to stay at the forefront of CRE treatment.

CONCLUSIONS: Clinicians treating patients with CRE infections need to be aware of challenges they may face when using ceftazidime /avibactam and meropenem/vaborbactam. Infectious disease (ID) pharmacists and antimicrobial stewardship teams play an important role in minimizing barriers and ensuring appropriate use of these antibiotics.

KEYWORDS: ceftazidime/avibactam, meropenem/vaborbactam, carbapenem-resistant Enterobacteriaceae, challenges

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Introduction

Carbapenem-resistant Enterobacteriaceae (CRE) are a highly drug-resistant family of bacteria with the potential to cause a multitude of infections that are associated with high mortality rates. The Centers for Disease Control and Prevention (CDC) considers CRE to be especially dangerous because of their transmissibility and limited treatment options, categorizing them as an urgent public health threat. In the United States, CRE are responsible for approximately 9300 infections and 600 deaths per year. Infections with carbapenem-resistant *Klebsiella pneumoniae* and *Escherichia coli* account for most cases.[1] On a global scale, CRE have substantial variability in their distribution, but are becoming more widespread.[2] CRE can be split into 2 categories: non-carbapenemase-producing CRE and carbapenemase-producing CRE. Non-carbapenemase-producing CRE cause resistance via alterations in membrane permeability, development of drug efflux pumps, or alterations in antimicrobial target site binding. Carbapenemase-producing CRE cause resistance via the production of enzymes such as *Klebsiella pneumoniae* carbapenemases (KPCs), oxacillinases (OXA), or metallo-beta-lactamases. Resistance by means of carbapenemase-producing CRE is believed to be primarily responsible for the increasing spread of CRE.[3]

In response to the growing burden of CRE, several organizations have launched campaigns to combat antimicrobial resistance. The CDC formally called for action to reduce the spread and prevent the development of resistance, with a goal of reducing hospital-acquired CRE infections by 60% by the year 2020. One of the core actions recommended by the CDC was the development new drugs and diagnostic tests.[4] Likewise, the Infectious Diseases Society of America initiated the "10 x '20" campaign, in pursuit of development of 10 new antibiotics by the year 2020.[5] Passage of the Generating Antibiotic Incentives Now (GAIN) Act in 2013 provided incentives for drug companies to develop and market new antibiotic agents.[6]

Since these initiatives began, 2 antibiotic agents with activity against CRE have received Food and Drug Administration (FDA) approval. Clinicians are now faced with the challenge of implementing the use of these agents in to clinical practice given their broad spectrums of activity, need for appropriate antibiotic stewardship, hospital formulary restrictions, and gaps in the widespread availability of appropriate diagnostic tests. The purpose of this review is to describe the practical implications of ceftazidime/avibactam and meropenem/vaborbactam for the treatment of CRE in clinical practice.

A literature search of PubMed was conducted using the following search terms: ceftazidime/avibactam, meropenem /vaborbactam, carbapenem-resistant Enterobacteriaceae, antimicrobial stewardship, and clinical laboratory standards institute. Abstracts from infectious diseases conferences, article bibliographies, and relevant drug monographs were also reviewed.

Relevant English-language studies published before January 2019 were considered for inclusion. Studies aiming to evaluate clinical outcomes of ceftazidime/avibactam or meropenem/vaborbactam for the treatment of CRE infections were included.

Ceftazidime/Avibactam

Ceftazidime/avibactam received FDA approval in 2015 and is indicated for the treatment of complicated urinary tract infections, hospital-associated and ventilator-associated bacterial pneumonia, and complicated intra-abdominal infections when used in combination with metronidazole. Ceftazidime is a third generation cephalosporin antibiotic, and avibactam is synthetic non-beta-lactam, beta-lactamase inhibitor that inactivates certain beta-lactamases. Ceftazidime/avibactam has a broad spectrum of activity covering most gram-negative bacilli, including *Pseudomonas*. In vitro, ceftazidime/avibactam is active against some extended spectrum beta-lactamases (ESBLs), including KPCs and OXA. Ceftazidime/avibactam has no activity against bacteria that produce metallo-beta-lactamases and may not have activity against non-carbapenemase-producing CRE.[7]

Meropenem/Vaborbactam

Meropenem/vaborbactam received FDA approval in 2017 and is indicated for the treatment of complicated urinary tract infections in individuals who are at least 18 years old. Meropenem is a carbapenem antibiotic and vaborbactam is a beta-lactamase inhibitor that prevents meropenems degradation by certain beta-lactamases, including KPCs. Meropenem/vaborbactam does not have activity against OXA, metallo-beta-lactamases, and may not have activity against non-carbapenemase-producing CRE.[8]

Utility in Clinical Practice

Clinical outcomes data with ceftazidime/avibactam and meropenem/vaborbactam for the management of CRE are limited; however, a few studies that demonstrate a clear role for both of these agents have been completed. First, King and colleagues conducted a multicenter retrospective chart review of 60 patients assessing outcomes of ceftazidime/avibactam therapy for CRE infection. They found an in-hospital mortality rate of 32%, microbiologic cure rate of 53%, and clinical success rate of 65%, showing that ceftazidime/avibactam is an appropriate treatment option for severely ill patients. Notably, almost half of the patients included in King et al's[9] study were treated with concomitant Gram-negative active agents, with no differences in outcomes between monotherapy and combination therapy observed.

