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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (K CLAEYS AND A VEGA, SECTION EDITORS)

Recognizing and Overcoming Resistance to New Beta-Lactam/Beta-Lactamase Inhibitor Combinations

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Abstract

Purpose of Review To describe the mechanisms and clinical relevance of emergent resistance to three recently introduced beta-lactamase inhibitor combinations (BLICs) active against resistant Gram-negative organisms: ceftolozane-tazobactam, ceftazidime-avibactam, and meropenem-vaborbactam.

Recent Findings Despite their recent introduction into practice, clinical reports of resistance to BLICs among typically susceptible organisms have already emerged, in some cases associated with therapeutic failure. The resistance mechanisms vary by agent, including mutations in beta-lactamase active sites, upregulation of efflux pumps, and alterations in the structure or expression of porin channels. These changes may confer cross-resistance or, rarely, increased susceptibility to related agents. Clinicians need to be aware of the potential for initial or emergent resistance to BLICs and ensure appropriate antimicrobial susceptibility testing is performed. Dose optimization and novel combinations of agents may play a role in preventing and managing resistance.

Summary Recently approved BLICs have provided important new therapeutic options against resistant Gram-negative organisms, but are already coming up against emergent resistance. Awareness of the potential for resistance, early detection, and dose optimization may be important in preserving the utility of these agents.

Keywords Antimicrobial resistance · Ceftazidime-avibactam · Ceftolozane-tazobactam · Meropenem-vaborbactam · *Pseudomonas aeruginosa* · Carbapenem-resistant Enterobacteriaceae

Introduction

The tide of antibacterial resistance among key Gram-negative pathogens has been relentlessly rising since the introduction of these agents into widespread clinical practice. In the early antibiotic era, robust drug discovery and development programs were able to introduce new agents active against the waves of newly resistant organisms, allowing areas of medicine strongly dependent on antimicrobial chemotherapy (such as cytotoxic chemotherapy and organ transplantation) to continue to advance. Around the start of the twenty-first century, there was a significant lull in the introduction of new agents active against Gram-negatives. This has allowed the development of a large wave of resistance, such that projections suggest that without significant intervention, deaths due to antimicrobial-resistant organisms may exceed deaths due to cancer by the middle of the twenty-first century [1]. A recent resurgence in antibacterial drug development, along with new governmental and organizational initiatives advocating antimicrobial stewardship, has provided some

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hope that medicine may be able to stave off the return to a pre-antibiotic era.

Arguably, the most important group of the newly developed antibacterial agents for Gram-negative agents are new beta-lactamase inhibitor combinations (BLICs). The current generation of these agents pair either a novel beta-lactam agent with a standard beta-lactamase inhibitor (BLI), as with ceftolozane/tazobactam, or an established beta-lactam with a novel BLI (ceftazidime/avibactam and meropenem/vaborbactam). Unfortunately, in the few short years since their introduction into practice and despite their currently limited use, resistance to these new BLICs is already of concern. How rapidly this resistance will diminish the utility of these agents is not yet known. Clinicians should be aware of the prevalence, mechanisms, and risk factors for resistance to new BLICs. This paper will provide a review of these considerations for the three aforementioned BLICs.

Mechanisms of Resistance

Beta-Lactamases

First, we will briefly review the major mechanisms of antibacterial resistance in Gram-negative rods (GNRs) before discussing resistance concerns in each BLIC. Beta-lactamases are the most important mechanism by which beta-lactam resistance develops and spreads in GNRs [2••]. Many excellent in-depth reviews of this topic have been published [2••, 3, 4]. Briefly, beta-lactamases inactivate beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams) through catalyzing hydrolysis of the beta-lactam ring, rendering the beta-lactam unable to exert its effect on its target penicillin-binding proteins (PBPs). Two major types of beta-lactamases can be distinguished based on the method of hydrolysis: serine-based or metal (usually zinc)-based. Functionally, substantial diversity exists within these groups with regard to the rate of beta-lactam hydrolysis, as well as the degree of susceptibility of these enzymes to inhibition by BLIs. Table 1 provides an overview of these considerations with important example enzymes. It is important to note that beta-lactamase diversity is immense, with more than 400 distinct enzymes noted in recent registries, and that changes to enzymes via mutation are commonplace [5]. Another important concept is that beta-lactamases may be expressed at different levels and the mere presence of a gene encoding a beta-lactamase may not confer clinically relevant resistance, if it is not expressed or if it is only expressed at low levels.

