



## New $\beta$ -lactamase Inhibitor Combinations: Options for Treatment; Challenges for Testing

### Background

The  $\beta$ -lactam class of antimicrobial agents has played a crucial role in the treatment of infectious diseases since the discovery of penicillin, but  $\beta$ -lactamases (enzymes produced by the bacteria that can hydrolyze the  $\beta$ -lactam core of the antibiotic) have provided an ever expanding threat to their successful use. Over a thousand  $\beta$ -lactamases have been described. They can be divided into classes based on their molecular structure (Classes A, B, C and D) or their function (e.g., penicillinase, oxacillinase, extended-spectrum activity, or carbapenemase activity).<sup>1</sup> While the first approach to addressing the problem of  $\beta$ -lactamases was to develop  $\beta$ -lactamase stable  $\beta$ -lactam antibiotics, such as extended-spectrum cephalosporins, another strategy that has emerged is to combine existing  $\beta$ -lactam antibiotics with  $\beta$ -lactamase inhibitors. Key  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations that have been used widely for over a decade include amoxicillin/clavulanic acid, ampicillin/sulbactam, and piperacillin/tazobactam.

The continued use of  $\beta$ -lactams has been threatened by the emergence and spread of extended-spectrum  $\beta$ -lactamases (ESBLs) and more recently by carbapenemases. The global spread of carbapenemase-producing organisms (CPOs) including Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, limits the use of all  $\beta$ -lactam agents, including extended-spectrum cephalosporins (e.g., cefotaxime, ceftriaxone, and ceftazidime) and the carbapenems (doripenem, ertapenem, imipenem, and meropenem). This has led to international concern and calls to action, including encouraging the development of new antimicrobial agents, enhancing infection prevention, and strengthening surveillance systems.

Carbapenem resistance has become a global problem. In the United States, according to the Centers for Disease Control and Prevention (CDC),<sup>2</sup> the *Klebsiella pneumoniae* carbapenemase (or KPC) is the most widely distributed of the carbapenemases, but as a recent outbreak of the VIM (Verona integron-mediated) carbapenemase-containing isolates in Kentucky indicates, it is not the only enzyme of concern.<sup>3</sup> The remaining members of the “BIG 5” carbapenemase classes include OXA-48, NDM, and IMP,<sup>4</sup> all of which have been isolated from patients in the United States (<http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html>). The major carbapenemases present in the United States are shown in (Table 1).

Multiple approaches to developing antimicrobial agents that are active against ESBLs and CPOs are being pursued, but the strategy of combining both new and existing  $\beta$ -lactams with  $\beta$ -lactamase inhibitors has already yielded new and effective agents.<sup>5-7</sup> These include:

1. **Ceftazidime/avibactam** (Avycaz™ – AstraZeneca/Actavis [now Allergan]) has recently been approved in the United States for complicated urinary tract infections and complicated intra-abdominal infections ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/206494s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206494s000lbl.pdf)). Ceftazidime is a well-established third-generation cephalosporin that, in combination with avibactam, is active against most ESBLs and KPC carbapenemases, and some OXA-enzymes. However it is not active against metallo- $\beta$ -lactamases, such as NDM, IMP, or VIM.

- ● ● 2. **Ceftolozane/tazobactam** (Zerbaxa™- Merck & Co.) is a recently approved combination of a novel cephalosporin with enhanced activity against *Pseudomonas aeruginosa* with a well-established β-lactamase inhibitor ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/206829lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206829lbl.pdf)). While it does have activity against most strains containing ESBLs, it has limited activity against anaerobes, such as *Bacteroides fragilis*, and is not effective against any of the carbapenemases.
- 3. **Aztreonam/avibactam** (AstraZeneca/Actavis [now Allergan]) is a promising agent in development that may address the problem of metallo-β-lactamases as aztreonam appears to be able to evade the action of these enzymes and the addition of avibactam allows inhibition of ESBLs and Amp C enzymes.
- 4. **Ceftaroline/avibactam** (AstraZeneca/Actavis [now Allergan]) is a combination that combines activity against gram-positive bacteria including MRSA with enhanced activity against gram-negatives including carbapenemase producers, but not metallo-β-lactamases.
- 5. **RPX7009/meropenem** (Carbavance™ – The Medicines Company) RPX7009 is a novel boronic acid inhibitor, which appears to enhance activity against KPC carbapenemases and potentially OXA-48 type enzymes. This combination does not have activity against metallo-β-lactamases.
- 6. **MK7655 (relebactam)/imipenem/cilastatin** (Merck & Co.) Relebactam is a novel class A and C β-lactamase inhibitor that has activity against a broad range of gram-negative and beta-lactam-resistant pathogens including Enterobacteriaceae and *Pseudomonas aeruginosa*.