Shields and colleagues conducted a retrospective chart review comparing definitive therapy with ceftazidime/avibactam to other treatment regimens such as a carbapenem plus aminoglycoside or colistin. In total, 109 patients with CRE *K pneumoniae* bacteremia were included, and 13 patients were treated with ceftazidime/avibactam. Clinical success was achieved more frequently in the ceftazidime/avibactam group than in other groups, including those with more than 1 active agent.[10] Van Duin and colleagues evaluated 137 patients with CRE infection who received ceftazidime/avibactam or colistin as initial therapy in the Consortium on Resistance Against Carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE) observational study. They also found lower all-cause 30 day hospital-mortality in those treated with ceftazidime/avibactam than in those treated with colistin (8% versus 33%).[11] Most recently, Tumbarello and colleagues retrospectively evaluated the efficacy of ceftazidime/avibactam salvage therapy in 138 patients with KPC producing *K pneumoniae* infections. They observed a significantly lower 30 day mortality rate in patients with KPC bacteremia treated with ceftazidime/avibactam than those who received drugs other than ceftazidime/avibactam (36.5% versus 55.8%).[12] Despite these studies being small and retrospective in nature, they highlight a potential benefit of ceftazidime/avibactam over older treatment options for the management of CRE.

TANGO II, a phase 3, randomized, controlled trial compared meropenem/vaborbactam to best available therapy for CRE infections. The study included 43 patients with a baseline CRE infection, nearly half of which had bacteremia. There was no consensus best available therapy regimen used; however, majority of the regimens used combination therapy. End of treatment cure rates and test of cure rates were significantly higher in the meropenem/vaborbactam group than in the best available therapy group.[13]

The above studies support ceftazidime/avibactam and meropenem/vaborbactam as integral agents in management of CRE; however, clinicians still face notable challenges in positioning the use of these agents into routine practice. Considerations such as laboratory technology, hospital formulary, and antimicrobial stewardship need to be made to best use these agents.

Laboratory/Diagnostic Challenges

One of the major challenges of using ceftazidime/avibactam and meropenem/vaborbactam in clinical practice is the lack of widespread laboratory technology to provide real-time information on bacterial identification, antimicrobial susceptibility, and presence of resistance markers. Rapid diagnostic tools such as matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) and real-time polymerase chain reaction (PCR) are commercially available and provide insight into some of these areas; however, most laboratories do not have this technology available.[14] Instead, older automated instruments, such as Vitek2, Microscan, and Phoenix, are being used for organism identification and susceptibility testing in most institutions. These older methods can take several days to produce results and often do not provide information on the susceptibility of the new antibiotics or the presence of resistance markers.[15]

Moreover, the Clinical Laboratory Standards Institute (CLSI) currently does not recommend routine susceptibility testing of ceftazidime/avibactam or meropenem/vaborbactam for Enterobacteriaceae. Both ceftazidime/avibactam and meropenem/vaborbactam susceptibility testing is considered to be optional by the 2019 CLSI antimicrobial susceptibility testing document.[16] If laboratories using Vitek2, Microscan, or Phoenix wished to test susceptibility of ceftazidime/avibactam or meropenem/vaborbactam, they must do so via disk diffusion or gradient diffusion strips. Both of these methods would require laboratories to complete in-house verifications, a process which would necessitate collection of multiple bacterial isolates. Most laboratories do not have the resources to do this; therefore, additional antibacterial susceptibility testing is often completed by a reference laboratory. This, in turn, will further delay the time to results.

Because susceptibility testing of these agents is not yet routine, and often requires send out to reference laboratories, the process for obtaining susceptibility information often does not begin until a special request is made to the microbiology laboratory, after initial susceptibility, testing suggests the presence of a CRE. In the clinical setting, this can mean an additional 24- to 48-hour delay, on top of the several day process of initial testing. This time lag in usable information can be a deterrent to the use of ceftazidime/avibactam and meropenem /vaborbactam as exposing patients to prolonged empiric therapy with broad-spectrum agents can result in significant collateral damage. However, if therapy with either of these agents was warranted, then a patient would be several days into his disease course before providers could confirm antibacterial susceptibility and appropriately escalate therapy. Because of this, providers are forced to balance their stewardship obligations with potential benefits of empiric use, making the decision to use these agents on a case-by-case basis.