Target Alterations

Among Gram-positive organisms, resistance mediated by changes to the beta-lactam target—the penicillin-binding proteins (PBPs)—is common and problematic; examples are the PBP2a protein in methicillin-resistant *Staphylococcus aureus* (MRSA) and the PBP2x alterations in penicillin-resistant *Streptococcus pneumoniae.* Relative to what is seen in Gram-positive organisms, this mechanism of resistance is considered to be less common in GNRs [6]. Nevertheless, isolated clinical cases of resistance associated with low-affinity PBPs have been reported, and in particular, there may be a greater role than previously suspected of PBP mutations and expression patterns in development of resistance in *Pseudomonas aeruginosa* [7–9].

Restriction of Access to Targets

In Gram-negative organisms, the PBP targets of beta-lactams lay deep to the outer cell membrane, which acts a barrier to beta-lactam target access. Beta-lactams typically traverse the outer cell membrane by taking advantage of existing porin channels, proteins that bridge the outer membrane that the bacteria use to access environmental nutrients [10]. Mutations that cause complete loss of or reduction in the quantity of porin channel expression may confer varying degrees of beta-lactam resistance, depending on the degree of loss and the reliance of the specific beta-lactam on that porin channel [11]. BLIs may also be reliant on porins to effectively cross the outer membrane and reduction in porin channel expression may reduce the ability of these agents to “protect” their co-formulated beta-lactam from beta-lactamases present in the periplasmic space [12].

Gram-negative bacteria also may express efflux pumps, which are energy-driven, multi-component proteins that span the outer bacterial membrane [11]. These proteins function to actively transport substrates from the bacterium’s periplasmic space to the external environment. Antibacterials are frequently a substrate for efflux pumps, many of which are capable of effluxing a variety of chemically unrelated antibacterial agents and even antiseptics. As with beta-lactamases, the degree of expression, rather than mere presence or absence, may be an important mediator of the level of resistance conferred by the efflux pump.

The effects of porin channel loss and/or efflux pump upregulation can work in combination with beta-lactamase expression to confer higher levels of resistance than either alone would confer. Slowing the rate or extent of beta-lactam and beta-lactamase inhibitor penetration into the periplasmic space allows beta-lactamases to much more effectively “protect” target PBPs. Thus, it may be the case that organisms with high-level resistance have multiple mechanisms of resistance working in concert [13].

Ceftolozane/Tazobactam

Drug Summary

Ceftolozane is a potent antipseudomonal beta-lactam that is structurally similar to ceftazidime, but with a heavier R2 side chain that increases its stability to hydrolysis by AmpC-type beta-lactamases. This results in improved activity against

Table 1 Classification, activity, and examples of key beta-lactamases

Molecular Class	Functional Class	Example Enzymes	Beta-lactamase hydrolytic activity against beta-lactams					Inhibition of beta-lactamases by beta-lactamase inhibitors		
			PIP	CTZ	CTOL	MER	ATM	CLA	AVI	VBR
Serine-based mechanism										
A	2b	SHV-1	+	-	-	-	-	Y	Y	Y
	2be	CTX-M (ESBL)	+	+	+	-	+	Y	Y	Y
	2f	KPC	+	+	+	+	+	N	Y	Y
C	1	AmpC	+	+	-	-	+	N	Y	Y
D	2df	OXA-48	+	-	+	+	-	N	Y	N
Zinc-based mechanism										
B	3a	NDM	+	+	+	+	-	N	N	N

