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REVIEW

New β-Lactam–β-Lactamase Inhibitor Combinations

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SUMMARY The limited armamentarium against drug-resistant Gram-negative bacilli has led to the development of several novel β-lactam–β-lactamase inhibitor combinations (BLBLIs). In this review, we summarize their spectrum of *in vitro* activities, mechanisms of resistance, and pharmacokinetic-pharmacodynamic (PK-PD) characteristics. A summary of available clinical data is provided per drug. Four approved BLBLIs are discussed in detail. All are options for treating multidrug-resistant (MDR) *Enterobacterales* and *Pseudomonas aeruginosa*. Ceftazidime-avibactam is a potential drug for treating *Enterobacterales* producing extended-spectrum β-lactamase (ESBL), *Klebsiella pneumoniae* carbapenemase (KPC), AmpC, and some class D β-lactamases (OXA-48) in addition to carbapenem-resistant *Pseudomonas aeruginosa*. Ceftolozane-tazobactam is a treatment option mainly for carbapenem-resistant *P. aeruginosa* (non-carbapenemase producing), with some activity against ESBL-producing *Enterobacterales*. Meropenem-vaborbactam has emerged as treatment option for *Enterobacterales* producing ESBL, KPC, or AmpC, with similar activity as meropenem against *P. aeruginosa*. Imipenem-relebactam has documented activity against *Enterobacterales* producing ESBL, KPC, and AmpC, with the combination having some additional activity against *P. aeruginosa* relative to imipenem. None of these drugs present *in vitro* activity against *Enterobacterales* or *P. aeruginosa*

producing metallo-β-lactamase (MBL) or against carbapenemase-producing *Acinetobacter baumannii*. Clinical data regarding the use of these drugs to treat MDR bacteria are limited and rely mostly on nonrandomized studies. An overview on eight BLBLIs in development is also provided. These drugs provide various levels of *in vitro* coverage of carbapenem-resistant *Enterobacterales*, with several drugs presenting *in vitro* activity against MBLs (cefepime-zidebactam, aztreonam-avibactam, meropenem-nacubactam, and cefepime-taniborbactam). Among these drugs, some also present *in vitro* activity against carbapenem-resistant *P. aeruginosa* (cefepime-zidebactam and cefepime-taniborbactam) and *A. baumannii* (cefepime-zidebactam and sulbactam-durlobactam).

KEYWORDS β-lactam–β-lactamase inhibitor combinations, ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam

INTRODUCTION

Infections caused by drug-resistant Gram-negative bacilli have become an important public health threat. Older drugs available to treat these infections, such as colistin, fosfomycin, aminoglycosides, and tigecycline, are limited in their efficacy, safety profile (e.g., colistin and nephrotoxicity), and by the emergence of resistance. The development of drugs active against these pathogens is a top priority. The World Health Organization (WHO) has issued a priority list of pathogens to direct efforts for drug development. Carbapenem-resistant *Pseudomonas aeruginosa* and cephalosporin/carbapenem-resistant *Enterobacterales* were listed as a critical priority (1). The Infectious Diseases Society of America (IDSA) launched in 2010 an initiative calling for development and approval of 10 new antibiotics effective against resistant Gram-negative bacteria by 2020 (2).

One of the prominent groups of new antibiotics with broad spectrum activity is the β-lactam–β-lactamase inhibitor combinations (BLBLIs). Several such combinations are currently in different stages of development and approval. In the manuscript, we aimed to review these drugs' features, including spectrum of activity, current resistance rates, pharmacokinetics/pharmacodynamics (PK-PD), clinical data on efficacy, adverse events, and what is known on their potential to select for resistance and cross-resistance. We aimed to put emphasis on clinical data regarding infections caused by resistant bacteria and subgroups of patients at high risk for such infections, such as immunocompromised patients. The main drugs of interest were those already approved for use, with a brief review on drugs still in development stages.

Old and New β-Lactam–β-Lactamase Inhibitor Combinations—Similarities, Differences, and the Background for the Need for New Drug Development

β-Lactams are a broad class of bactericidal agents that have been integral to the treatment of infections caused by Gram-positive and Gram-negative pathogens. The bactericidal activity of β-lactams is mediated by inhibition of penicillin-binding proteins (PBPs) essential to cell wall formation. The development of β-lactamase inhibitors has contributed to the preservation of the efficacy of β-lactams against β-lactamase-producing pathogens. Traditionally, these inhibitors lack antibacterial activity at clinically relevant concentrations, and consequently, there are no model regulatory pathways for their development as stand-alone agents. Instead, they are coformulated with a partner β-lactam based on two key considerations: (i) the activity of the inhibitor against β-lactamases capable of hydrolyzing the β-lactam, and (ii) similarities in pharmacokinetic properties (such as elimination half-lives, metabolic pathways, and biodistribution) to ensure the protection of the β-lactam's structural integrity over a given dosing interval (3).

Optimal dosing of a BLBLI would likely be patient specific and is a complex interplay between the pathogen, bacterial burden at the site of infection, β-lactamase(s) involved, β-lactamase transcription level(s), the involvement of other resistance mechanism(s), the potency of the inhibitor, the potency of the β-lactam, the pharmacokinetics/biodistribution of the β-lactamase inhibitor, and the pharmacokinet-

ics/biodistribution of the β-lactam. With the exception of amoxicillin-clavulanic acid, commercially available in different β-lactam-to-inhibitor ratios, all other commercially available BLBLIs are supplied as fixed dose ratio combinations. While the rationale for these fixed dose pairings is less apparent for older combinations such as piperacillin-tazobactam (PIP-TAZ), the development programs for newer combinations lend some insights into the selection of commercial dose ratio formulations. Dose ratios of BLBLIs are based (in part) on *in vitro* activity and *in vivo* antimicrobial efficacy. For instance, ceftolozane-tazobactam (TOL-TAZ) is featured as a 2:1 ratio of ceftolozane to tazobactam, because this ratio resulted in comparatively lower MICs against extended-spectrum β-lactamase (ESBL)-producing strains than either the 8:1 or 4:1 dose ratio (4). Additionally, the 2:1 ratio was found to yield either comparable or greater reductions in $\log_{10}$ CFU than other ratios evaluated in a murine thigh infection model.

Similarly, the commercial 4:1 ratio of ceftazidime-avibactam was supported by survival studies in infected mice treated with various ratios of ceftazidime-avibactam (5). While these commercial formulations have exhibited high rates of efficacy in clinical trials, allowing some flexibility in the pairing and dosing of the individual components of the combination may be warranted in some clinical scenarios (such as when enzyme hyperproduction or severe [high inoculum] infections are encountered). The design of stand-alone inhibitors could also facilitate expedient pairings to suit unique clinical needs (e.g., readily pairing aztreonam with avibactam against isolates suspected of harboring class A and B β-lactamases).

The optimal approach for susceptibility testing for BLBLIs is a topic of ongoing debate. For susceptibility testing of older combinations (such as amoxicillin-clavulanic acid and ampicillin-sulbactam), a fixed ratio of β-lactam to inhibitor is used, though concentrations vary. For newer combinations, *in vitro* susceptibility testing is conducted with a fixed concentration of inhibitor. For ampicillin-sulbactam, the fixed 2:1 ratio employed in susceptibility testing reflects the 2:1 dose ratio used in all commercial formulations. Given the similarities in pharmacokinetics of ampicillin and sulbactam, this susceptibility testing arrangement is expected to reflect the concentration ratios achievable *in vivo* (6). For clavulanic acid, this same 2:1 ratio is used for *in vitro* susceptibility testing. Yet, the rationale for this practice is less evident, as amoxicillin-clavulanic acid is available in various fixed dose ratios as oral and intravenous (i.v.) formulations. While CLSI has always used a fixed ratio, the approach of EUCAST has been to use a fixed concentration for antibiotic susceptibility testing of combinations of aminopenicillins and inhibitors.

For combinations such as PIP-TAZ, ceftazidime-avibactam (CAZ-AVI), and imipenem-relebactam (IMI-REL), a fixed inhibitor concentration of 4 μg/ml is used alongside a range of parent β-lactam concentrations. While the concentrations of β-lactam reflect the dynamic concentrations observed *in vivo*, a static concentration of inhibitor is assumed to be adequate. In this scheme, it is generally expected that beyond the threshold concentration of 4 mg/liter, the impact of the inhibitor concentration on MIC is minimal. However, if *in vivo* concentrations that range beyond this value are associated with further MIC reductions (i.e., nonsaturable effect), the fixed concentration approach may not reflect realistically the contribution of the inhibitor on MIC reduction and, ultimately, *in vivo* efficacy.

PK-PD of New BLBLIs

Traditionally, antibacterial drug development has relied on the identification of PK-PD indices (such as the Maximum concentration of the free, unbound drug in serum [fC_{max}]/MIC, area under the concentration-time curve for the free, unbound fraction of a drug [*f*AUC]/MIC, and cumulative percentage of a 24-h period that the free, unbound drug concentration exceeds the MIC under steady-state pharmacokinetic conditions [%$fT_{>MIC}$]) through preclinical *in vitro* and *in vivo* dose fractionation studies to describe the killing activity of antibiotics. It is well established that the fraction of a 24-h period wherein free drug concentrations exceeds the MIC (i.e., %$fT_{>MIC}$) is the PK-PD index predictive of microbiologic efficacy for β-lactams. The magnitude of %$fT_{>MIC}$ required

TABLE 1 Reported activity of various β-lactamase inhibitors from the BLBLIs against β-lactamase enzymes

	Inhibited by:			
Enzyme	**Avibactam**	**Tazobactam**	**Vaborbactam**	**Relebactam**
Class A				
KPC	Yes	No	Yes	Yes
SHV	Yes	Yes	Yes	Yes
TEM	Yes	Yes	Yes	Yes
CTX-M	Yes	Yes	Yes	Yes
Class B				
MBL	No	No	No	No
Class C				
AmpC	Yes	No	Yes	Yes
Class D				
OXA	VD[a]	No	No	VD

[a]VD, variable data.

for maximum bactericidal effect derived from preclinical and clinical PK-PD studies ranges from 40% to 70% for the various subclasses of β-lactams (7). While these targets are often defined with respect to plasma concentrations, consideration of the extent of distribution of any antibiotic is critical to ensuring adequate exposure at the site of infection. Population PK modeling and Monte Carlo simulations have been used to predict the probability of achieving these PK-PD targets in patients, propose susceptibility breakpoints, and support proposed dosing regimens (8).

For β-lactamase inhibitors, however, delineating the driver of efficacy is a relatively novel and complex undertaking (9–13). Since currently approved β-lactamase inhibitors lack appreciable intrinsic antimicrobial activity, PK-PD studies are carefully designed to demonstrate the contribution of the inhibitor in the combination. The most widely used approach involves the identification of a PK-PD index to characterize the effect of the β-lactamase inhibitor and has been applied to inhibitors in all 4 of the most recently approved BLBLIs (see below) (4, 5, 14, 15). However, unlike β-lactams, there is no consensus PK-PD index used to describe the efficacy of all β-lactamase inhibitors (16).

Clinical data on optimal dosing (intermittent versus continuous infusion) and dosing in special patient populations (such as the critically ill) are generally lacking for newer BLBLIs. As hydrophilic drugs, β-lactams and β-lactamase inhibitors have a characteristically low volume of distribution (*V*), akin to extracellular water, and are predominantly renally excreted (17). Thus, variations in extracellular volume and renal dysfunction often observed in critically ill patients may impact the disposition of both β-lactams and β-lactamase inhibitors (18). The current body of PK-PD knowledge surrounding the newly approved BLBLIs is discussed in the subsequent sections of this review.

CEFTAZIDIME-AVIBACTAM

Spectrum of Activity

Ceftazidime is hydrolyzed by class A ESBLs and carbapenemases, class B carbapenemases, and class C cephalosporinases but not by most class D carbapenemases. Avibactam inhibits class A, class C, and some of the class D β-lactamases, providing the combination a broad coverage of Gram-negative bacilli (Table 1) (19–24). Contrarily, the activity of CAZ-AVI against class B β-lactamase-producing isolates, Gram-negative anaerobes, and Gram-positive bacteria is limited (25, 26).