After a long period of time with few new antibiotics on the horizon, there now appears to be several options for treating multi-drug resistant organisms (MDROs), including a number of β-lactam/β-lactamase inhibitor combinations available for clinical use with additional antimicrobial agents in the pipeline. These are costly to purchase and their use will likely be restricted to prevent the emergence of further resistance mechanisms.

**TABLE 1. CARBAPENEMASE FAMILIES BY AMBLER CLASS AND TYPE, AND ACTIVITY OF NEW β-LACTAM/ β-LACTAMASE INHIBITOR COMBINATIONS**

Beta-lactam/beta-lactamase Inhibitor combination	Current status; indications	Carbapenemase Type Ambler Class Enzyme type				
		KPC	NDM	OXA-48	VIM	IMP
		A	B	D	B	B
Avycaz™ (ceftazidime/ Avibactam)	Approved in US; complicated UTI and complicated IAI*	Yes	No	Limited	No	No
Zerbaxa™ (ceftolozane/ tazobactam)	Approved in US & Europe; complicated UTI and complicated IAI*	No	No	No	No	No
Aztreonam/Avibactam	Phase 1	Yes	Yes	Yes	Yes	Yes
Ceftaroline/Avibactam	Phase 2	Yes	No	Limited	No	No
Carbavance™ RPX7009/ Meropenem	Phase 3	Yes	No	Limited	No	No
MK7655 (relebactam)/ Imipenem	Phase 3	Yes	No	No	No	No

\*UTI - urinary tract infection, IAI - intra-abdominal infection

### ● ● ● Antimicrobial susceptibility testing issues

The differences in activity among the new  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations creates challenges for many clinicians and it will become increasingly important for microbiology laboratories to be able to produce meaningful results that will aid in the appropriate choice of these new agents. However, as pointed out by Humphries and Hindler,<sup>8</sup> microbiology laboratories have few options available to determine the susceptibility of organisms to these novel antimicrobial agents as few of them are yet available on commercial AST platforms. Disk diffusion is the only option for testing some of these new drugs, but disks are often difficult to get. Clinical microbiology laboratories face a dilemma when it comes to providing information about the susceptibility or resistance of bacterial isolates to ceftazidime/avibactam and ceftolozane/tazobactam.

**TABLE 2. OPTIONS FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING**

	Disk Diffusion	MicroScan	Vitek 2	Phoenix	Sensititre	Etest
Ceftazidime/avibactam	Available	Not available	Not available	Not available	Available	Not available
Ceftolozane/tazobactam	Available	Not available	Not available	Not available	Available	Not available

### Molecular testing to detect and differentiate among carbapenem-resistance genes

The CDC has developed a procedure for screening rectal swabs from patients who are suspected of being colonized with CRE ([http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella\\_or\\_Ecoli.pdf](http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_Ecoli.pdf)) and defined PCR primers for detecting the genes that encode the KPC and NDM carbapenemases from bacterial isolates (<https://www.cdc.gov/HAI/settings/lab/kpc-ndm1-lab-protocol.html>).

In addition, there are several molecular assays that can differentiate among carbapenem-resistance genes<sup>9</sup> including hyperplex SuperBug ID, Check-Direct CPE, and Xpert Carba-R<sup>®</sup>,<sup>4</sup> but only Xpert Carba-R has received FDA clearance in the United States. The Xpert Carba-R test is a qualitative *in vitro* diagnostic test for the detection and differentiation of the *bla*<sub>KPC</sub>, *bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>OXA-48</sub>, and *bla*<sub>IMP</sub> gene sequences associated with carbapenem non-susceptible pure colonies of Enterobacteriaceae, *Acinetobacter baumannii*, or *Pseudomonas aeruginosa* grown on blood agar or MacConkey agar, or it can be used directly with rectal swab specimens. The intended use of the assay is for infection control, where it can be very useful for following the epidemiologic spread of carbapenemase-producing gram-negative bacilli in healthcare facilities. The confirmation of the presence of carbapenemase-producing organisms in the hospital can be helpful to Infection Control Committees.

## ● ● ● REFERENCES:

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### CORPORATE HEADQUARTERS

904 Caribbean Drive  
Sunnyvale, CA 94089 USA

TOLL FREE 1.888.336.2743  
PHONE 1.408.541.4191  
FAX 1.408.541.4192

### EUROPEAN HEADQUARTERS

Vira Soleih  
81470 Maurens-Scopont France

PHONE 33.563.82.53.00  
FAX 33.563.82.53.01

www.Cepheid.com