PIP, piperacillin; *CTZ*, ceftazidime; *CTOL*, ceftolozane; *MER*, meropenem; *ATM*, aztreonam; *CLA*, clavulanic acid; *AVI*, avibactam; *VBR*, vaborbactam; +, beta-lactamase displays significant hydrolysis against beta-lactam; −, beta-lactamase typically does not significantly hydrolyze beta-lactam; *Y*, beta-lactamase inhibitor generally inhibits activity of the beta-lactamase; *N*, beta-lactamase inhibitor generally does not inhibit of activity of the beta-lactamase; Cells in grey are not favorable for therapy (beta-lactam hydrolysis or lack of beta-lactamase inhibition). Adapted from references [32, 66, 67]

P. aeruginosa isolates with derepressed AmpC. It is commercially available in combination with the BLI tazobactam, which enhances its activity against extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. Ceftolozane/tazobactam does not appreciably improve upon the activity of ceftazidime against most carbapenem-resistant Enterobactericeae (CRE), including isolates expressing *Klebsiella pneumoniae* carbapenemase (KPC)-, New Delhi metallo-beta-lactamase (NDM)-, or oxacillinase (OXA)-type beta-lactamases. Ceftolozane/tazobactam was approved by the FDA in 2014 for the indications of intra-abdominal infection and urinary tract infection on the basis of two phase III trials. In the ASPECT-cIAI trial, ceftolozane/tazobactam in combination with metronidazole demonstrated non-inferiority to meropenem (clinical cure, 83.0 vs. 87.3%; difference, −4.2%; 95% CI, −8.91 to 0.54%) [14]. In the ASPECT-cUTI trial, ceftolozane/tazobactam demonstrated non-inferiority to levofloxacin (composite cure, 76.9 vs. 68.4%; difference 8.5%; 95% CI 2.3 to 14.6%) [15]. A phase III trial for nosocomial pneumonia (ASPECT-NP) was completed in 2018, but results have not been published at this time. General characteristics of ceftolozane/tazobactam are noted in Table 2.

Mechanisms of Resistance

In clinical practice, the primary place in therapy for ceftolozane/tazobactam is in the management of multidrug-resistant (MDR) *P. aeruginosa* infections. *P. aeruginosa* wild-type isolates encode chromosomal, inducible AmpC beta-lactamases capable of hydrolyzing amino- and ureido-penicillins, cephamycins, and oxyiminocephalosporins such as ceftazidime and ceftriaxone [16]. Ceftolozane was designed to be relatively more stable against hydrolysis by these AmpC enzymes. However, resistance to ceftolozane/tazobactam mediated by AmpC has been described. In vitro studies have demonstrated that multiple mutations are typically required, involving the overexpression and structural modification of AmpC, resulting in decreased susceptibility to ceftolozane [17]. In an analysis of five *P. aeruginosa* isolates obtained from patients treated with ceftolozane/tazobactam, mutations in *ampR* resulting in *ampC* overexpression were found to be the main mechanism leading to ceftolozane/tazobactam resistance [18]. Mutational derepression of *ampC* has been associated with cross-resistance to ceftolozane/tazobactam and ceftazidime/avibactam. This double resistance pattern was characterized by mutations in *ampD*. Of note, *ampD* mutations

Table 2 Characteristics of new beta-lactamase inhibitor combinations

	Ceftolozane/tazobactam	Ceftazidime/avibactam	Meropenem/vaborbactam
Brand name	Zerbaxa	Avycaz	Vabomere
Manufacturer	Merck	Allergan	Melinta
FDA approval	December 2014	February 2015	August 2017
Description	Novel cephalosporin; old beta-lactamase inhibitor	Old cephalosporin; novel beta-lactamase inhibitor	Old carbapenem; novel beta-lactamase inhibitor
Approved doses (CrCL > 50)	1.5 g (1000 mg ceftolozane and 500 mg tazobactam) IV q8h over 1 h	2.5 g (2000 mg ceftazidime and 500 mg avibactam) IV q8h over 2 h	4 g (2000 mg meropenem and 2000 mg vaborbactam) IV q8h over 3 h
Approved indications	Complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired/ventilator-associated pneumonia	Complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired/ventilator-associated pneumonia	Urinary tract infections, complicated
Indications under study	None currently	None currently	Hospital-acquired pneumonia/ventilator--associated pneumonia

were only observed in isolates resistant to both ceftolozane/tazobactam and ceftazidime/avibactam [19].