Published data have shown that CAZ-AVI is active against *Enterobacterales*, including ESBL-producing and AmpC-producing isolates, as well as some of the bacteria producing class D carbapenemases, such as OXA-24, OXA-40, OXA-69 (in *Acinetobacter baumannii*) and OXA-48 (*in Klebsiella pneumoniae*) (27–35). In the global surveillance study INFORM (International Network for Optimal Resistance Monitoring), 34,062 isolates of *Enterobacteriaceae* were collected between 2012 and 2014, and the overall suscepti-

TABLE 2 Breakpoints for interpretation of MICs and zone diameters approved by EUCAST (version 10.0, valid from January 2020), FDA, and CLSI (M100 30th edition, valid from January 2020)[a]

	EUCAST						FDA						CLSI					
	MIC (mg/liter)			Zone diameter (mm)			MIC (mg/liter)			Zone diameter (mm)			MIC (mg/liter)			Zone diameter (mm)		
Antibiotic(s)	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
CAZ-AVI for zone diameter breakpoints, disk content 10/4 μg (EUCAST), 30/20 μg/ml (CLSI/FDA)																		
Enterobacterales	≤8[b]		>8[b]	13		13	M100[c]						≤8/4		≥16/4	≥21[d]		≤20[c]
P. aeruginosa	8[b]		8[b]	17		17	M100						≤8/4		≥16/4	≥21		≤20
TOL-TAZ for zone diameter breakpoints, disk content 30/10 μg/ml (EUCAST/FDA/CLSI)																		
Enterobacterales	≤2[e]		>2[e]	22		22	M100			>22	19–21	<18	≤2/4	4/4	≥8/4	≥21	18–20	≤17
P. aeruginosa	≤4[e]		>4[e]	24		24	M100						≤4/4	8/4	≥16/4	≥21	17–20	≤16
Haemophilus influenzae (pneumonia)	≤0.5[e]		>0.5[e]	IP		IP	≤0.5/4											
Streptococcus viridans group	IE		IE	IE		IE	M100						≤8/4	16/4	≥32/4			
Bacteroides fragilis							≤8/4	16/4	≥32/4									
MER-VAB for zone diameter breakpoints, disk content 20/10 μg/ml (CLSI/FDA)																		
Enterobacterales	≤8[f]		>8[f]	IP		IP	M100						≤4/8	8/8	≥16/8	≥18	15–17	≤14
P. aeruginosa	8[f]		8[f]	IP		IP												
IMI-REL for zone diameter breakpoints, disk content 10/25 μg/ml (FDA)																		
Enterobacterales[g]	≤2[h]		>2[h]	IP		IP	≤1/4	2/4	≥4/4	≥25	21–24	≤20						
P. aeruginosa	≤2[h]		>2[h]	IP		IP	≤2/4	4/4	≥8/4	≥23	20–22	≤19						
Acinetobacter spp.	≤2[h]		>2[h]	IP		IP												
Viridans group streptococci	≤2[h]		>2[h]	IP		IP												
Gram-positive anaerobes	≤2[h]		>2[h]				≤4/4[i]	8/4[i]	≥16/4[i]									
Gram-negative anaerobes	≤2[h]		>2[h]				≤4/4[i]	8/4[i]	≥16/4[i]									

[a]CAZ-AVI, ceftazidime/avibactam; TOL-TAZ, ceftolozane/tazobactam; MER-VAB, meropenem/vaborbactam; IMI-REL, imipenem/relebactam; IP, in preparation; IE, insufficient evidence. The respective dosages for each β-lactam/β-lactamase inhibitor are shown in Table 3.

[b]For susceptibility testing purposes, the concentration of avibactam is fixed at 4 mg/liter.

[c]M100 standard is recognized.

[d]Confirmatory MIC testing is indicated for isolates with zones of 20 to 22 mm to avoid reporting false-susceptible or false-resistant results.

[e]For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/liter.

[f]For susceptibility testing purposes, the concentration of vaborbactam is fixed at 8 mg/liter.

[g]EUCAST-approved breakpoints for *Enterobacteriales*, except *Morganella* spp.; FDA-approved breakpoints for *Enterobacteriaceae*: clinical efficacy was shown for *Klebsiella aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, and *Klebsiella oxytoca*.

[h]For susceptibility testing purposes, the concentration of relebactam is fixed at 4 mg/liter.

[i]FDA-approved breakpoints for anaerobes using agar dilution method, clinical efficacy shown for *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Fusobacterium nucleatum*, and *Parabacteroides distasonis*.

TABLE 3 Antimicrobial susceptibility of isolates to ceftazidime-avibactam

Pathogen[a]	No. of isolates	MIC (mg/liter)		Susceptible (%)
		50%	90%	
Enterobacteriaceae	3,269	0.12	0.5	99.9[b]
Pseudomonas aeruginosa	2,215	2	8	96.6[b]

[a]United States isolates, 2019 (276).
[b]CLSI- and EUCAST-approved breakpoints applied.

bility to CAZ-AVI using Food and Drug Administration (FDA)-approved breakpoints was 99.5%. The combination was active against ESBL- and AmpC-producing isolates of *Escherichia coli*, *K. pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* (36). Subsequent data from the INFORM, including 16,656 *Enterobacteriaceae* isolates between 2015 and 2016, showed that CAZ-AVI was active against 99.9% to 100.0% of the respective isolates (37). Meanwhile, in meropenem-nonsusceptible strains collected between 2015 and 2017, 73.0% were susceptible to CAZ-AVI (38). The combination has also shown activity against bacteria carrying $bla_{\text{KPC-2}}$, $bla_{\text{KPC-3}}$, or $bla_{\text{OXA-48-like}}$ genes (39, 40). A recent study showed that a combination of CAZ-AVI with aztreonam is active in resistant *Enterobacter* isolates carrying $bla_{\text{NDM-1}}$ and $bla_{\text{KPC-4}}$ on conjugative plasmids. The combination was demonstrated to show *in vitro* synergism. In addition, since aztreonam is not hydrolyzed by NDM, the addition of avibactam provides protection against class A enzymes to allow its action (41). The combination CAZ-AVI with aztreonam has also been described to successfully control a case of persistent bacteremia caused by *Stenotrophomonas maltophilia* carrying L1 (metallo-β-lactamase [MBL]) and L2 (cephalosporinase) β-lactamases (42). Analyzing resistant strains of *P. aeruginosa*, several studies have reported a high susceptibility rate to CAZ-AVI (43–47). However, in a study on piperacillin-tazobactam-resistant *P. aeruginosa* isolates from cystic fibrosis patients, the proportion with resistance to CAZ-AVI was 37.5%. The resistant isolates showed inactivating mutations in the chromosomal porin encoding gene *oprD* (48). In a recently published study including *P. aeruginosa* isolates collected between 2013 and 2018, 35.9% were resistant to CAZ-AVI, most of them identified as sequence type 235 (ST235) clone (49). The respective EUCAST-, FDA-, and CLSI-approved breakpoints for the interpretation of the susceptibility of particular pathogens to CAZ-AVI are summarized in Table 2. For antimicrobial susceptibility data of various pathogens to CAZ-AVI, see Tables 3 and 4.

Resistance Rate and Mechanisms

The most common mechanism of resistance against CAZ-AVI is the presence of class B and some of the class D β-lactamases (OXA-24/40 in *A. baumannii*, but not OXA-10 or OXA-48 in *Enterobacterales*) (50). Other mechanisms would include increased activity in the efflux pump, the loss of porins, and increased expression of the bla_{KPC} gene (51, 52). Also, single point mutations in PBPs are associated with resistance to ceftazidime, which is not reversible with avibactam (53). Several studies have reported emerging CAZ-AVI resistance after the exposure, i.e., due to the mutations on the Ω-loop of *Klebsiella pneumoniae* carbapenemase (KPC) enzymes leading to enhanced ceftazidime hydrolysis, which is not completely inhibited by avibactam (54–56). At Ambler amino acid position 179 in the Ω-loop, substitutions of tyrosine for aspartic acid (D179Y) or asparagine for aspartic acid (D179N) have been reported to confer resistance to CAZ-AVI, combined with additional mutations outside the loop (57). Avibactam has been demonstrated to cause strong AmpC induction for some *Enterobacter cloacae* and *P. aeruginosa* strains, but no induction for *Citrobacter freundii* strains in one study (58). However, in another publication, no induction for *E. cloacae* was demonstrated (59). The clinical relevance of induction is not clear. An additional mechanism of resistance recently described is the acquisition of other β-lactamases, such as Vietnamese extended-spectrum β-lactamase (VEB)-25 (60).

Addressing *P. aeruginosa* isolates collected between 2005 and 2008. the overall resistance rate against CAZ-AVI was 18%, mostly related to loss of porin and efflux

TABLE 4 Antimicrobial susceptibility to BLBLIs

Pathogen (no. of isolates, source [reference])	Yr published	Sample collection yr(s)	% of isolates susceptible to:[a]			
			CAZ-AVI	TOL-TAZ	MER-VAB	IMI-REL
Pseudomonas aeruginosa						
n = 14,330, globally (277)	2020	2012–2016	91.5[b]			
n = 3,193, U.S. (182)	2020	2014–2018			88.8–89.5[c]	
n = 1,445, Spain (220)	2020	2017	94.2[b]	94.6[b]		97.3[b]
n = 414, globally (278)	2020		93.0[c]	97.0[c]		
n = 1,513, U.S. (124)	2019	2012–2016		97.5[b,c]		
n = 413, globally (127)	2019	2012–2016		93.2[b,c]		
n = 80, Spain (279)	2019	2016–2017		91.3[b,c]		
n = 188, Italy (280)	2019	2010–2016	85.1[b]			
n = 1,794, Latin America (281)	2019	2012–2015	87.4[c]			
n = 100, Taiwan (282)	2019	2016–2019	91.0[c]	93.0[c]		
n = 2,215, U.S. (276)	2019	2017–2018	96.0[b,c]	95.9[b,c]		
n = 433, U.S. (283)	2019	2015–2017	98.2[b,c]	98.7[b,c]		
n = 524, China (128)	2019	2017	86.5[c]	88.5[c]		
n = 12,170, globally (284)	2019	2012–2016				90.8[c]
n = 896, U.S. (208)	2018	2016				94.4[d]
n = 1,705, Europe (285)	2018	2015				94.7[c]
n = 3,229, Canada (126)	2018	2008–2016		98.3[c]		
n = 355, U.S. (286)	2018	2013–2015		97.5[c]		
n = 1,909, U.S. (287)	2018	2017	96.9[b,c]	97.5[b,c]		
n = 100, Australia (288)	2018	2008–2018		96.0[b,c]		
n = 368, China (289)	2018	2012–2014	75.6[c]			
n = 1,259, U.S. (22)	2018	2015–2017	96.8[c]			
n = 423, U.S. (22)	2018	2017	96.2[c]	96.5[c]		
n = 5,716, Europe (290)	2018	2012–2015	92.4[b]			
n = 56, globally (84)	2018		66.1[c]			
n = 4,175, U.S. (37)	2018	2015–2016	97.6[c]			
n = 4,175, U.S. (291)	2018	2011–2015	96.5[c]			
n = 935, Italy (292)	2018	2013–2014		90.9[c]		
n = 3,737, U.S. (293)	2018	2013–2016		97.3[b,c]		
n = 489, Asia-Pacific Region (125)	2018	2013–2015		90.8[b,c]		
n = 598, U.S. (294)	2017	2015				93.1[c]
n = 16, globally (225)	2017	2012–2015				100.0[c]
n = 603, Europe (295)	2017	2012–2015		91.7[b]		
n = 1,099, United Kingdom (119)	2017	2011–2015		99.8[b]		
n = 537, Latin America (296)	2017	2013–2015		86.8[b,c]		
n = 7,868, U.S. (24)	2017	2013–2016	97.1[b,c]			
n = 3,402, U.S. (30)	2017	2011–2015	96.6[b,c]			
n = 440, Australia/New Zealand (297)	2017	2013–2015		95.7[b,c]		
n = 442, U.S. (298)	2016	2012–2014	97.7[c]			
n = 210, U.S. (299)	2016	2012–2014	97.1[c]			
n = 1,257, U.S. (123)	2015	2013–2014		97.0[c]		
n = 490, U.S. (216)	2015	2013–2014				98.0[c]
n = 5,328, U.S. (300)	2015	2011–2014	96.8[c]			
Average susceptibility			66.1–98.2	86.8–99.8	88.8–89.5	90.8–100.00
Pseudomonas aeruginosa, MDR						
n = 3,770, globally (277)	2020	2012–2016	68.2[b]			
n = 697, U.S. (182)	2020	2014–2018			59.0–59.7[c]	
n = 307, U.S. (124)	2019	2012–2016		87.9[b,c]		
n = 20, Italy (280)	2019	2010–2016	70.0[b]			
n = 205, Qatar (301)	2019	2014–2015	68.8[c]	62.9[c]		
n = 526, U.S. (276)	2019	2017–2018	83.5[b,c]	83.7[b,c]		
n = 80, Germany (49)	2019	2013–2018	85.0[b]			
n = 750, U.S. (302)	2019	2015–2017				79.7[c]
n = 3,708, globally (284)	2019	2012–2016				70.7[c]
n = 462, Canada (126)	2018	2008–2016		90.5[c]		
n = 327, U.S. (22)	2018	2015–2017	88.1[c]			
n = 121, U.S. (22)	2018	2017	86.2[c]	87.6[c]		
n = 879, U.S. (37)	2018	2015–2016	89.3[c]			
n = 32, U.S. (303)	2018	2015	71.9[c]			
n = 783, U.S. (293)	2018	2013–2016		88.6[b,c]		

(Continued on next page)

TABLE 4 (Continued)