As noted earlier, ceftazidime/avibactam and meropenem /vaborbactam only have activity against certain types of carbapenemases. This can further complicate the role of these agents if institutions are not aware of what type of CRE is circulating at their institution. For example, if an institution had non-carbapenemase-producing CRE as its predominate mechanism of resistance, ceftazidime/avibactam and meropenem/vaborbactam may not work as reliably as expected.

Hospital Formulary Considerations

Despite these laboratory challenges, it is crucial to consider the inclusion of ceftazidime/avibactam and/or meropenem/vaborbactam into the hospital formulary. These agents have revolutionized the management of CRE infections by providing a more effective and safer alternative compared with polymyxin-based therapies.[10,11,13,17,18] If these agents are not readily available, clinicians may be compelled to use combination therapies that have less predictable pharmacokinetics and are associated with serious toxicities such as renal failure.

When considering the preferred CRE agent between ceftazidime/avibactam and meropenem/vaborbactam, local epidemiology of CRE must be evaluated. If the predominate mechanism of resistance is due to OXA-48 carbapenemases, then ceftazidime/avibactam may be preferred because ceftazidime does not get hydrolyzed by OXA-48.[7] However, due to the emergence of resistance to ceftazidime/avibactam while on therapy,[19] it is imperative for institutions to routinely monitor local epidemiology. Pharmacy and therapeutics committees should seek insight from microbiology departments and Infection Control to determine institution-specific resistance mechanisms to ensure appropriate formulary inclusion.

Drug acquisition and costs is often a factor to be considered when adding new agents to the hospitals formulary. The listed average wholesale price for ceftazidime/avibactam and meropenem/vaborbactam are as follow: US$430 for a vial of ceftazidime 2 grams/avibactam 0.5 grams and US$198 for a vial of meropenem 1 gram/vaborbactam 1 gram.[20,21] For patients with normal renal function, this equates to total daily costs of US$1290 and US$1188 for ceftazidime/avibactam and meropenem/vaborbactam, respectively. It is important to note that average wholesale price may not reflect actual drug acquisition costs because they are subject to change and vary based on institution-specific contracting.

Antimicrobial Stewardship

Use of ceftazidime/avibactam and meropenem/vaborbactam in clinical practice requires high levels of antimicrobial stewardship. Stewardship teams are tasked with minimizing barriers to utilization, but must also be careful not to promote overuse of these agents. Minimizing barriers will ensure that these agents can be appropriately used when needed. Protecting the use of ceftazidime/avibactam and meropenem/vaborbactam will help mitigate development of resistance and maintain their use as CRE active agents for as long as possible. Development of criteria for use or a system of protected use is essential to make sure both of these antibiotics are safeguarded.

Infectious diseases (ID) pharmacists play a crucial role in overcoming some of the laboratory barriers previously discussed. Coordination between ID pharmacists and the microbiology lab has been shown to be a valuable stewardship tool that can allow for real-time interventions, including earlier in vitro susceptibility testing of alternative/salvage antimicrobials such as ceftazidime/avibactam and meropenem/vaborbactam for multi-drug–resistant organisms.[22] The potential clinical impact of this is a decrease in the time to susceptibility information and appropriate antibiotic therapy. In institutions with particularly high rates of CRE, reflex testing of ceftazidime/avibactam, and meropenem/vaborbactam susceptibility for organisms identified as carbapenem-resistant should be considered to further reduce time to susceptibility information. ID pharmacists can also work with microbiology labs to determine their institution-specific CRE epidemiology to help guide formulary decisions.

In addition, ID pharmacists and stewardship teams should serve as advocates for implementation of rapid diagnostic tools at their institutions. A recent cost analysis showed that despite the expense of implementing rapid diagnostic technology and associated personnel, a cost-savings of more than US$2 million was achieved as well as a mortality benefit.[23] Framing discussions with hospital administration in the context of the cost-savings and mortality benefit of rapid diagnostics may help strengthen rationale for investing into these new tools.

Conclusions

With rates of Gram-negative resistance on the rise, providers must stay at the forefront of management of CRE. Understanding and overcoming the challenges to use of ceftazidime/avibactam and meropenem/vaborbactam will allow providers to better use these agents in routine clinical practice. Pharmacists and antimicrobial stewardship teams play a critical role in minimizing barriers faced by providers in the management of CRE infection.

Author Contributions

NB and YL conceived this project, conducted the literature search and data synthesis, and prepared the manuscript. Both authors reviewed and approved the final manuscript.

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