A recent study investigated the molecular structure of *Pseudomonas*-derived cephalosporinases (PDC) in clinical isolates resistant to ceftolozane/tazobactam. One Ω-loop variant of the PDC β-lactamase, named E221K, was associated with the highest MIC against ceftolozane. Amino acid substitutions in PDC-3 led to conformational changes resulting in increased affinity for and increased hydrolytic activity against ceftolozane. Interestingly, two boronic acid transition state inhibitors were found to lower the MIC values of ceftolozane among all variant strains, representing a potential avenue for overcoming this resistance mechanism [20].

Clinical Reports of Resistance

Clinical reports of emergent resistance to ceftolozane/tazobactam have been described in case reports and larger retrospective studies. The larger series provide a sense of the magnitude of the problem. A large retrospective study describing the clinical experience with ceftolozane/tazobactam across 22 hospitals in Italy reported that three of 101 patients (3%) treated with ceftolozane/tazobactam developed resistance to the drug [21•]. Of 47 MDR *P. aeruginosa* infections treated with ceftolozane/tazobactam at a hospital in Spain, five cases (10.6%) developed resistance to ceftolozane/tazobactam. All five isolates also developed cross-resistance to ceftazidime/avibactam [18]. Of 21 patients with MDR *P. aeruginosa* infections treated with ceftolozane/tazobactam at the University of Pittsburgh Medical Center, the emergence of ceftolozane/tazobactam resistance was identified in 3 patients (14.3%). Of those three cases, two were classified as clinical failures [22]. Across these studies, it is important to note that not all cases of resistance were associated with clinical failure; many were characterized as recurrent colonization with a resistant organism that did not warrant treatment.

Resistance has also been described in individual case reports. In one case, a patient with a *P. aeruginosa* bloodstream infection developed resistance to ceftolozane/tazobactam after 5 weeks of exposure to the antibiotic. Testing revealed synergistic effects with the combination of tobramycin and ceftolozane/tazobactam. The patient was treated with this combination and achieved microbiologic clearance [23]. The emergence of resistance on therapy has also been reported in a *P. aeruginosa* left ventricular assist device infection after 10 weeks of ceftolozane/tazobactam therapy. This patient was treated with a combination of polymyxin B and meropenem until his heart transplant [24].

Prior exposure to other antibiotics besides ceftolozane/tazobactam may also select for resistance to this agent. This was described in the case of a bloodstream infection due to *P. aeruginosa* that recurred after a course of aztreonam and ceftazidime. The recurrent isolate was resistant to ceftolozane/tazobactam despite no prior exposure. This patient was treated with a combination of polymyxin B and ceftolozane/tazobactam, but did not survive despite achieving microbiologic clearance [24].

Potential Avenues for Overcoming Resistance

The optimal dosing of antibiotics to ensure adequate exposure is critical in the management of resistant infections. The FDA-approved dose for ceftolozane/tazobactam is 1.5 g every 8 h. In the nosocomial pneumonia trial (ASPECT-NP, NCT02070757), a higher dose of 3 g every 8 h was studied. This was the dose required for nosocomial pneumonia patients with normal renal function to achieve a > 90% probability of target attainment against pathogens with an MIC of ≤ 8 mg/L in lung epithelial lining fluid [25]. While data to support this higher dosing regimen in non-pulmonary infections is limited, it has been used in clinical practice successfully [21•, 23]. In vitro studies suggest that optimized dosing of ceftolozane/tazobactam may suppress emergence of resistant subpopulations [26]. The utilization of extended infusions of ceftolozane/tazobactam may also have potential benefit in managing infections due to *P. aeruginosa* with higher ceftolozane/tazobactam MICs [27].