Pathogen (no. of isolates, source [reference])	Yr published	Sample collection yr(s)	% of isolates susceptible to:[a]			
			CAZ-AVI	TOL-TAZ	MER-VAB	IMI-REL
n = 134, Asia-Pacific Region (125)	2018	2013–2015		67.2[b,c]		
n = 227, U.S. (208)	2018	2016				82.2[d]
n = 44, Germany (304)	2017	2013–2016		95.2[b]		
n = 1,562, U.S. (24)	2017	2013–2016	86.5[b,c]			
n = 47, Australia/New Zealand (297)	2017	2013–2015		68.1[b,c]		
Average susceptibility			68.2–89.3	62.9–95.2	59.0–59.7	70.7–82.2
Pseudomonas aeruginosa, XDR						
n = 1,652, globally (277)	2020	2012–2016	43.0[b]			
n = 440, U.S. (182)	2020	2014–2018			47.1–48.6[c]	
n = 193, U.S. (124)	2019	2012–2016		82.9[b,c]		
n = 20, Italy (280)	2019	2010–2016	58.1[b]			
n = 326, U.S. (276)	2019	2017–2018	78.2[b,c]	76.5[b,c]		
n = 112, Germany (49)	2019	2013–2018	49.1[b]			
n = 84, Canada (126)	2018	2008–2016		78.6[c]		
n = 145, U.S. (22)	2018	2015–2017	78.6[c]			
n = 54, U.S. (22)	2018	2017	77.8[c]	79.6[c]		
n = 393, U.S. (37)	2018	2015–2016	80.4[c]			
n = 348, U.S. (293)	2018	2013–2016		77.6[b,c]		
n = 44, Germany (304)	2017	2013–2016		50.0[b]		
n = 717, U.S. (24)	2017	2013–2016	75.9[b,c]			
Average susceptibility			43.0–80.4	50.0–82.9	47.1–48.6	
Pseudomonas aeruginosa, meropenem nonsusceptible						
n = 73, Italy (280)	2019	2010–2016	70.0[b]			
n = 368, U.S. (124)	2019	2012–2016		90.8[b,c]		
n = 614, Canada (126)	2018	2008–2016		94.8[c]		
n = 138, Asia-Pacific Region (125)	2018	2013–2015		70.3[b,c]		
n = 712, U.S. (293)	2018	2013–2016		88.6[b,c]		
n = 192, Latin America (296)	2017	2013–2015		66.1[b,c]		
n = 31, Australia/New Zealand (297)	2017	2013–2015		68.1[b,c]		
n = 126, Europe (295)	2017	2012–2015		65.9[b]		
Average susceptibility			70.0	65.9–94.8		
Pseudomonas aeruginosa, imipenem nonsusceptible						
n = 3,776, globally (284)	2019	2012–2016				70.3[c]
n = 227, U.S. (208)	2018	2016				78.0[d]
n = 477, Europe (285)	2018	2015				81.1[c]
n = 191, U.S. (294)	2017	2015				78.5[c]
n = 144, U.S. (216)	2015	2013–2014				92.0[c]
Average susceptibility						70.3–92.0
Enterobacter spp.						
n = 510, U.S. (124)	2019	2012–2016		73.9[b]–79.8[c]		
n = 855, Latin America (281)	2019	2012–2015	99.2[c]			
n = 33, Spain (279)	2019	2016–2017		66.7[b]–72.7[c]		
n = 772, Europe (285)	2018	2015				96.8[c]
n = 233, China (289)	2018	2012–2014	59.9[c]			
n = 163, U.S. (22)	2018	2017	100.0[c]	78.4[c]		
n = 270, U.S. (286)	2018	2013–2015		85.5[c]		
n = 1955, U.S. (293)	2018	2013–2016		78.9[b]–83.6[c]		
n = 159, Asia-Pacific Region (125)	2018	2013–2015		75.5[b]–83.0[c]		
n = 29, globally (180)	2018	2014–2015	100.0[c]		100.0[c]	
n = 1,009, United Kingdom (119)	2017	2011–2015		91.5[b]		
n = 537, Latin America (296)	2017	2013–2015		79.2[b]–84.0[c]		
n = 118, Australia/New Zealand (297)	2017	2013–2015		78.8[b]–85.6[c]		
n = 432, Europe (295)	2017	2012–2015		69.7[c]–78.0[c]		

(Continued on next page)

TABLE 4 (Continued)

Pathogen (no. of isolates, source [reference])	Yr published	Sample collection yr(s)	% of isolates susceptible to:[a]			
			CAZ-AVI	TOL-TAZ	MER-VAB	IMI-REL
n = 211, U.S. (216)	2015	2013–2014				99.0[c]
n = 3970, U.S. (300)	2015	2011–2014	99.9[c]			
Average susceptibility			59.9–100.0	66.7–91.5	100.0	96.8–96.8
Enterobacter spp., imipenem nonsusceptible						
n = 34, Europe (285)	2018	2015				70.6[c]
Enterobacteriaceae						
n = 273, U.S. (124)	2019	2012–2016		87.5[b]–90.3[c]		
n = 1,347, globally (127)	2019	2012–2016		89.4[b]–91.4[c]		
n = 7,665, Latin America (281)	2019	2012–2015	99.7[c]			
n = 3,269, U.S. (276)	2019	2017–2018	99.9[b,c]	86.9–90.1[b,c]		
n = 3,746, U.S. (283)	2019	2015–2017	99.9[b,c]	95.7–96.9[b,c]		
n = 1,774, China (128)	2019	2017	94.6[c]	72.0[c]		
n = 11,559, globally (178)	2018	2015			99.3[c]	
n = 2,362, U.S. (305)	2018	2013–2015		90.6[c]		
n = 2,647, U.S. (286)	2018	2013–2015		95.5[c]		
n = 45,872, globally (247)	2018	2012–2015	99.4[c]			
n = 2,125, U.S. (22)	2018	2015–2017	100.0[c]			
n = 694, U.S. (22)	2018	2017	100.0[c]	92.0[c]		
n = 509, globally (84)	2018		99.2[c]			
n = 18,656, U.S. (37)	2018	2015–2016	99.9[c]			
n = 31,512, U.S. (291)	2018	2011–2015	99.9[c]			
n = 15,223, U.S. (293)	2018	2013–2016		92.5[b]–94.4[c]		
n = 1,474, Asia-Pacific Region (125)	2018	2013–2015		85.8[b]–89.2[c]		
n = 991, globally (180)	2018	2014–2015	98.2[c]		99.0[c]	
n = 3,419, U.S. (208)	2018	2016				96.1[d]
n = 1,878, Latin America (296)	2017	2013–2015		80.9[b]–84.2[c]		
n = 36,380, U.S. (24)	2017	2013–2016	99.9[b,c]			
n = 6,209, U.S. (30)	2017	2011–2015	99.9[b,c]			
n = 5,950, Europe (295)	2017	2012–2015		91.3[b]–93.5[c]		
n = 1,019, Australia/New Zealand (297)	2017	2013–2015		95.9[b]–97.7[c]		
n = 6,773, U.S. (326)	2016	2012–2014	>99.9[c]			
n = 1,312, U.S. (327)	2016	2012–2014	99.9[c]			
Average susceptibility			94.6–100.0	72.0–97.7	99.0–99.3	96.1
Enterobacteriaceae, ESBL						
n = 1,701, Latin America (281)	2019	2012–2015	99.9[c]			
n = 391, U.S. (283)	2019	2015–2017	100.0[b,c]	83.2–88.8[b,c]		
n = 285, U.S. (276)	2019	2017–2018	100.0[b,c]	76.8–84.1[b,c]		
n = 271, U.S. (286)	2018	2013–2015		87.1[b]		
n = 1,474, Asia-Pacific Region (125)	2018	2013–2015		70.4[b]–79.1[c]		
n = 1,450, U.S. (293)	2018	2013–2016		79.3[b]–87.5[c]		
n = 906, Europe (295)	2017	2012–2015		74.9[b]–82.8[c]		
n = 67, Australia/New Zealand (297)	2017	2013–2015		88.1[b]–97.0[c]		
n = 495, Latin America (296)	2017	2013–2015		66.9[b]–74.7[c]		
Average susceptibility			99.9–100.0	66.9–97.0		
Enterobacteriaceae, OXA-48						
n = 45,872, globally (247)	2018	2012–2015	92.5[c]			
Carbapenem-resistant *Enterobacteriaceae*						
n = 131, U.S. (182)	2020	2014–2018			98.5–100.0[c]	
n = 216, Italy (306)	2020	2016–2017	91.6[b]			
n = 97, China (307)	2020		78.4[c]			
n = 79, U.S. (276)	2019	2017–2018	97.5[b,c]	2.6[b,c]		
n = 28, U.S. (283)	2019	2015–2017	89.3[b,c]	0.0[b,c]		
n = 372, China (128)	2019	2017	75.3[c]	6.2[c]		
n = 62, U.S. (308)	2019	2013–2016	87.1[c]	27.4[c]	79.0[c]	71.0[c]
n = 120, U.S. (309)	2019		82.0[c]		98.0[c]	
n = 330, globally (178)	2018	2015			73.9[c]	

(Continued on next page)

TABLE 4 (Continued)

Pathogen (no. of isolates, source [reference])	Yr published	Sample collection yr(s)	% of isolates susceptible to:[a]			
			CAZ-AVI	TOL-TAZ	MER-VAB	IMI-REL
n = 37, U.S. (305)	2018	2013–2015		2.7[c]		
n = 50, U.S. (22)	2018	2015–2017	100.0[c]			
n = 238, U.S. (37)	2018	2015–2016	97.5[c]			
n = 286, U.S. (293)	2018	2013–2016		2.4[b]–4.5[c]		
n = 513, U.S. (24)	2017	2013–2016	97.5[b,c]			
Average susceptibility			75.3–100.0	0.0–27.4	73.9–100.0	71.0
KPC-producing *Enterobacteriaceae*						
n = 103, U.S. (218)	2018		100.0[c]			100.0[c]
Klebsiella spp.						
n = 95, Spain (279)	2019	2016–2017		66.3[b]–72.9[c]		
n = 692, U.S. (286)	2018	2013–2015		93.1[c]		
n = 223, U.S. (22)	2018	2017	100.0[c]	96.0[c]		
n = 627, U.S. (305)	2018	2013–2015		85.8[c]		
n = 594, Asia-Pacific Region (125)	2018	2013–2015		80.8[b]–84.7[c]		
n = 1,296, U.K. (119)	2017	2011–2015		97.6[b]		
n = 1,112, Europe (295)	2017	2012–2015		78.2[b]–82.1[c]		
n = 246, Australia/New Zealand (297)	2017	2013–2015		96.3[b]–98.8[c]		
n = 1,484, U.S. (298)	2016	2012–2014	99.9[c]			
Average susceptibility			99.9–100.0	66.3–98.8		
Klebsiella pneumoniae						
n = 280, globally (127)	2019	2012–2016		80.0[b]–83.6[c]		
n = 2,128, Latin America (281)	2019	2012–2015	99.5[c]			
n = 100, Taiwan (282)	2019	2016–2019	100.0[c]	80.0[c]		
n = 863, U.S. (276)	2019	2017–2018	100.0[b,c]	88.6–91.9[b,c]		
n = 666, China (128)	2019	2017	93.8[c]	52.7[c]		
n = 1,591, Europe (285)	2018	2015				94.9[c]
n = 2,458, globally (178)	2018	2015			97.0[c]	
n = 564, China (289)	2018	2012–2014	74.2[c]			
n = 123, globally (84)	2018		98.4[c]			
n = 3,796, U.S. (37)	2018	2015–2016	99.9[c]			
n = 6,803, U.S. (291)	2018	2011–2015	99.9[c]			
n = 2,979, U.S. (293)	2018	2013–2016		88.7[b]–90.6[c]		
n = 570, Asia-Pacific Region (125)	2018	2013–2015		80.2[b]–84.2[c]		
n = 233, Germany (310)	2018	2014–2015		99.1[b]		
n = 878, globally (180)	2018	2014–2015	98.2[c]		98.9[c]	
n = 717, U.S. (208)	2018	2016				99.4[d]
n = 238, U.S. (294)	2017	2015				91.7[c]
n =34, globally (225)	2017	2012–2015				100.0[c]
n = 594, Latin America (296)	2017	2013–2015		60.4[b]–64.6[c]		
n = 917, Europe (295)	2017	2012–2015		75.8[b]–79.3[c]		
n = 190, Australia/New Zealand (297)	2017	2013–2015		96.8[b]–98.4[c]		
n = 891, U.S. (216)	2015	2013–2014				99.3[c]
n = 1205, U.S. (123)	2015	2013–2014		89.0[c]		
Average susceptibility			74.2–100.0	52.7–99.1	97.0–98.9	94.9–100.0
Klebsiella pneumoniae, ESBL						
n = 20, Poland (311)	2019	2017		65.0[b]		
n = 22, Spain (279)	2019	2016–2017		59.1[b]–77.3[c]		
n = 843, globally (178)	2018	2015			91.2[c]	
n = 49, U.S. (286)	2018	2013–2015		73.5[c]		
n = 1,474, Asia-Pacific Region (125)	2018	2013–2015		56.6[b]–69.4[c]		
n = 40, Germany (310)	2018	2014–2015		62.5[b]		
n = 119, U.K. (119)	2017	2011–2015		84.0[b]		
n = 226, Latin America (296)	2017	2013–2015		46.0[b]–56.6[c]		
n = 12, Australia/New Zealand (297)	2017	2013–2015		66.7[b]–83.3[c]		
n = 373, Europe (295)	2017	2012–2015		41.6[b]–49.1[c]		

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TABLE 4 (Continued)

