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The role of ceftolozane/tazobactam (Zerbaxa®), ceftazidime/avibactam (Avycaz®), and meropenem/vaborbactam (Vabomere®) in treating infections caused by MDR GNB

Introduction

Gram-negative bacteria (GNB) are a common cause of human disease including intra-abdominal and urinary tract infections, pneumonia, and bacteremia. Recent studies from community and academic hospitals have demonstrated antibiotic resistance among GNB is increasing.[1-4] This pattern is particularly concerning because infections caused by antibiotic-resistant bacteria are associated with increased mortality,[5] hospital readmissions,[6] and cost.[7] Over the last few years, three promising beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations with activity against multidrug-resistant (MDR) GNB have been approved in the US. The focus of this review is the role of ceftolozane/tazobactam (Zerbaxa®), ceftazidime/avibactam (Avycaz®), and meropenem/vaborbactam (Vabomere®) in treating infections caused by MDR GNB.

Gram-Negative Bacteria: Mechanisms of Resistance

In general, four mechanisms for bacterial resistance to antibiotics exist: 1) decreased penetration to the target site; 2) increased efflux from the target site; 3) alteration of the target site; and 4) inactivation of the antibiotic by enzymatic degradation.[8,9] Enzymatic degradation of beta-lactams occurs primarily through the production of beta-lactamases. This mechanism of resistance is particularly concerning because genes encoding these enzymes are easily transferred among GNB, which can result in rapid dissemination of antibiotic resistance or outbreaks. Examples of notable beta-lactamases include extended-spectrum beta-lactamases (ESBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs).

Susceptibility testing should ALWAYS guide treatment of MDR GNB

Beta-Lactam/Beta-Lactamase Inhibitors: Mechanism of Action

Beta-lactams (BL) bind to penicillin binding proteins (PBP) on the cell wall and inhibit cell wall synthesis. Beta-lactamase inhibitors (BLI) are often combined with BLs to inhibit beta-lactamase enzymes thus preserving BL activity. Although all GNB are capable of producing beta-lactamases, they are more common among the Enterobacteriaceae (e.g., *Escherichia*, *Klebsiella*, *Proteus*, *Citrobacter*, and *Enterobacter spp*.). In contrast, non-lactose fermenting GNB (e.g., *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas spp*.) often deploy alternative resistance mechanisms and therefore are not always susceptible to BLIs. It is important to recognize that the new BL/BLIs are not interchangeable or active against all GNB. Therefore, susceptibility testing should always guide treatment of MDR GNB. Unfortunately testing of these newer antimicrobials is not widely available, and there is often a lag until they are incorporated into commercial testing panels. It is important, however, for clinical laboratories to develop a process for performing susceptibility tests to guide clinical use of these new BL/BLI.

What Makes Ceftolozane/Tazobactam (Zerbaxa®) Unique?

Ceftolozane is a novel third-generation cephalosporin with two specific advantages over other anti-pseudomonal agents. First, ceftolozane has more affinity to PBPs on the surface of *P. aeruginosa*.[10,11] Second, ceftolozane has less affinity to AmpC beta-lactamases that result in resistance to cephalosporins.[12] The addition of tazobactam increases the efficacy of ceftolozane against select ESBL-producing organisms; however, ceftolozane/tazobactam is not active against carbapenem resistant Enterobacteriaceae (CRE).[13] Ceftolozane/tazobactam is approved for treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). For more detailed clinical information on ceftolozane/tazobactam,

see our March 2015 DASON Newsletter (please see page 4 for hyperlink). In short, ceftolozane/tazobactam is active against MDR *Pseudomonas* with lower risk of toxicity compared to alternative agents such as polymyxin B, colistin, and aminoglycosides. It may also be substantially less expensive than the other new BL/BLI (Table 1).

What makes Ceftazidime/Avibactam (Avycaz®) Unique?

Ceftazidime is a third-generation cephalosporin with anti-pseudomonal activity originally approved in 1985. Avibactam is a novel BLI that inhibits a wide range of beta-lactamases.[14] This new combination restores activity against KPC-producing Enterobacteriaceae, even in the presence of co-produced ESBLs and/or AmpC beta-lactamases.[15] However, ceftazidime/avibactam is not reliably active against *Acinetobacter spp*. or NDM-1-producing organisms (Table 1).[16] To date, three Phase 3 clinical trials support the FDA-approved indications of cUTI and cIAI, and studies in patients with nosocomial pneumonia are under way.[17-19] In addition, a recent prospective observational study demonstrated all-cause, propensity-adjusted mortality was lower for patients with CRE infections started on ceftazidime/avibactam compared to colistin (absolute risk reduction 23%, p=0.0012).[20] Overall, ceftazidime/avibactam is a promising, less toxic alternative to colistin, polymyxin B, and tigecycline for infections caused by carbapenemase-producing bacteria, particularly CRE infections due to KPC- or OXA-producers.