Ceftolozane is commercially paired with the BLI tazobactam, which does not significantly enhance its activity against *P. aeruginosa*. However, combinations with other beta-lactamase inhibitors can potentially expand its spectrum. In in vitro studies, avibactam and two boronic acid transition state inhibitors (which have different chemical structures compared to tazobactam and avibactam) were found to lower MIC values and restore susceptibility to ceftolozane [20].

Combination therapy represents another potential avenue for overcoming resistance. In vitro pharmacodynamic studies have demonstrated synergistic interactions when either amikacin or colistin were combined with ceftolozane/tazobactam [28, 29]. Clinical success has also been reported with the use of combination therapy in ceftolozane/tazobactam-resistant infections [23, 24]. Additional studies investigating optimal dosing strategies, novel beta-lactamase inhibitor combinations with ceftolozane, and combination therapy are warranted.

Ceftazidime-Avibactam

Drug Summary

Ceftazidime-avibactam is a combination of a third-generation antipseudomonal cephalosporin and avibactam, a BLI with activity against several beta-lactamase types [30]. Avibactam is a diazabicyclooctane (DBO, i.e., non-beta-lactam) BLI that exhibits considerable activity against Ambler functional classes A (CTX-M extended-spectrum beta-lactamases, KPCs), C (AmpC), and some D (OXA-48 carbapenemase) beta-lactamases [31]. Avibactam is inactive against Ambler class B metallo-beta-lactamases (MBLs). Consequently, ceftazidime-avibactam has activity against many clinically important resistant gram-negative organisms including most CRE and some *P. aeruginosa* [32].

Ceftazidime-avibactam is currently approved for complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) in combination with metronidazole, and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) (Table 2). Several phase 3 clinical trials comprised the development program including RECAPTURE 1 and 2 for cUTI, RECLAIM 1 and 2 for cIAI, and REPROVE for nosocomial pneumonia [33–35]. These trials were of a non-inferiority design, enrolled patients at various international sites, and compared ceftazidime-avibactam against carbapenem monotherapy. These trials did not study this antibiotic in the population of primary interest (i.e., those with resistant infections). Subsequently, the REPRISE trial enrolled patients with cUTI and cIAI from ceftazidime-resistant Enterobacteriaceae and *P. aeruginosa* with best available therapy as the comparator group, largely carbapenem monotherapy [36]. A small proportion of patients had ceftazidime-avibactam-resistant isolates. In addition to data from clinical trials, this antibiotic has been in clinical use for several years, allowing for more real-world evidence in the form of observational studies.

Mechanisms of Resistance

Ceftazidime-avibactam resistance has been documented in both pre-clinical and clinical studies. In *E. cloacae* and *K. pneumoniae* expressing KPC-3 enzymes, serial passage studies demonstrate that several mutations in the omega loop of the enzyme render ceftazidime-avibactam ineffective [37]. Interestingly, the same group conducted ceftaroline-avibactam serial passage studies and were unable to select for resistance in isolates with KPCs or ESBLs with the exception of CTX-M-15 [38]. It is thought that the omega-loop mutations affect ceftazidime binding affinity and hydrolysis, which then prevents avibactam from subsequently binding to inhibit the enzyme [39]. This mechanism appears specific to ceftazidime and perhaps even spares other beta-lactams such as aztreonam and imipenem [40]. Among these mutations, D179Y remains the predominant variant and while it confers ceftazidime-avibactam resistance, this substitution conversely restores meropenem susceptibility [41]. However, susceptibility is not sustained and sub-lethal meropenem exposure in serial passage studies selected for new KPC mutations and the *ompK36* porin gene mutation in clinical *K. pneumoniae* isolates [39]. Of note, omega-loop substitutions another Ambler functional class A ESBL enzyme, CTX-M, did not result in ceftazidime-avibactam resistance. Resistance requires multiple mutations to occur and is considered rare for ESBLs [42]. Furthermore, overt resistance was not observed among isolates with derepressed AmpC and ESBLs and between the two enzymes reduced susceptibility is more likely to occur in isolates with derepressed AmpC [36]. Currently, resistance mechanisms for KPC-2 and KPC-3-expressing isolates generally occur in combination with KPC hyper-expression, MBL co-production, and/or porin mutations [43]. Of note, KPC enzymes are no longer exclusive to *K. pneumoniae* having transferred horizontally via plasmid to other Enterobacteriaceae including *E. coli*, *Pseudomonas* spp., *K. oxytoca*, *Enterobacter* spp., *Citrobacter* spp., *S. marcescens*, and others [44] (Table 3).