Pathogen (no. of isolates, source [reference])	Yr published	Sample collection yr(s)	% of isolates susceptible to:[a]			
			CAZ-AVI	TOL-TAZ	MER-VAB	IMI-REL
n = 207, U.S. (298)	2016	2012–2014	99.5[c]			
Average susceptibility			99.5	41.6–84.0	91.2	
Klebsiella pneumoniae, MDR						
n = 2,821, globally (312)	2016	2012–2014	96.6[c]			
Klebsiella pneumoniae, carbapenem resistant						
n = 872, China (71)	2020	2017	96.3[c]			
n = 19, Spain (279)	2019	2016–2017		0.0[b]–5.0[c]		
n = 295, Greece (212)	2019	2015–2016	99.7[b]			8.0[b]
n = 267, China (128)	2019	2107	85.0[c]	1.9[c]		
n = 203, U.S. (293)	2018	2013–2016		0.5[b]–2.5[c]		
Average susceptibility			85.0–99.7	0.0–5.0		8.0
Klebsiella pneumoniae, imipenem nonsusceptible						
n = 179, Europe (285)	2018	2015				54.2[c]
Escherichia coli						
n = 435, U.S. (124)	2019	2012–2016		96.1[b]–96.6[c]		
n = 608, globally (127)	2019	2012–2016		96.9[b]–97.5[c]		
n = 209, Spain (279)	2019	2016–2017		95.2[b]–96.2[c]		
n = 2,705, Latin America (281)	2019	2012–2015	99.9[c]			
n = 100, Taiwan (282)	2019	2016–2019	99.0[c]	88.0[c]		
n = 565, U.S. (276)	2019	2017–2018	100.0[b,c]	95.3–96.4[b,c]		
n = 618, China (128)	2019	2017	96.8[c]	90.5[c]		
n = 4,921, globally (178)	2018	2015			99.8[c]	
n = 441, U.S. (305)	2018	2013–2015		98.0[c]		
n = 1,306, U.S. (286)	2018	2013–2015		98.5[c]		
n = 674, China (289)	2018	2012–2014	98.7[c]			
n = 144, U.S. (22)	2018	2017	100.0[c]	95.8[c]		
n = 323, globally (84)	2018		100.0[c]			
n = 7,111, U.S. (37)	2018	2015–2016	>99.9[c]			
n = 10,471, U.S. (291)	2018	2011–2015	>99.9[c]			
n = 6281, U.S. (293)	2018	2013–2016		97.6[b]–98.6[c]		
n = 568, Asia-Pacific Region (125)	2018	2013–2015		92.6[b]–94.5[c]		
n = 202, Germany (310)	2018	2014–2015		96.0[b]		
n = 35, globally (180)	2018	2014–2015	100.0[c]		100.0[c]	
n = 1,321, U.S. (208)	2018	2016				100.0[d]
n = 159, globally (225)	2017	2012–2015				100.0[c]
n = 2,676, U.K. (119)	2017	2011–2015		99.7[b]		
n = 661, Latin America (296)	2017	2013–2015		95.0[b]–96.7[c]		
n = 3,460, Europe (295)	2017	2012–2015		98.0[b]		
n = 497, Australia/New Zealand (297)	2017	2013–2015		99.8[b]–100.0[c]		
n = 2,876, U.S. (298)	2016	2012–2014	100.0[c]			
n = 2,778, U.S. (216)	2015	2013–2014				100.0[c]
n = 1,306, U.S. (123)	2015	2013–2014		98.0[c]		
Average susceptibility			96.8–100.0	88.0–100.0	99.8–100.0	100.0
Escherichia coli, ESBL						
n = 31, Poland (311)	2019	2017		93.5[b]		
n = 116, U.S. (124)	2019	2012–2016		66.4[b]–80.2[c]		
n = 46, Spain (279)	2019	2016–2017		80.4[b]–84.8[c]		
n = 976, globally (178)	2018	2015			99.2[c]	
n = 153, U.S. (286)	2018	2013–2015		92.8[c]		
n = 966, U.S. (293)	2018	2013–2016		86.5[b]–92.2[c]		
n = 198, Asia-Pacific Region (125)	2018	2013–2015		82.3[b]–87.9[c]		
n = 281, U.K. (119)	2017	2011–2015		97.9[b]		
n = 32, Germany (310)	2017	2014–2015		81.3[b]		
n = 238, Latin America (296)	2017	2013–2015		87.0[b]–91.6[c]		

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TABLE 4 (Continued)

Pathogen (no. of isolates, source [reference])	Yr published	Sample collection yr(s)	% of isolates susceptible to:[a]			
			CAZ-AVI	TOL-TAZ	MER-VAB	IMI-REL
n = 559, Europe (295)	2017	2012–2015		87.8[b]–92.7[c]		
n = 47, Australia/New Zealand (297)	2017	2013–2015		97.9[b]–100.0[c]		
n = 330, U.S. (298)	2016	2012–2014	100.0[c]			
Average susceptibility			100.0	66.4–100.0	99.2	
Proteus spp.						
n = 19, Spain (279)	2019	2016–2017		100.0[b,c]		
n = 182, China (289)	2018	2012–2014	95.6[c]			
Acinetobacter baumannii						
n = 486, Europe (285)	2018	2015				10.3[c]
n = 158, U.S. (216)	2015	2013–2014				51.0[c]
Average susceptibility						10.3–51.0
Acinetobacter baumannii, OXA-23						
n = 58, U.S. (216)	2015	2013–2014				12.0[c]

[a]CAZ-AVI, ceftazidime-avibactam; TOL-TAZ, ceftolozane–tazobactam; MER-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam.
[b]EUCAST-approved breakpoints applied.
[c]CLSI-approved breakpoints applied.
[d]MICs interpreted using CLSI breakpoints for imipenem.

pump (61). Resistance due to the presence of VIM metallo-β-lactamase (MBL) or mutations in the chromosomal AmpC gene in *P. aeruginosa* isolates has also been reported (62–64). In *Acinetobacter* spp., resistance to CAZ-AVI is mainly due to a failure of avibactam to penetrate the outer membrane (65, 66).

In *Citrobacter freundii*, resistance to the combination has been documented due to mutations within the coding region of the bla_{KPC-2} Ω-loop. (67) In cases of the CAZ-AVI-resistant *K. pneumoniae*, most of the isolates were ST258 mutant bla_{KPC-3} (34, 52, 68, 69). There are also reports of decreased CAZ-AVI susceptibility in KPC-producing *K. pneumoniae* isolates enhanced by OmpK35 porin deficiency (53, 70). A recent study from China reported 3.7% resistance rate to the CAZ-AVI in carbapenem-resistant *K. pneumoniae*, mainly due to the production of MBL but also in isolates harboring mutated bla_{KPC-2} (D179Y). In these isolates, avibactam does not inhibit the β-lactamase, enabling it to hydrolyze ceftazidime (71, 72). Cases of nonfunctional OmpK35-OmpK37 and altered OmpK36 porins associated with a higher copy number of the bla_{KPC} gene have also been reported (71, 73).

Assessing the resistance development following exposure to CAZ-AVI, a study with KPC-producing *K. pneumoniae* reported that 8% of the isolates became resistant within 10 to 19 days of exposure (74). Similar data were reported by Gaibani et al. when the resistance in KPC-producing *K. pneumoniae* against CAZ-AVI emerged after 17 days of combination therapy with CAZ-AVI and gentamicin due to D179Y substitution in the bla_{KPC-3} gene (56). Recently published findings in the *K. pneumoniae* ST307 documented the resistance development within 12 days of CAZ-AVI exposure through a bla_{KPC-2} point mutation. Researchers also identified an additional phenotype with combined CAZ-AVI and meropenem resistance (55). Fraile-Ribot et al. (75) reported a case of carbapenem-resistant *P. aeruginosa* developing resistance to CAZ-AVI under the treatment. The resistant isolate contained a 3-bp insertion leading to the duplication of a key residue, designated OXA-539 (75). Moreover, the expeditious development of CTX-M-14 isoforms with increased ceftazidime hydrolytic activity may limit the usefulness of CAZ-AVI in monotherapy, in particular, against isolates carrying $bla_{CTX-M-14}$ and bla_{OXA-48} (54).

PK-PD Characteristics

Ceftazidime and avibactam exhibit numerous similarities in pharmacokinetic prop-

TABLE 5 Pharmacokinetic properties of newly approved BLBLIs

Parameter	Value for drug combination by dose ratio[a]							
	4:1 (2.5 g q8h [over 2 h]):		2:1 (1.5 g or 3 g q8h [over 1 h]):		1:1 (4 g q8h [over 3 h]):		2:1 (1.25 g q6h [over 0.5 h]):[b]	
	CAZ	AVI	TOL	TAZ	MER	VAB	IMI	REL
V_{ss} (liter)[c]	17	22.2	13.5	18.2	20.2	18.6	24.3	19.0
Half-life (h)	2.76	2.71	3.12	1.03	2.3	2.3	1.0	1.2
% protein bound	<10	5.7–8.2	16–21	30	2	33	20	22
AUC_{ELF}:$fAUC_{plasma}$[d]	0.26–0.31	0.35	0.50	0.62	0.63	0.79	0.55	0.54
CL (ml/min)[e]								
Renal	100	158	57–112	210	130	99	115	123
Total	115	218	68–112	340	175	133	223	133

[a]CAZ, ceftazidime; AVI, avibactam; TOL, ceftolozane; TAZ, tazobactam; MER, meropenem; VAB, vaborbactam; IMI, imipenem; REL, relebactam.
[b]Formulated as 500 mg imipenem plus 500 mg cilastatin plus 250 mg relebactam.
[c]V_{ss}, volume of distribution at steady state.
[d]AUC, area under the curve; ELF, epithelial lining fluid.
[e]CL, clearance.

erties: both have short plasma half-lives, low plasma protein binding, and similar volumes of distribution (*V*s) and epithelial lining fluid (ELF) penetration ratios, as summarized in Table 5. Additionally, both ceftazidime and avibactam are primarily renally excreted as unchanged drugs (76).

The clinical pharmacology program used to support the approval of CAZ-AVI by the FDA and European Medicines Agency (EMA) relied on the published plasma $\%fT_{>MIC}$ of ceftazidime required for efficacy against *Enterobacterales* and *P. aeruginosa*. For avibactam, it was proposed that adequate protection of ceftazidime (against β-lactamases) would allow the PK-PD of the combination to resemble that of ceftazidime alone. On that basis, the PK-PD index for avibactam was defined as a critical avibactam concentration below which sufficient inhibition of ceftazidime was lost (i.e., $\%fT > C_T$). (5) A plasma target of 50% *fT* of >1 μg/ml was determined through a series of dose fractionation studies with avibactam against a fixed backdrop of sub-MICs of ceftazidime in a neutropenic murine thigh infection model (5). In phase 2 studies with adult complicated intra-abdominal infection (cIAI) patients with normal renal function, 2 g ceftazidime was administered with 0.5 g avibactam as a 30-min i.v. infusion every 8 h. However, population PK models predicted that joint probability of target attainment (which simultaneously evaluates the probability of achieving the respective PK-PD targets of ceftazidime and avibactam) would fall below the conventional threshold of >90% used to support susceptibility breakpoints.

Since the efficacies of both ceftazidime and avibactam are described as time dependent, an extended duration of infusion (2 h) was proposed to optimize dosing of the combination for phase 3 studies in complicated urinary tract infection (cUTI) and cIAI patients. (5) For the treatment of hospital-acquired bacterial pneumonia (HABP) (including ventilator-associated bacterial pneumonia [VABP]), dose selection accounted for the disposition of ceftazidime and avibactam at the infection site by evaluating the ELF penetration ratio in a murine lung infection model and in healthy human volunteers. Ultimately, a 2.5-g dose (2 g ceftazidime plus 0.5 g avibactam) infused over 2 h was approved for all indications in patients with normal renal function.

Given that ceftazidime and avibactam are eliminated by the kidneys, various population PK models have illustrated creatinine clearance (CrCL) to be a key covariate accounting for differences in the pharmacokinetics of both agents (5). Thus, dosage adjustment is recommended for patients with CrCL of ≤50 ml/min, with specific recommendations for the different renal impairment groups (i.e., moderate versus severe versus end-stage renal diseases [ESRDs], estimated using the Cockcroft-Gault formula) based on achievement of >90% probability of target attainment (PTA) while mitigating potential safety risks. Population PK models indicate that no dosage adjustments are required in the elderly or on the basis of race, body weight, or sex. In

pediatric patients aged 3 months to 17 years with cIAI and cUTI, the approved dosage regimens of 50 mg/kg body weight to 2.5 g CAZ-AVI (in patients with normal renal function) are designed to match the exposures corresponding to the approved adult dose, since the disease processes are age independent (76).

A recent retrospective study evaluating the use of CAZ-AVI for the treatment of infections due to carbapenem-resistant *Enterobacterales* (CRE) found pneumonia and the need for renal replacement therapy (RRT) as risk factors for clinical and microbiological failure (77). The higher rates of treatment failure in patients receiving RRT may be attributed to the absence of appropriate dosing recommendations for this patient cohort. However, the rationale for the higher rate of treatment failures in patients with pneumonia is less apparent. Nonetheless, these observations may point to a need to further evaluate the robustness of the fixed dose ratio approach for dosing CAZ-AVI irrespective of infection severity/site, causative pathogen, β-lactamase(s) present, or patient-specific factors.

Clinical Data

Approval date and indications. CAZ-AVI is approved by both the EMA and the FDA. It was first approved by FDA in 2015 for use in adults with cIAI (in combination with metronidazole) and cUTI, including pyelonephritis. It was later approved for use in pediatric patients 3 months and older for these indications and also for HABP/VABP in adults (76). EMA approval also refers to the indication of infections due to aerobic Gram-negative organisms in patients with limited treatment options (78).

Randomized controlled trials evaluating CAZ-AVI. Seven publications, representing 8 randomized controlled trials (RCTs) were published evaluating CAZ-AVI with or without metronidazole versus carbapenems/quinolones. For efficacy outcomes from these trials, see Table 6. The representation of third-generation cephalosporin resistant Gram-negatives in these trials varied, between 11% (79) to 78% (21). Data from these RCTs evaluating the efficacy and safety of CAZ-AVI in adults were compiled in several meta-analyses. Sternbach et al. (80) reported results of eight trials, 4,093 patients, which compared CAZ-AVI with or without metronidazole versus any other antibiotic regimen (mostly carbapenem) for treatment of cUTI, cIAI, and nosocomial pneumonia. No difference in all-cause mortality at late follow-up was demonstrated in this meta-analysis between CAZ-AVI and the comparator, though the mortality in total was ~3%, probably limiting the external validity of these trials. The trials excluded immunocompromised patients, patients with severe renal or liver impairment, and patients not expected to respond to antibiotics within 5 to 21 days. No significant differences in clinical cure or microbiological cure at test of cure (TOC) were demonstrated as well. In the subgroup of patients with UTI, higher microbiological cure rates were demonstrated with CAZ-AVI at TOC. Similar results of higher microbiological cure with CAZ-AVI were also reported in a meta-analysis by Zhang et al., compiling trials of patients with cUTI and cIAI (81). Though no significant difference was demonstrated for the outcome of any adverse events (AEs), the rate of serious AEs (SAEs) was significantly higher with CAZ-AVI versus comparator, mostly carbapenem. Detailed data on the nature of these AEs were missing (80). Two additional meta-analyses did not demonstrate a significant difference between CAZ-AVI versus comparator in any efficacy or safety outcomes for infections caused by *Enterobacterales* (82) and serious Gram-negative infections (83). In the latter meta-analysis, a subgroup analysis of patients with CRE infections (4 studies, $n = 281$) showed significantly lower mortality and higher clinical cure rates with CAZ-AVI. However, this subgroup analysis was based on three cohort studies and one *post hoc* analysis of a randomized controlled trial, limiting the validity of the results.