What makes Meropenem/Vaborbactam (Vabomere®) Unique?

Meropenem is an anti-pseudomonal carbapenem that was originally approved in 1996. Vaborbactam is a novel BLI that was designed to be a potent inhibitor of serine carbapenemases. The addition of vaborbactam restored activity against CRE isolates and KPC producers in *in vitro* studies; however, no appreciable effect was observed on *P. aeruginosa*, *Acinetobacter spp.*, and *S. maltophilia*.[21] Like other new BL/BLI mentioned in this review, vaborbactam does not inhibit the NDM-1 carbapenemase.[21] At this time, one Phase 3 clinical trial supports the FDA-approved indication of cUTI, and one Phase 3 clinical trial comparing meropenem/vaborbactam to "best available therapy" in patients with serious infections caused by CRE was stopped early due to a clear observed benefit from meropenem/vaborbactam.[22] Ongoing studies in nosocomial pneumonia are under way. Of note, vaborbactam should not be used in pregnant women due to limited data on safety. Overall, meropenem/vaborbactam is a promising new agent with activity against CRE. At this point, however, use should be limited to infections caused by CRE that are resistant to ceftazidime/avibactam given the paucity of data evaluating the safety and efficacy in invasive infections. Detailed instructions for obtaining susceptibility testing materials for meropenem/vaborbactam can be found here (please see page 4 for hyperlink).

Summary and Role in Community Hospitals

Each of these new treatment options have specific advantages in helping treat patients with infections caused by MDR GNB. Despite data for indications such as cUTI and cIAI, we feel the current role for these agents is to conserve them for patients with documented MDR GNB infections or those at significant risk for developing such infections. Ongoing studies are underway evaluating the utility of these agents in the treatment of nosocomial pneumonia and other invasive infections, and the role for these agents will likely evolve with more experience and additional research. In such difficult cases where alternative options are not available, we recommend performing susceptibility testing when using these new BL/BLI. This may require partnership with reference laboratories and/or planning for acquisition of susceptibility testing resources in your local clinical microbiology laboratory. See our September 2017 DASON Newsletter (please see page 4 for hyperlink) for more information on CRE testing.

Take Home Points:

1. Susceptibility testing is always necessary when treating MDR GNB due to complex mechanisms of resistance. Testing against the newly available agents requires planning with the clinical microbiology laboratory.
2. Ceftolozane/tazobactam is a novel 3rd generation cephalosporin active against MDR *P. aeruginosa*, but not CRE. It is less toxic than other older antibiotics that are often used for MDR *P. aeruginosa* infections.
3. Ceftazidime/avibactam is a novel BL/BLI useful in patients with known or suspected infections due to CRE.
4. Meropenem/vaborbactam is a novel BL/BLI with potent activity against KPC-producing CRE. The advantages over alternative CRE treatments are uncertain due to limited safety and efficacy data.
5. Novel agents for MDRGNB should be limited to patients with known resistant pathogens; widespread use in community hospitals should be avoided.

Table 1. Comparison of new beta-lactam/beta-lactamase inhibitor combinations

Agent	Studies/ indications			Activity				Potential Niche	Dosing*	Price/day (AWP)
	cIAI	cUTI	HAP/VAP	CRE	CR-Pseudomonas	CR-Acinetobacter	NDM-1			
ceftolozane/ tazobactam	✓	✓	under study	-	most	-	-	Treating MDR *P. aeruginosa*	1.5g IV q8h (infused over 1h)	$361.83
ceftazidime/ avibactam	✓	✓	under study	✓	+/-	+/-	-	Treating CRE infections	2.5g IV q8h (infused over 2h)	$1,077.30
meropenem/ vaborbactam		✓	under study	✓	+/-	+/-	-	Treating CRE infections	4g IV q8h (infused over 3h)	$990

*dosing adjustment required in patients with CrCl < 50 mL/min

cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections; HAP, hospital-acquired pneumonia; VAP, ventilator associated pneumonia; CR, carbapenem resistant; AWP, average wholesale price

Hyperlinks

March 2015 DASON Newsletter:
https://dason.medicine.duke.edu/system/files/march_2015_dason_newsletter-_ceftolozane-tazobactam_rwm-revised_final.pdf

Meropenem/Vaborbactam Susceptibility Testing Information:
http://meropenemandvaborbactamruo.com/

September 2017 DASON Newsletter:
https://dason.medicine.duke.edu/system/files/newsletters/708/9-2017dasonnewsletter.pdf

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