Resistance mechanisms in *P. aeruginosa* are largely from low membrane permeability and myriad efflux pumps that prevent effective ceftazidime-avibactam entry [45]. Sequencing studies of *P. aeruginosa* isolates in cystic fibrosis (CF) demonstrated large genome deletions that primarily affect efflux pumps, particularly related to aminoglycosides and beta-lactams.

Specifically, the *MexXY-OprM* deletion allows for *MexAB-OprM* expression. This results in aminoglycoside hyper-susceptibility and simultaneously contributes to enhanced beta-lactam efflux [46]. These ceftazidime-avibactam-resistant isolates produced pyomelanin and became more susceptible to aminoglycosides, suggesting a potential treatment strategy for these isolates. In addition, clinical *P. aeruginosa* isolates from CF patients also revealed AmpC cephalosporinase overexpression [13]. The deletions and overexpression collectively contribute to ceftazidime-avibactam resistance in *P. aeruginosa*.

Clinical Reports of Resistance

Initial clinical reports of ceftazidime-avibactam resistance were in *K. pneumoniae* expressing KPC enzymes [47, 48••]. Humphries et al. reported on a patient with no known prior ceftazidime-avibactam exposure but who had a bloodstream infection with a resistant isolate, presumably from an intra-abdominal source [47]. Isolate sequencing revealed KPC-3 hyper-expression and porin mutations [43]. Shields et al. reported that 3 of 37 patients (8%) with CRE infections developed resistance after 10 to 19 days of ceftazidime-avibactam exposure [48••]. These ceftazidime-avibactam-resistant isolates became susceptible to meropenem, which effectively eradicated a ceftazidime-avibactam-resistant isolate in a patient with a bloodstream infection [49]. However, the role of carbapenems as an alternative management strategy remains unclear. Meropenem exposure in a susceptible, ceftazidime-avibactam-resistant isolate resulted in resistance to both ceftazidime-avibactam and meropenem, posing great concern for effective treatment options in this situation [50•]. A case report of a respiratory *E. cloacae* isolate from a long-term acute care hospital patient described MBL and KPC co-expression. This isolate was not susceptible to ceftazidime-avibactam and clinicians should be aware of this co-expression and perform susceptibility testing prior to starting therapy [51]. Both et al. identified a *K. pneumoniae* isolate that co-expressed OXA-48 and CTX-M-14, which developed resistance during ceftazidime-avibactam exposure [52]. The authors also concluded that routine testing during treatment is warranted to detect resistance development.

Similar to the Humphries et al. case report, another patient with resistance but without exposure to ceftazidime-avibactam was identified in a multicenter observational study of 60 patients. Susceptibility was determined via non-commercial E-test and this patient required an unspecified combination of antibiotics for treatment [53]. More recently, clinical trial data from the TANGO II study comparing meropenem-vaborbactam against best available therapy found that of four patients receiving ceftazidime-avibactam, one developed resistance. The resistant isolate possessed the prevalent D179Y mutation in the omega loop of the KPC enzyme, consistent with previous in vitro and clinical reports [54]. The clinical evidence suggests ceftazidime-avibactam resistance occurs in both previously unexposed patients as well as those on treatment. A study at the University of Pittsburgh Medical Center determined that renal replacement therapy independently predicted resistance in their cohort, leading the authors to call for improved dosing strategies in this population [55]. Diminished efficacy among those with reduced renal function was also observed in the cIAI clinical trials and remains part of the labeled warning and precaution for ceftazidime-avibactam.