Clinical data on the efficacy of CAZ-AVI for infections caused by specific pathogens. (For details on studies addressing CAZ-AVI for resistant bacteria, see Table 7.)

(i) Ceftazidime-resistant pathogens. Overall, from available RCTs in adults, clinical response was reported for 782 patients with infection caused by ceftazidime-resistant pathogens, either *Enterobacterales* or *P. aeruginosa*. For these patients, clinical response

TABLE 6 Randomized controlled trials assessing ceftazidime-avibactam efficacy outcomes

Trial ID[a]; population (reference)	Comparator[b]	Phase	Design[c]	No. randomized	Indication[d]	Exclusion of immunocompromised patients	Outcomes[e]	
							No. (%; 95% CI) interventions vs control	Risk difference (95% CI)
Vazquez 2012; adults (313)	Imi	2	NS	137	cUTI	No	Clinical response TOC: 24/28 (85.7) vs 29/36 (80.6)	5.2 (−16.3 to 26.6)
							Microbiol response TOC: 19/27 (70.4) vs 25/35 (71.4)	−1.1 (−27.2 to 25.0)
Qin 2016; adults (85)	Mero	3	NI	441	cIAI	Neutropenia <1,000/mm^3; renal transplant	Mortality: 2/215 (0.9) vs 1/217 (0.5)	
							Clinical cure TOC: 166/177 (93.8) vs 173/184 (94.0)	−0.2 (−5.53 to 4.97)
							Microbiol responses were presumed from clinical responses for all subjects	
Carmeli 2016; adults (21)	Mostly carbapenems	3	NS	333	cUTI, cIAI	Solid organ transplant	Mortality: 4/164 (2.4) vs 5/168 (3.0)	
							Clinical cure TOC: 140/154 (91; 85.6–94.7) vs 135/148 (91; 85.9–95.0)	
							Microbiol response TOC: 118/144 (82; 75.1–87.6) vs 88/137 (64; 56.0–71.9)	
Torres 2016; adults (87)	Mero	3	NI	879	NP	Lung or heart transplant; HIV (CD4 <200/mm^3); chemotherapy; immunosuppressive therapy; neutropenia <500/mm^3	Mortality: 42/436 (9.6) vs 36/434 (8.3)	
							Clinical cure TOC: 245/356 (68·8) vs 270/370 (73·0)	−4.2 (−10.76 to 2.46)
							Microbiol response TOC: 95/171 (55.6) vs 118/184 (64.1)	−8.6 (−18.65 to 1.64)
Lucasti 2013; adults (314)	Mero	2	NS	204	cIAI	HIV (CD4 <200/mm^3); chemotherapy; immunosuppressive therapy; neutropenia <1,500/mm^3	Mortality: 3/101 (3.0) vs 2/102 (2.0)	
							Clinical cure TOC: 80/87 (92.0) vs 85/90 (94.4)	−2.5 (−19.5 to 10.1)
							Microbiol response TOC: 62/68 (91.2) vs 71/76 (93.4)	
Mazuski 2016; adults (79)	Mero	3	NI	1,066	cIAI	HIV (CD4 <200/mm^3); chemotherapy; immunosuppressive therapy; neutropenia <1,000/mm^3	Mortality: 13/529 (2.5) vs 8/529 (1.5)	
							Clinical cure TOC: 337/413 (81.6) vs 349/410 (85.1)	−3.5 (−8.64 to 1.58)
							Microbiol response presumed based on clinical outcome	
Wagenlehner 2016; adults (86)	Dori	3	NI	1,033	cUTI	Renal transplant; HIV (CD4 <200/mm^3); chemotherapy; immunosuppressive therapy; neutropenia <500/mm^3	Mortality: 0/511 vs 0/509	
							Clinical cure TOC: 355/393 (90.3) vs 377/417 (90.4)	−0.1 (−4.23 to 4.03)
							Microbiol response: 304/393 (77.4) vs 296/417 (71.0)	6.4 (0.33 to 12.36)

(Continued on next page)

TABLE 6 (Continued)

Trial ID[a]; population (reference)	Comparator[b]	Phase	Design[c]	No. randomized	Indication[d]	Exclusion of immunocompromised patients	Outcomes[e]	
							No. (%; 95% CI) interventions vs control	Risk difference (95% CI)
Bradley 2019; children (95)	Mero	2	Noninferential	83	cIAI	No	Mortality: 0/61 vs 0/22 Clinical cure TOC: 56/61 (91.8) vs 21/22 (95.5) Microbiol response TOC: 45/50 (90.0) vs 18/19 (94.7)	
Bradley 2019; children (96)	Cefepime	2	Noninferential	97	cUTI	Renal transplant	Mortality: 0/68 vs 0/29 Clinical cure TOC: 48/54 (88.9) vs 19/23 (82.6) Microbiol response TOC: 43/54 (79.6) vs 14/23 (60.9)	

[a]ID, identifier.
[b]Imi, imipenem; Mero, meropenem; Dori, doripenem.
[c]NI, noninferiority; NS, not specified.
[d]cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; NP, nosocomial pneumonia.
[e]CI, confidence interval; TOC, test of cure; microbiol, microbiological.

TABLE 7 Studies evaluating CAZ-AVI for MDR *Enterobacterales* and *P. aeruginosa* infections

Study ID; main pathogen(s) tested (reference)[a]	Design	No. included (p/i)[b]	Comp (no. [%])	No. and source(s) of infection[c]	No. of isolates by type	No. of isolates by susceptibility	No. with combination treatment	Outcomes (no. [%])[d]
Enterobacterales								
Caston 2017; CRE CPE in hematological patients (315)	Retrospective comparative study	31 p with hematological malignancy, 8 C-A, 23 comp	Combination in 17/23 (94)[e]	31 BSI	C-A: 7 *Klebsiella* spp., 1 *E. coli*; comp: 20 *Klebsiella* spp., 2 *S. marcescens*, 1 *E. cloacae*	All CPE, C-A: 5 OXA-48, 3 KPC; comp: 14 OXA-48, 9 KPC	All 8 in the C-A group	Mortality: C-A, 2/8 (25); comp, 12/23 (52.2) Clinical cure 14 days: 6/8 (75) vs 8/23 (34.8)
King 2017; CRE (93)	Retrospective study	60 p		23 BSI, 17 UTI, 16 LRTI, 4 IAI, 10 others	50 *K. pneumoniae*, 5 *E. coli*, 5 others	CRE, mechanism not reported	19	Mortality: 19/60 (32) Clinical cure EOT: 9/60 (65) Microbiol cure EOT: 2/60 (53)
Shields 2017; CRE (~80% CPE) (74)	Retrospective study	37 p, 37 i		10 BSI, 4 UTI, 4 IAI, 12 LRTI, 4 SSTI, 3 others	31 *K. pneumoniae*, 3 *E. coli*; 3 *Enterobacter* spp.	All CRE, 29 KPC	11	Mortality: 9/37 (24.3) Clinical success 30 days: 22/37 (59) Microbiol cure 7 days: 27/37 (73)
Shields 2017; CRE CPE, KPC (92)	Retrospective study	109 p, 13 C-A, 96 comp	Combination in 67/96 (70)[c]	109 BSI	*K. pneumoniae*	CRE KPC, C-A: 9 KPC-2, 4 KPC-3; comp, 72 KPC-2, 21 KPC-3	5	Mortality: C-A, 1/13 (7.7%); comp, 30/96 (31.3) Clinical success 30 days: C-A, 5/13 (38.4); comp, 39/96 (40.6)
Temkin 2017; CRE CPE, KPC, OXA-48 (316)	Case series (salvage treatment C-A)	38 p, 38 i		IAI mostly, 26 BSI	36 p CRE infection (35 *Klebsiella* sp., 1 *E. coli*), 2 p with CR[f] *P. aeruginosa*	23 KPC, 13 OXA-48, 2 *P. aeruginosa*	25	Mortality: 15/38 (39.5) Clinical cure: 26/38 (68.4) Microbiol cure: 24/38 (63.2)
Sousa 2018; CRE CPE, OXA-48-producing *Enterobacterales* (317)	Prospective study (noninterventional)	57 p		16 IAI, 15 LRTI, 14 UTI, 26, BSI, 6 others	54 *K. pneumoniae*, 2 *E. coli*, 1 *Enterobacter cloacae*	OXA-48	11	Mortality: 13/57 (22) Clinical cure 7 days: 44/57 (77) Microbiol cure 7 days: 37/57 (65)
van Duin 2018; CRE CPE (90)	Prospective comparative study (noninterventional)	38 p C-A, 99 p colistin	Colistin	63 BSI (15 C-A, 48 colistin), 30 LRTI (9 C-A, 21 colistin), 44 others	*K. pneumoniae*: 37 C-A, 96 colistin 96; *Enterobacter* sp.: 1 C-A, 3 colistin	54 isolates tested: 28 KPC-2 (52%), 24 KPC-3 (44%)	24 C-A, 93 colistin	Mortality: C-A, 3/38 (8); colistin, 33/99 (33)
Alraddadi 2019; CRE CPE (32)	Retrospective comparative study	38 p: 10 p C-A, 28 p comp	Combination in 25/28 (89)[c]	C-A: 5 LRTI, 3 UTI, 3 IAI, 2 SSTI, 7 BSI; comp: 14 LRTI, 8 UTI, 5 IAI, 3 SSTI, 15 BSI	*K. pneumoniae*: 7 C-A, 3 comp; *E. coli*: 3 C-A, 5 comp	OXA-48-8 C-A: 19 comp; NDM: 1 C-A, 5 comp; NDM+OXA-48: 0 C-A, 1 comp; no carbapenemase gene: 1 C-A, 3 comp	None	Mortality: C-A, 5/10 (50); comp, 16/28 (57.1) Clinical cure 30 days: C-A, 4/10 (40); comp, 11/28 (39)
De la Calle 2019; CRE CPE, OXA-48 (33)	Retrospective study	23 p, 24 e (9 salvage)		7 IAI, 6 UTI, 5 LRTI, 5 other, 6 BSI	23 e *K. pneumoniae*, 1 e *E. coli*	OXA-48	10 e	Mortality: 2/23 (8) Clinical cure 30 days: 15/23 (65.2)
Guimaraes 2019; CRE CPE, KPC2 coresistant to polymyxin (98)	Case series (salvage treatment C-A)	29 p, 30 i		12 BSI, 8 UTI, 2 IAI, 3 LRTI, 2 SSTI	28 *K. pneumoniae*, 2 *S. marcescens*, KPC-2 producers	All KPC-2, coresistant to carbapenems and polymyxin	14	Mortality: 15/29 (51.7) Clinical success EOT: 24/29 (82.7) Microbiol success EOT: 12/29 (41.3)

(Continued on next page)

TABLE 7 (Continued)

Study ID; main pathogen(s) tested (reference)[a]	Design	No. included (p/i)[b]	Comp (no. [%])	No. and source(s) of infection[c]	No. of isolates by type	No. of isolates by susceptibility	No. with combination treatment	Outcomes (no. [%])[d]
Iannaccone 2019; CRE CPE, KPC (109)	Retrospective study	23 p		23 BSI	*K. pneumoniae*	All KPC, *K. pneumoniae*	20	Mortality: 6/23 (26) Clinical cure in-hospital: 17/23 (73.9)
Tsolaki 2019; CRE CPE, KPC (91)	Retrospective comparative study	41 C-A vs 36 BAT	Combination in 35/36 (97)[e]	C-A: 22 BSI, 19 LRTI, 4 IAI, 3 other; comp: 28 BSI, 7 LRTI, 4 IAI, 2 other	*K. pneumoniae*	C-A all KPC, BAT, 31/36 p KPC; colistin-susceptible/C-A 17/41, comp 31/36	32	Mortality: C-A, 6/41 (15); comp, 14/36 (38) Clinical cure 10 days: C-A, 33/41 (80.4); comp, 19/36 (52.8) Microbiol cure 10 days: C-A, 33/35 (94.3); comp, 21/31 (67.7)
Tumbarello 2019; CRE CPE (318)	Retrospective comparative study, salvage treatment	138 p C-A, 104 p BSI, matched 104 p BSI comp	Combination in 77/104 (74)[e]	104 BSI, 13 LRTI, 12 IAI, 9 UTI, 3 other	*K. pneumoniae*	CPE	109	Mortality: 47/138 (34.1) Mortality BSI, 38/104 (36.5); comp, 58/104 (55.7)
Enterobacterales and *P. aeruginosa*								
Jorgensen 2019; CRE and any *Pseudomonas* spp. (88)	Retrospective study	203 p		76 LRTI, 40 UTI, 38 IAI, 39 other, 22 BSI	159 *Enterobacteriaceae* (78.3%), 63 *Pseudomonas* sp. (31.0%)	117 CRE, 63 any *Pseudomonas*	65 (45 CRE, 20 *P. aeruginosa*)	Mortality: CRE, 19/117 (16.2); *P. aeruginosa*, 11/63 (17.5) Clinical response 30 days: CRE, 83/117 (70.9); *P. aeruginosa*, 44/63 (69.8)
Rodriguez-Nunez 2018; MDR and XDR *P. aeruginosa* (89)	Case series	8 p		5 LRTI, 3 others, 3 BSI	*P. aeruginosa*	MDR and XDR	5	Mortality: 1/8 (12.5) Clinical cure: 4/8 (50)
Stone 2018; MDR *Enterobacteriaceae* and *P. aeruginosa* (84)	*Post hoc* analysis of 5 RCTs	1,146 p: 565 p C-A, 581 p comp	Carbapenem	C-A: 181 IAI, 237 UTI, 56 LRTI; comp: 207 IAI, 184 UTI, 59 LRTI	*E. coli*: 323 C-A, 329 other; *K. pneumoniae*: 123 C-A, 153 other; *E. cloacae*: 29 C-A, 29 comp; other *Enterobacterales*: 31 C-A, 28 comp; *P. aeruginosa*: 56 C-A, 39 comp	MDR *Enterobacteriaceae* and *P. aeruginosa*	None	Clinical cure TOC, *Enterobacterales*: C-A, 478/560 (85.4); comp, 508/578 (87.9); *P. aeruginosa*: C-A, 32/56 (57.1), comp, 21/39 (53.8) Microbiol response TOC: C-A, 399/509 (78.4); comp, 388/542 (71.6)

[a]CPE, carbapenem-producing *Enterobacterales*; CRE, carbapenem-resistant *Enterobacterales*; KPC, *Klebsiella pneumonia* carbapenem producing; MDR, multidrug resistant; XDR, extensively drug resistant.
[b]p, patient; i, isolate; e, episode; C-A, ceftazidime-avibactam; comp, comparator; BAT, best available therapy; BSI, bloodstream infection.
[c]LRTI, lower respiratory tract infection; UTI, urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft tissue infection.
[d]Microbiol, microbiological; EOT, end of treatment; TOC, test of cure.
[e]Combinations or monotherapy with any of aminoglycosides, carbapenems, tigecycline, and/or colistin, and less common fosfomycin, quinolones, trimethoprim-sulfamethoxazole, and aztreonam (1 [3.6%]).
[f]CR, carbapenem resistant.

was 86% (326/378) in the CAZ-AVI arm versus 85% (342/404) in the comparator arm (carbapenem based) (80).