Potential Avenues for Overcoming Resistance

Avibactam is the only BLI of its particular type currently available and represents an opportunity for combining with other beta-lactams that are more stable to resistance selection. Three potential strategies to combat resistance are (1) valid and reliable susceptibility testing for ceftazidime-avibactam,

Table 3 Mechanisms of resistance to beta-lactamase inhibitor combinations among typically susceptible organisms

Mechanism		Ceftolozane-tazobactam	Ceftazidime-avibactam	Meropenem-vaborbactam
Beta-lactamase	Hyperproduction of beta-lactamase	AmpC overexpression [17]	KPC overexpression [43] AmpC overexpression in *P. aeruginosa* [13]	Not yet described as a significant resistance mechanism
	Altered beta-lactamase structure	AmpC mutations [17]	KPC-3 omega loop mutations [37]	Increased bla_{KPC} copy number [63]
Target alterations	Penicillin-binding protein mutations	Not yet described as a significant resistance mechanism	Not yet described as a significant resistance mechanism	Not yet described as a significant resistance mechanism
Restriction of access to target	Reduction in porin channel number	Not yet described as a significant resistance mechanism	Not yet described as a significant resistance mechanism	Non-functional porin channels due to *ompK35* and *ompK36* [63]
	Mutations in porin channel structure	Not yet described as a significant resistance mechanism	OmpK35 mutations [68]	Mutations in major porin genes *ompK35* and *ompK36* [63]
	Upregulation of efflux pump	Not yet described as a significant resistance mechanism	MexAB efflux pump [46] Enhanced efflux pumps in *P. aeruginosa* [46]	Not yet described as a significant resistance mechanism

(2) appropriate dosing for patients on renal replacement therapy, and (3) combination treatment with other antibiotics (e.g., aztreonam with ceftazidime-avibactam).

Firstly, ceftazidime-avibactam susceptibility testing should be performed prior to and during treatment with this combination. Testing prior to treatment may detect KPC-producers that co-express other beta-lactamases (e.g., MBL) to render ceftazidime-avibactam ineffective. Routine testing especially during prolonged treatment is recommended to detect resistance development while on treatment. Secondly, clinicians should exercise caution when considering ceftazidime-avibactam in patients with moderate to severe renal impairment (e.g., CrCl < 50 mL/min) as cIAI clinical trial data indicates diminished efficacy in this group when using approved dosing strategies. In the trial, patients received a 33% greater reduction in daily dose than is currently recommended. However, perhaps another antibiotic should be considered until more effective dosing strategies have been studied for this group especially for those on renal replacement therapy. Lastly, ceftazidime-avibactam and aztreonam combinations have reportedly proven successful for infections due to KPC/MBL co-producers [56, 57]. These and other novel combinations may leverage the unique effects of avibactam to solve emergent resistant problems. Currently, aztreonam-avibactam and ceftaroline-avibactam trials are in their initial phases and while still a few years from approval, these combinations may prove to be promising options in the antibiotic armamentarium.

Meropenem-Vaborbactam

Drug Summary

Meropenem is one of the main treatment options for severe, complicated multidrug-resistant infections. Vaborbactam is a non-beta-lactam, cyclic boronic acid with a high affinity towards class A and class C beta-lactamases. However, it has no in vitro activity against class B MBL producers or class D OXA-48 beta-lactamases [58]. The boron atom in vaborbactam mimics the beta-lactam ring and forms a covalent bond with beta-lactamases serving as a reversible competitive inhibitor. When combined with meropenem, vaborbactam reduces meropenem MICs against organisms expressing ESBLs and KPCs [59, 60•, 61].