(ii) *P. aeruginosa*. Stone et al. (84) conducted a *post hoc* analysis of five randomized controlled trials (21, 79, 85–87), evaluating outcomes among 1,146 patients with multidrug-resistant (MDR) pathogens treated with CAZ-AVI versus comparator; among them, 95 were MDR *P. aeruginosa* (see Table 7 for details). Mortality was not reported, but clinical cures reported specifically for *P. aeruginosa* were similar between study arms (57.1% with CAZ-AVI versus 53.8% with the comparator). Microbiological responses for *P. aeruginosa* were similar between CAZ-AVI and comparator (32/56 [57.1%] versus 21/39 [53.8%], respectively, $P = 0.83$). A few additional studies addressed CAZ-AVI effectiveness in *P. aeruginosa* infections: Jorgensen et al. (88) reported on 63 patients with *Pseudomonas* spp. infections, mostly pneumonia (60%), treated with CAZ-AVI. Among the isolates tested, 47.5% were ceftazidime resistant and 77.5% were meropenem resistant. Mortality at 30 days was 11/63 (17.5%), and clinical response rates were 69.8% (44/63) (88). One small case series reported on eight patients with MDR/extensively drug resistant (XDR) *P. aeruginosa* infections treated CAZ-AVI, with 50% clinical response (4/8) and 12.5% 30-day mortality (1/8) (89).

(iii) MDR *Enterobacterales*. Stone et al. (84), in their *post hoc* analysis, included 1,051 MDR *Enterobacterales* isolates. Clinical cures at test of cure were similar between CAZ-AVI and comparator for both *Enterobacterales* and *P. aeruginosa* (overall 478/560 [85.4%] versus 508/578 [87.9%], $P = 0.222$). Microbiological response at TOC was significantly higher with CAZ-AVI for MDR *Enterobacterales* (399/509 [78.4%] versus 388/542 [71.6%], $P = 0.013$) (84).

(iv) Carbapenem-resistant *Enterobacterales*. As mentioned above, one meta-analysis showed significantly lower mortality and higher clinical cure rates with CAZ-AVI versus those for the comparator in CRE infections (83). Specifically, for KPC, three comparative studies demonstrated significant reduction in mortality compared to that with the best available therapy (BAT) (90–92).

In addition, 14 nonrandomized studies evaluated CAZ-AVI for the treatment of CRE. These are summarized in Table 7. Five studies were comparative; most studies evaluated patients with CRE carbapenemase-producing *Enterobacterales* (CPE) isolates, but two studies did not report mechanism of carbapenem resistance (88, 93). Overall, 632 patients were treated with CAZ-AVI in these studies, demonstrating overall mortality (30-days or in-hospital mortality) of 25.6% (162/632) and a clinical response rate of 67.5% (318/471). Microbiological response at end of treatment (EOT) was 64.5% (165/256) with CAZ-AVI. In one comparative study, higher microbiological response rate was demonstrated with CAZ-AVI than with BAT (mostly colistin/tigecycline based combination) (33/35 [94.3%] versus 21/31 [67.7%], respectively) (91).

Since these studies were mostly retrospective, using various comparators and various rates of combination therapy, and not all adjusting for a possible bias of receiving a new expensive drug versus the less expensive alternative, it is difficult to draw conclusions on the drug's efficacy.

Onorato et al. (94) performed a meta-analysis compiling 11 retrospective studies and case series, evaluating the efficacy of CAZ-AVI administered as monotherapy versus a combination for the treatment of CRE and carbapenem-resistant *P. aeruginosa* infections. Three hundred ninety-six subjects were included (only 19 with *P. aeruginosa*): 202 received the combination and 194 received monotherapy. The mortality rates were similar between combination therapy (38.1%) and monotherapy (30.9%). Similarly, no difference was found between the two groups for the outcome of microbiological cure. Clinical cure was not compiled in this meta-analysis. CAZ-AVI resistance emergence was reported in 6 patients (3.0%) in the combination group and 8 patients (4.1%) in the monotherapy group (94).

In summary, clinical data regarding the use of CAZ-AVI for CRE infections are limited to observational, mostly retrospective, noncomparative studies. Indications for using CAZ-AVI over older drugs in these studies were the failure of older drugs, risk factors for toxicity with older drugs or actual toxicity, or routine use in more recent periods, when

the new drugs were readily available. Thus, no methodologically adequate comparison has ever been performed. Data regarding *P. aeruginosa* are scarce.

Clinical use of CAZ-AVI in special patient populations. (i) Pediatric population. Two phase II RCTs were conducted in a pediatric population (total, 180 patients), evaluating CAZ-AVI versus cefepime for cUTI and CAZ-AVI plus metronidazole versus meropenem for cIAI. No cases of fatality were reported in either of these trials. Clinical cure rates at TOC were similar between groups; microbiological cure rates were similar for cIAI and nonsignificantly higher with CAZ-AVI for cUTI (Table 7). Rates of any AEs were similar, and SAEs were nonsignificantly more common with CAZ-AVI (10.1% versus 6.0%) (95, 96).

Iosifidis et al. (97) reported a case series of 8 critically ill children less than 5 years old who received CAZ-AVI as part of combination therapy for XDR/pandrug-resistant (PDR) *K. pneumoniae* infections. At 30 days, all children survived the infection, and a favorable clinical and microbiological outcome was reported. In all children, no severe adverse events were reported, with no discontinuation or dose modification of the drug (97).

(ii) Chronic renal failure. Patients with severe renal or liver impairment were excluded from RCTs evaluating CAZ-AVI. Hence, data can be obtained only from observational studies, mostly evaluating CAZ-AVI for CRE infections, as detailed above. Shields et al. (74) reported lower clinical success among patients requiring continuous renal replacement therapy (CRRT) (1/6 [17%] versus 21/31 [68%]), though numbers are small. Among patients other than those requiring CRRT, success rates were not influenced by lower baseline creatinine clearance (CrCL) (74). King et al. (93) evaluated CAZ-AVI for CRE infections in hematological patients. In this study, 33 patients required renal dose adjustment of the drug. Among them, mortality was 42% (14/33), clinical success was 58% (19/33), and microbiological response was 55% (18/33), all similar to the entire cohort (93). De La Calle et al. reported 90-day mortality of 20% (2/10) and 60% (6/10) clinical cure among 10 patients with chronic renal failure at baseline (33). Guimaraes et al. (98) reported 44% (4/9) mortality among nine patients who received adjusted renal dosage of CAZ-AVI, while 5 patients with renal impairment at baseline and no dose adjustment remained alive. These few data may suggest a need to reevaluate dose adjustment for renal impairment (98).

(iii) Other populations. *(a) Immunocompromised patients*. Most studies conducted in CRE patients (Table 7) included immunocompromised patients, such as organ transplant recipients (13% to 50% of patients included) and patients with malignancy (14% to 100% of included patients). Very few data are available for the outcomes specifically in these populations.

(b) Elderly patients. Clinical cures among older adults (aged 65 years and older) were similar between CAZ-AVI and comparator in 3 RCTs for 576 patients (79, 85, 86).

CAZ-AVI for specific bacteria. (i) *Burkholderia cepacia* complex. Several case reports described the favorable clinical response to a CAZ-AVI-containing regimen in the treatment of infections caused by *B. cepacia* complex. These include one case report in a 2-month-old infant with *B. cepacia* bacteremia (99) and several cases of lung transplant and cystic fibrosis patients with *B. cepacia* serious infections (100–104). In an *in vitro* study, CAZ-AVI was demonstrated to have greater activity specifically against *Burkholderia multivorans* than ceftazidime (MIC_{90} values of 4 and 16 mg/liter, respectively). In this study, XDR *Burkholderia* strains were susceptible to CAZ-AVI in 22% of cases (inhibited by ≤4 mg/liter of the drug). CAZ-AVI was less active against *Burkholderia gladioli* than against *B. cepacia*. (105).

(ii) *In vitro* data regarding other bacteria. *(a) Mycobacteria*. In an *in vitro* model, CAZ-AVI was demonstrated to be effective against *Mycobacterium avium* at concentrations achievable by using clinical doses. The MIC of ceftazidime in the presence of avibactam was 16 mg/liter with the broth microdilution method (106). These findings were supported by an *in vitro* study showing favorable kill rates with a CAZ-AVI-based regimen. The drug achieved high intracellular penetration with intracellular concentrations above the MIC throughout the dosing interval (107). In addition, potential *in vitro* activity was also demonstrated for *Mycobacterium tuberculosis*. In a study using drug-

resistant *M. tuberculosis* isolates, the MICs of 96% of 25 isolates were below CAZ-AVI peak concentrations, achieved at standard doses (108).

(b) Others. A recent study tested the *in vitro* activity of several BLBLIs against *Burkholderia*, *Achromobacter*, *and Stenotrophomonas* strains, most of them isolated from respiratory specimens collected from cystic fibrosis patients. CAZ-AVI was demonstrated to have activity (MIC_{50} of 8 mg/liter; MIC_{90} of 32 mg/liter) against *Achromobacter* spp., with 78% of isolates susceptible to the drug according to CLSI breakpoints for *P. aeruginosa*; *in vitro* activity was also demonstrated against *S. maltophilia*, with 40% of isolates susceptible according to same breakpoints (105).

Safety data. As mentioned above, no significant difference in rates of any adverse events in general was demonstrated between CAZ-AVI and comparators in RCTs. Specifically, gastrointestinal AEs (~20% of patients) and increase in creatinine (~2%) were significantly more common with CAZ-AVI than with carbapenems. Other AEs reported included pyrexia, peripheral edema, hypersensitivity reactions, and neurological AEs, each in ~3% to 6% of patients receiving CAZ-AVI. Sternbach et al. described higher rates of SAEs with CAZ-AVI in a meta-analysis of RCTs (80). Unfortunately, these SAEs are not described in detail in the trials. In nonrandomized studies, AEs were not comprehensively reported, and overall acute kidney injury (AKI) was reported in up to 5% of patients; other reported AEs were mainly gastrointestinal and neurological AEs, with sporadic cases of rash, leukopenia, and abnormal liver function.

Emergence of resistance to CAZ-AVI during treatment. Two RCTs reported ≥4-fold increase in the MIC to CAZ-AVI during treatment in persistent *Enterobacterales* and *P. aeruginosa* strains between baseline and TOC. Wagenlehner et al. reported an MIC increase (≥4-fold from baseline) in 8/393 isolates (2%) (86); Torres et al. reported a similar increase in 2/125 isolates (1.6%) (87). Several case reports have also described the emergence of CAZ-AVI resistance during therapy. Shields et al. reported resistance emergence (MIC > 8 mg/liter) within a median of 15 days (range, 10 to 19) of treatment in 3/10 (30%) patients among those treated with CAZ-AVI and experiencing microbiological failure (74). In another publication, Shields et al. (68) reported 3 cases of CAZ-AVI-resistant *K. pneumoniae*, cultured following CAZ-AVI treatment of 10 to 19 days. Performing whole-genome sequencing (WGS) on these isolates revealed new mutations in plasmid-borne bla_{KPC-3} (68).

Another case report of a single patient showed mixed subpopulations of CAZ-AVI resistant KPC *K. pneumoniae* emerging following CAZ-AVI treatment (56). Though most cases of resistance to CAZ-AVI were described in *K. pneumoniae* sequence type 258 (ST258) bla_{KPC-3}-producing isolates, resistance has also been reported in bla_{KPC-2} isolates, in other sequence types, with various mechanisms, and even without exposure to CAZ-AVI (52, 55). Iannaccone et al. (109) reported 23 bacteremia cases of KPC *K. pneumoniae* treated with CAZ-AVI. Four cases had relapse of bacteremia: two of them with a CAZ-AVI-resistant isolate, one with an MIC increase from 2 to 8 μg/ml, and one without relevant MIC variation. This corresponded to an incidence of 8.7% (2/23) for CAZ-AVI resistance (109).

Future clinical studies evaluating CAZ-AVI. No RCTs evaluated the use of CAZ-AVI versus BAT for CRE or carbapenem-resistant *P. aeruginosa* infections. Available data are limited by study design, selection bias, and common use of combination therapy. Currently, no RCTs are listed in ClinicalTrials.gov for CAZ-AVI. One listed retrospective study aims to compare CAZ-AVI versus BAT for CRE infections in adults. The study plans to include 344 patients and is currently recruiting patients (110). Since RCTs are unlikely to be performed, large observational studies are needed to fully describe efficacy of CAZ-AVI monotherapy, SAEs caused by the drug, and rates of resistance emergence during/following therapy.

CEFTOLOZANE-TAZOBACTAM

Spectrum of Activity

The combination of antipseudomonal cephalosporin-β-lactamase inhibitor ceftolozane-tazobactam (TOL-TAZ) is active against common Gram-negative pathogens. It has doc-

umented activity against ESBL-producing *Enterobacterales*, including *E. coli* carrying CTX-M-14 and CTX-M-15, MDR *P. aeruginosa*, as well as some anaerobes (*Bacteroides fragilis* and non-*Bacteroides* Gram negatives) and some *Streptococcus* spp. (111–121). However, TOL-TAZ has limited activity against ESBL-producing *K. pneumoniae*, carbapenemase-producing *Enterobacterales*, and anaerobic Gram-positive cocci (1, 5, 7, 11, 13–16) (Table 4).

Looking in more detail at specific bacterial targets, TOL-TAZ has shown particularly high activity against *P. aeruginosa*. Ceftolozane enhanced affinity for the PBPs of the *P. aeruginosa*; thus, it is significantly less affected by the changes in the porin permeability or efflux pumps (122). Data collected in the United States between 2011 and 2014 reported up to 97% susceptibility to TOL-TAZ in *P. aeruginosa*, including MDR and carbapenem nonsusceptible strains (111, 123). Equivalent data were reported from the United States between 2015 and 2017, showing 97.5% susceptibility in *P. aeruginosa* ($MIC_{50/90}$, 0.5/2 mg/liter), including MDR (82.8% susceptible to TOL-TAZ) and XDR (82.9% susceptible) isolates (124). Previous susceptibility rates are consistent with the results from the Asia-Pacific region and Canada, where the highest susceptibility to TOL-TAZ was in *P. aeruginosa* and *Enterobacterales*, including MDR and XDR isolates, and the combination had limited activity against bacteria with a CRE phenotype (125, 126). Sader et al. reported slightly diminished overall susceptibility rates in *P. aeruginosa* isolates from Europe, 86.3% (at ≤8 mg/liter) and 84.5% (≤4 mg/liter), respectively (114). However, in a recent Spanish nationwide study, 94.6% from *P. aeruginosa* were susceptible to TOL-TAZ ($MIC_{50/90}$ = 1/2 mg/liter) (6). Also, a subsequent study from Shortridge et al. reported data about more than 6,000 Gram-negative isolates collected from pediatric patients in Europe and the United States, where susceptibility to TOL-TAZ was 94.6% and 97.4% of *Enterobacterales* and *P. aeruginosa* isolates, respectively (127).

A study by Tato et al. (115) showed that TOL-TAZ was highly active not only against MDR *P. aeruginosa* but also against *E. coli*, including wild-type, AmpC-like phenotype, and ESBL-producing isolates. The activity was diminished against ESBL-producing *Klebsiella* spp. ($MIC_{50/90}$, 4/16 mg/liter) and the combination was not active against carbapenemase-producing bacteria (MIC ≥ 64 mg/liter) (115). Analyzing *E. coli* and *Proteus mirabilis* strains collected in China in 2017, the rates of susceptibility to TOL-TAZ reached 90.5% and 93.8%, respectively. However, in the case of carbapenem-resistant *P. aeruginosa*, the sensitivity was 68%, falling to 57.7% in *K. pneumoniae* and 1.9% in CRE isolates (128). Pazzini et al. (129) reported similar data: TOL-TAZ was active against 85% of ESBL-producing *E.coli* in contrast to 57.5% of ESBL-producing *K. pneumoniae*, but the majority of carbapenemase-producing Gram negatives (99.0%) were not susceptible to TOL-TAZ (129). Recent susceptibility data reported from Portugal showed TOL-TAZ activity against 86.6% of *Enterobacterales*, including 99.4% of *E. coli*. The rates were falling to 71.5% in *Klebsiella* spp. and 70.4% in *Enterobacter* spp. The decreased susceptibility was mostly due to the ESBL- and carbapenemase-producing phenotypes (120). EUCAST, FDA, and CLSI breakpoints for the interpretation of the susceptibility of particular pathogens to TOL-TAZ are summarized in Table 2. For antimicrobial susceptibility data of various pathogens to TOL-TAZ, see Table 4.

Resistance Rates and Mechanisms

Various TOL-TAZ resistance mechanisms have been described, predominantly overexpression and mutations in the Ambler class C β-lactamase. *P. aeruginosa* produces a chromosomally encoded class C cephalosporinase (*Pseudomonas*-derived cephalosporinase [PDC]) often responsible for the resistance to β-lactam antibiotics; but usually, PDCs are not efficient at hydrolyzing ceftolozane. Unlike tazobactam, ceftolozane inhibits PBPs, allowing tazobactam to target other serine β-lactamases (e.g., TEM-1) and ESBLs (e.g., CTX-M-15). Nevertheless, due to the emerging tendency in the acquisition of amino acid substitutions, PDCs can hydrolyze ceftolozane (130–134). In a study assessing the contribution of residues (V213, G216, E221, and Y223) in PDC-3 toward ceftolozane-tazobactam resistance, the E221K variant acquired an ability to efficiently

hydrolyze ceftolozane causing alarming resistance (133). Already in 2014, a study by Cabot et al. reported the development of high-level resistance to the TOL-TAZ due to overexpression and structural modifications of AmpC; however, it occurred only in a *P. aeruginosa* with mutator (PAOMS, Δ*mutS*) background (135). Meanwhile, in a study by Sader et al. the majority of TOL-TAZ-resistant isolates carried a VIM-type MBL gene (114).

Assessing the emerging resistance following the exposure to TOL-TAZ, a study by Haidar et al. (130) reported that resistance developed in 14% (3/21) of cases due to the *de novo* mutations, AmpC overexpression, and amino acid substitutions affecting the β-lactamase Ω-loop. Resistance in the respective cases emerged on days 8 and 19 under the treatment and 2 weeks after completion of a 30-day treatment course, respectively (130). Skoglund et al. (131) reported a case where TOL-TAZ resistance in *P. aeruginosa* PA2428 developed without previous TOL-TAZ exposure. The patient had received antimicrobial therapy with ceftazidime, cefepime, meropenem, amikacin, and finally aztreonam but not particularly TOL-TAZ before the resistant isolate was cultured (131). Meanwhile, data from Spain showed that 10.6% (5/47) of the patients developed resistance during the treatment of MDR *P. aeruginosa* infections with TOL-TAZ. The resistant strains were ST175 and ST179, and the underlying mechanisms for the resistance were a modification of AmpC and horizontally acquired β-lactamases in ST175 and the emergence of the extended-spectrum OXA β-lactamase OXA-14 in ST179 (132). A similar percentage was reported in a study by Jorgensen at al.: TOL-TAZ resistance was detected in 9.7% (3/31) of MDR *P. aeruginosa* after 3, 7 and 8 days after the initiation of monotherapy with TOL-TAZ (136). However, in a recent case series report by Buonomo et al., including four adult patients with *P. aeruginosa* infection, there were no cases with the emergence of the resistance registered during the therapy with TOL-TAZ (137). Nevertheless, the number of cases was limited; therefore, additional studies and surveillance of the emerging resistance following the exposure to TOL-TAZ are needed.

PK-PD Characteristics

The pairing of ceftolozane with tazobactam illustrates the feasibility of combining a β-lactam and β-lactamase inhibitor that are not perfectly matched pharmacokinetically. Ceftolozane and tazobactam share similar protein binding values (as summarized in Table 5) but differ in half-life and metabolic disposition. Ceftolozane is excreted unchanged, and less than 20% of tazobactam is metabolized to an inactive M1 metabolite. Unmetabolized tazobactam, the M1 metabolite, and ceftolozane are all excreted renally (4, 138). Similar to that for avibactam, preclinical studies identified the duration of time above a threshold value ($\%T_{>\text{threshold}}$) as the PK-PD index that best described the activity of tazobactam when it was administered in combination with ceftolozane.

In vitro hollow-fiber studies illustrated the dependence of $\%T_{>\text{threshold}}$ on the degree of β-lactamase expression; high expression of CTX-M-15 was associated with a higher threshold value for suppression of bacterial growth (4). PK-PD data from a neutropenic murine thigh infection model was used to identify a threshold value of 1 μg/ml in a collection of β-lactamase-producing *K. pneumoniae* and *E. coli*. A target of 65.6% T of >1 μg/ml was used for PTA analysis. Consistent with other β-lactams, $\%T_{>\text{MIC}}$ was identified as the index that best correlated with antimicrobial activity of ceftolozane against non-β-lactamase-producing *Enterobacterales* and *P. aeruginosa*. A plasma target of 32.2% associated with a 1-$\log_{10}$ CFU decrease was initially proposed for PTA analysis; however, final analysis relied on a more conservative target of 40% $T_{>\text{MIC}}$ associated with 2-$\log_{10}$ CFU reduction (4, 138).

For cUTI and cIAI indications, the approved dosing regimen is 1 g ceftolozane and 0.5 g tazobactam administered every 8 h as a 1-h i.v. infusion. (138) A higher dose of 2 g ceftolozane and 1 g tazobactam is indicated for the treatment of hospital-acquired bacterial pneumonia/ventilator-associated pneumonia (HABP/VABP) to account for the lower exposures of ceftolozane and tazobactam observed in the epithelial lining fluid

(ELF) than in plasma. As with ceftazidime-avibactam, the dosage adjustments required in patients with renal impairment (CrCL ≤ 50 ml/min) are consistent with the predominant renal elimination of the combination. While there are no formalized dosing recommendations in children, dose selection based on matching pediatric exposures to adult exposures in approved doses suggest that for cIAI and cUTI, children ≥12 years old may receive the approved adult dose (139). For pediatric patients aged <12 years, 20 mg/kg body weight ceftolozane and 10 mg/kg tazobactam administered as a 1-h infusion every 8 h is proposed for the phase 2 trials.

Clinical Data

Approval date and indications. TOL-TAZ is EMA and FDA approved. It was first approved by FDA in 2014 for use in adults with cIAI (in combination with metronidazole) and cUTI, including pyelonephritis. The dosage approved for these indications was 1.5 g every 8 h. It was later approved in 2019 for the treatment of adults with HABP/VABP at a dosage of 3 g every 8 h. It has not yet been approved for use in pediatric patients (138).

Randomized controlled trials evaluating TOL-TAZ for any infection. See Table 8 for a data summary from RCTs. To date, four RCTs have been published comparing TOL-TAZ versus other regimens, including versus meropenem for nosocomial pneumonia (140) and cIAI (141, 142) and versus levofloxacin for cUTI (143).

A meta-analysis by Cheng et al. (144) compiled three RCTs evaluating TOL-TAZ for cUTI or cIAI, including, overall, 2,198 patients. Clinical cures at TOC and microbiological responses were similar between study arms. Specifically, in the cUTI trial, higher microbiological response rates with TOL-TAZ were demonstrated. Nevertheless, addressing separately the Gram-positive pathogens, TOL-TAZ had a significantly lower eradication rate. No significant difference between groups was demonstrated in AEs, including SAEs and those resulting in discontinuation of the study drug (144).

An additional RCT evaluated TOL-TAZ versus meropenem for the treatment of nosocomial pneumonia (726 patients). No significant difference between study arms was demonstrated for any of the efficacy and safety outcomes, though SAEs were nonsignificantly more common with TOL-TAZ (42.1% versus 35.9%). This trial used a high dose of TOL-TAZ (3 g every 8 h compared to 1.5 g every 8 h administered in other trials). Most common AEs in this study included gastrointestinal adverse events (2%), abnormal liver function tests (5%), and *Clostridioides difficile* infection (2%) (140). No significant difference in SAEs was demonstrated in the other three RCTs described above, using the dose of 1.5 g every 8 h (141–143) (see Table 9 for dosages of new BLBLIs).

Clinical data on the efficacy of TOL-TAZ for infections caused by specific pathogens. (i) *Pseudomonas aeruginosa*. Twelve studies reported data on the efficacy of TOL-TAZ in *P. aeruginosa* infections (see Table 10), two were comparative versus polymyxin or aminoglycoside for XDR *P. aeruginosa* infections (145, 146). Overall, in these studies, mortality was 17.6% (110/624): 20.1% among MDR/XDR infected patients (105/523). Clinical and microbiological success rates were 76.6% (477/623) and 75.6% (480/635), respectively, for any *P. aeruginosa*, and 73.4% (380/512) and 74.2% (370/508), respectively, among MDR/XDR infected patients.

All these studies included patients treated with a dose of either 1.5 g every 8 h or 3 g every 8 h, with the high dose usually administered for cases of pneumonia, osteomyelitis, and abscess. Gallagher et al. reported the use of high-dose (3 g every 8 h) TOL-TAZ in 97/205 patients, without improved outcomes among these patients (147).