TANGO I, a multicenter, double-blind, randomized, phase III, non-inferiority trial, compared meropenem-vaborbactam to piperacillin-tazobactam in patients with complicated urinary tract infections, including acute pyelonephritis. Meropenem-vaborbactam proved to be non-inferior to piperacillin-tazobactam when assessing the primary outcome, a composite clinical cure (difference, 4.5% [95% CI, 0.7–9.1]; $p < 0.001$) [62]. In a subsequent study, TANGO II, a randomized, multinational open-label trial studied patients with cUTI, HABP/VABP, bacteremia, or cIAI due to carbapenem-resistant *Enterobacteriaceae*. TANGO II showed meropenem-vaborbactam was associated with higher rates of clinical cure rates versus best available therapy for treatment of CRE infected patients across all infections [54]. Currently, TANGO III is in recruitment phase, comparing meropenem-vaborbactam to piperacillin-tazobactam for treatment of HABP/VABP. In addition, a phase I pharmacokinetic study of meropenem-vaborbactam for treatment of pediatric patients with serious infections is ongoing and set to be completed in August 2019.

Mechanisms of Resistance

Resistance to meropenem-vaborbactam in KPC-producing isolates is mediated by both KPC overproduction, specifically via increased *blaKPC* gene copy number, and mutations in the genes for the major outer membrane porins OmpK36 and OmpK36 [63]. Both porins are involved in transporting vaborbactam across the outer membrane of *K. pneumoniae*, although OmpK36 plays the major role. Inactivation of *ompK35* increased the concentration of vaborbactam necessary achieve maximal reduction of meropenem MIC by 4-fold, while *ompK36* inactivation increased the same concentration necessary for vaborbactam to produce the same effect by 64-fold [60•]. Enhanced efflux appeared to play a minor role in diminishing the effects of vaborbactam on meropenem activity. Notably, meropenem-vaborbactam retains activity against KPC-producing strains that acquire resistance to ceftazidime-avibactam through mutations in the KPC binding site [64].

Clinical Reports of Resistance

Currently, there are few clinical studies reporting meropenem-vaborbactam resistance. In one surveillance study, there was a report of 1 *K. pneumoniae* isolate from Greece displaying a meropenem/vaborbactam MIC at 32/8 mg/L. Next-generation sequencing revealed there was a frameshift mutation in *ompK35* and an insertion mutation at *ompK36* [65]. Clinical details of the case, including whether the patient was exposed to meropenem and/or vaborbactam, were not provided. Analysis of isolates from the TANGO II trial revealed one isolate with a ≥ 4-fold increase in meropenem/vaborbactam MIC, where the MIC increased from 0.25/8 to 1/8 mcg/mL. However, the MIC increase remained in the susceptibility range; the clinical outcome of this patient was not separately reported [54].

Potential Avenues for Overcoming Resistance

Mutant selection studies have determined combining meropenem at 8 mcg/mL with vaborbactam at 8 mcg/mL was sufficient to suppress mutant emergence. The drug concentrations used in these experiments reflected dosage regimens used in clinical trials. Meropenem 2 g infused over 3 h every 8 h provided concentrations above 8 mg/L for 40% of the dosing interval. Using the same dosing regimen of 2 g IV every 8 h, vaborbactam also achieved concentrations of 8 mg/L in average human plasma concentrations [63].

Conclusions

Introduction of new BLICs has represented a significant advance in the struggle against MDR Gram-negatives. Unfortunately, resistance to these agents has already begun to emerge among typically susceptible pathogens. Early recognition and characterization of resistant isolates may help in patient management. Dose optimization and combination therapy may allow use of BLICs even when emergent resistant develops, but few examples of successful employment of these strategies exist to date.

Compliance with Ethical Standards

Conflict of Interest Stephanie Ho, Lynn Nguyen, and Trang Trinh declare no conflicts of interest.Conan MacDougall has received honoraria from Shionogi Pharmaceuticals and has served on an advisory board for Paratek Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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