(ii) Extended spectrum β-lactamase *Enterobacterales*. Three RCTs comparing TOL-TAZ versus meropenem did not report a difference in clinical cure between trial arms for patients with ESBL infections. In one trial evaluating TOL-TAZ versus levofloxacin for cUTI, clinical cure rates were higher with TOL-TAZ (143). Huntington et al. (148) performed a *post hoc* analysis of data from this RCT. This analysis included 212 patients with levofloxacin-resistant pathogens at baseline; 186 had *Enterobacterales* infection,

TABLE 8 Randomized controlled trials assessing TOL-TAZ efficacy outcomes

Trial ID (reference)	Comparator[a]	Phase	Design[b]	No. randomized	Indication[c]	Exclusion of immunocompromised patients	Outcomes[d]	
							No. (%) interventions vs control	Risk difference (95% CIs)
Kollef 2019 (140)	Mero	3	NI	726	NP	Organ transplant; HIV (CD4 <200/mm^3); Immunosuppressive therapy; neutropenia	Mortality: 87/362 (24.0) vs 92/364 (25.3)	1.1 (−5.1 to 7.4)
							Clinical cure TOC: 197/362 (54.4) vs 194/364 (53.3)	1.1 (−6.2 to 8.3)
							Microbiol response TOC: 193/264 (73.1) vs 168/247 (68.0)	4.5 (−3.4 to 12.5)
Lucasti 2014 (141)	Mero	2	Noninferential	122	cIAI	Immunocompromising illness; neutropenia <1,000/mm^3	Mortality: 3/61 vs 0/25	
							Clinical cure TOC: 51/61 (83.6) vs 24/25 (96.0)	−12.4 (−34.9 to 11.1)
							Microbiol response TOC: 48/53 (90.6) vs 23/24 (95.8)	
Solomkin 2015 (142)	Mero	3	NI	993	cIAI	No	Mortality: 11/482 (2.3) vs 8/497 (1.6)	
							Clinical cure TOC: 323/389 (83.0) vs 364/417 (87.3)	
Wagenlehner 2015 (143)	Levo	3	NI	1,083	cUTI	Organ transplant; AIDS; chemotherapy; immunosuppressive therapy; neutropenia <500/mm^3	Mortality: 1/543 vs 0/540	
							Clinical cure TOC: 366/398 (92.0) vs 356/402 (88.6)	3.4 (−0.7 to 7.6)
							Microbiol response TOC: 320/398 (80.4) vs 290/402 (72.1)	8.3 (2.4 to 14.1)

[a]Mero, meropenem; Levo, levofloxacin.
[b]NI, noninferiority.
[c]cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; NP, nosocomial pneumonia.
[d]CI, confidence intervals; TOC, test of cure; microbiol, microbiological.

TABLE 9 Novel β-lactam β-lactamase inhibitor dosages for adults[a]

Estimated CrCL (ml/min) or eGFR ml/min/1.73m²)[b]	Dosage for: Ceftazidime-avibactam (2-h infusion)	Ceftolozane-tazobactam (1-h infusion)[c]	Meropenem-vaborbactam (3-h infusion)	Imipenem-relebactam-cilastatin (0.5-h infusion)
≥90	2.5 g (2 g-0.5 g) × 3/day	cUTI/cIAI: 1.5 g (1 g-0.5 g) × 3/day HABP/VABP: 3 g × 3/day	4 g (2 g-2 g) × 3/day	1.25 g (500 mg-200 mg-500 mg) × 4/day
50–89	2.5 g × 3/day	cUTI/cIAI: 1.5 g × 3 days HABP/VABP: 3 g × 3/day	4 g (2 g-2 g) × 3/day	1 g (400 mg-400 mg-200 mg) × 4/day for CrCL ≥60 ml/min
30–49	1.25 g (1 g-0.25 g) × 3/day	cUTI/cIAI: 750 mg (500 mg-250 mg) × 3/day HABP/VABP: 1.5 g × 3/day	2 g (1 g-1 g) × 3/day	0.75 g (300 mg-300 mg-150 mg) × 4/day for CrCL <60 ml/min
15–29	0.94 g (0.75 g-0.19 g) × 2/day	cUTI/cIAI: 375 mg (250 mg-125 mg) × 3/day HABP/VABP: 750 mg × 3/day	2 g (1 g-g) × 2/day	0.5 g (200 mg-200 mg-100 mg) × 4/day
End stage renal disease on hemodialysis for CrCL of:		cUTI/cIAI: loading dose of 750 mg, followed by 150 mg (100 mg-50 mg) × 3/day	1 g (0.5 g-0.5 g) × 2/day[d]	0.5 g (200 mg-200 mg-100 mg) × 4/day[d]
6–15	0.94 g (0.75 g-0.19 g) × 1/day	HABP/VABP: loading dose of 2.25 g (1.5 g-0.75 g), followed by 450 mg (300 mg-150 mg) × 3/day[d]		
≤5	0.94 g (0.75 g-0.19 g) every 48 h[d]			

[a]Adopted from relevant FDA labels, see these labels for pediatric dosages (76, 138, 187, 222).
[b]Creatinine clearance (CrCL) calculated for ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam-cilastatin according to Cockroft-Gault formula, and estimated glomerular filtration rate (eGFR) calculated for meropenem-vaborbactam according to the Modification of Diet in Renal Disease (MDRD) formula.
[c]cUTI/cIAI, complicated urinary tract infection and complicated intra-abdominal infection; HABP/VABP, hospital-acquired and ventilator-associated bacterial pneumonia.
[d]Administered after hemodialysis on hemodialysis days.

TABLE 10 Studies evaluating ceftolozane-tazobactam for *P. aeruginosa* infections

Study ID; main pathogen (reference)	Design[a]	No. included (p/i)[b]	No. and source(s) of infection[c]	No. of *P. aeruginosa* isolates by type	No. of *P. aeruginosa* isolates by susceptibility[d]	No. of isolates with combination treatment	Outcomes (no. [%])[e]
Miller 2016; any *P. aeruginosa* (319)	*Post hoc* analysis of RCT (142) (C-T + M vs Mero)	26 p C-T, 29 p Mero	IAI	26 i C-T, 29 i Mero	MDR, 3 i Mero arm	No	Clinical cure TOC: C-T, 26/26 (100); Mero, 27/29 (93.1)
Caston 2017; MDR *P. aeruginosa* (164)	Case series, salvage therapy with C-T	12 p	6 LRTI, 5 BSI, 3 IAI, 3 others		MDR	NS[f]	Mortality: 3/12 (25) Clinical cure 30 days: 9/12 (75) Microbiol cure 30 days: 7/12 (58.3)
Dinh 2017; XDR *P. aeruginosa* (320)	Case series, salvage therapy with C-T	15 p (14 adults, 1 child)	7 LRTI, 3 UTI, 2 IAI, 3 others		XDR	10	Mortality: 4/15 (27) Clinical cure EOT: 10/15 (67) Microbiol cure EOT: 6/8 (75)
Haidar 2017; MDR *P. aeruginosa* (130)	Retrospective study	21 p	18 LRTI, 1 BSI, 1 UTI, 1 IAI		MDR, 15 XDR	16	Mortality: 2/21 (10) Clinical success 90 days: 15/21 (71.4)
Munita 2017; CR *P. aeruginosa* (321)	Retrospective study	35 p	18 LRTI, 6 BSI		CR	8	Mortality: 8/35 (22.3) Clinical success in hospital: 26/35 (74) Microbiol success in hospital: 25/25
Diaz-Cañestro 2018; MDR XDR *P. aeruginosa* (165)	Prospective observational study	58 p	35 LRTI, 10 UTI, 4 IAI, 6 other, 3 BSI		6 MDR, 50 XDR	37	Mortality: 16/58 (27.6) Clinical cure 7 days: 37/58 (63.8) Microbiol cure 7 days: 21/30 (70)
Escola-Verge 2018; XDR *P. aeruginosa* (166)	Retrospective study	38 p	14 LRTI, 6 UTI, 6 SSTI, 4 IAI, 8 other, 11 BSI		XDR	24	Mortality: 5/38 (13.2) Clinical response EOT: 33/38 (86.8); 90 days, 26/38 (68.4) Microbiol cure 90 days: 26/38 (68.4)
Gallagher 2018; MDR *P. aeruginosa* (147)	Retrospective	205 p	121 LRTI, 28 UTI, 20 IAI, 25 BSI, 42 others	205 p	205 MDR (96.8% CR)	81	Mortality: 39/205 (19) Clinical success EOT: 151/205 (73.7) Microbiol cure EOT: 145/205 (70.7)
Xipell 2018; MDR *P. aeruginosa* (163)	Case series, salvage therapy with C-T	23 p, 24 e	8 LRTI, 7 UTI, 6 SSTI, 3 IAI		4 MDR, 19 XDR, 1 PDR	16	Mortality: 5/23 (22) Clinical cure: 21/24 (88) Microbiol cure: 12/16
Bassetti 2019; Any *P. aeruginosa* (158)	Retrospective study	101 p	32 LRTI, 21 SSTI, 14 UTI, 13 IAI, 6 other, 22 BSI		30 non-MDR, 18 MDR, 51 XDR, 2 PDR	36	Mortality: 5/101 (5) Clinical success EOT: 84/101 (83.2)

(Continued on next page)

TABLE 10 (Continued)

Study ID; main pathogen (reference)	Design[a]	No. included (p/i)[b]	No. and source(s) of infection[c]	No. of *P. aeruginosa* isolates by type	No. of *P. aeruginosa* isolates by susceptibility[d]	No. of isolates with combination treatment	Outcomes (no. [%])[e]
Pogue 2019; MDR/XDR *P. aeruginosa* (145)	Retrospective comparative study	200 p: 100 p C-T, 100 p polymyxin or aminoglycoside-based regimen	C-A: 64 LRTI, 16 UTI, 13 SSTI, 7 other, 6 BSI; comp: 75 LRTI, 11 UTI, 6 SSTI, 6 other, 6 BSI		MDR XDR	15	Mortality: C-T, 20/100 (20); comp, 25/100 (25) Clinical cure on therapy: C-T, 81/100 (81); comp, 61/100 (61)
Vena 2019; MDR/XDR *P. aeruginosa* (146)	Case control	48 p: 16 p C-T, 32 p colistin/aminoglycoside	27 LRTI, 21 BSI		30 MDR, 18 XDR	9 C-T, 29 comp	Mortality: C-T, 3/16 (18.8%); comp, 9/32 (28.1) Clinical cure 14 days: C-T, 13/16 (81.3), comp, 18/32 (56.3)

[a]RCT, randomized controlled trial; M, metronidazole; Mero, meropenem; C-T, ceftolozane-tazobactam.
[b]p, patients; i, isolate; e, episode.
[c]IAI, intra-abdominal infection; LRTI, lower respiratory tract infection; BSI, bloodstream infection; UTI, urinary tract infection; SSTI, skin and soft tissue infection; comp, comparator.
[d]MDR, multidrug resistant; XDR, extensively drug resistant; CR, carbapenem resistant; PDR, pandrug resistance.
[e]Microbiol, microbiological; TOC, test of cure; EOT, end of treatment.
[f]NS, nonspecified.

and 85 were ESBL positive. Among patients with ESBL infection, both clinical and microbiological cure rates were significantly higher in the TOL-TAZ arm (148) (for details see Table 11).

Two additional studies were noncomparative prospective interventional studies, aiming to evaluate the efficacy and safety of TOL-TAZ for the treatment of cUTI (149) and cIAI (150). Overall, 18 patients with ESBL infection were included, with no mortality cases. All 5 patients with cIAI had clinical and microbiological response. Five of 13 (38.5%) patients with cUTI had microbiological response; this rate was low, at approximately one-half of that of non-ESBL infections (Table 11).

Clinical use of TOL-TAZ in special patient populations. (i) Pediatric population. To date, only one phase 1 study was published evaluating the safety of TOL-TAZ in pediatric patients. This study included 37 children in various age groups and showed no mortality cases, no serious clinical adverse events, and no clinically significant laboratory abnormalities (151). Two phase 2 trials in children are ongoing and currently recruiting patients. One trial aims to compare TOL-TAZ with meropenem for treatment of cUTI in 120 children (152), the other will compare TOL-TAZ plus metronidazole versus meropenem for an additional 120 children with cIAI (153). In addition, few case reports have described successful clinical use of TOL-TAZ in children with *P. aeruginosa* infections (154–156).

(ii) Chronic renal failure. Patients with severe impairment of renal function were excluded from RCTs evaluating TOL-TAZ. Kullar et al. (157) summarized data on patients with moderate renal impairment (CrCL 30 to 50 ml/min) from RCTs by Solomkin et al. (142) (36 patients) and Wagenlehner et al. (59 patients) (143). In both trials, moderate renal impairment, age $\geq$65 years, and diabetes mellitus were risk factors for clinical failure. Patients with moderate renal impairment in the cIAI trial (142) but not the cUTI trial (143) had lower clinical response rates with TOL-TAZ (48% [11/23]) than with meropenem (69% [9/13]). Dosage of TOL-TAZ for moderate renal impairment in this trial was 750 mg every 8 h.

Kollef et al. (140) reported similar clinical cure rates between TOL-TAZ and comparator in the subgroup of patients with reduced renal clearance, though a trend for lower clinical response is reported for moderate-severe renal impairment (38.4% TOL-TAZ versus 44.6% meropenem) (140).

Bassetti et al. (158) reported retrospectively the results of 101 patients treated with TOL-TAZ for different *P. aeruginosa* infections, mainly, nosocomial pneumonia and skin and soft tissue infections. Multivariate analysis of risk factors for clinical failure demonstrated chronic renal replacement therapy (CRRT), in addition to sepsis, as a risk factor for failure. The TOL-TAZ dosage used for CRRT patients was 1.5 g every 8 h. The authors suggested considering therapeutic drug monitoring in this setting (158). Other suggested solutions for CRRT patients are raising the dosage to 3 g every 8 h (159) or using continuous infusion of 6 g in 24 h (160).

(iii) Diabetes mellitus. Popejoy et al. (161) reported outcomes of 245 diabetic patients compared to 1,802 nondiabetic patients from two RCTs (142, 143). Patients with diabetes had lower clinical response overall; however, no difference between TOL-TAZ and comparator was demonstrated (161).

(iv) Immunocompromised. RCTs and prospective studies evaluating TOL-TAZ did not include immunocompromised patients. All the retrospective studies (Tables 10 and 11) reported on including immunocompromised patients (transplant recipients, 8% to 43% of included patients; patients with malignancy or other immunosuppression, 10% to 34% of included patients); however, few reported outcomes for these patients specifically.

(v) Elderly patients. Three RCTs reported outcomes for 639 elderly patients, none of them demonstrating a significant difference in clinical cure rates between TOL-TAZ and comparator (140, 142, 143). As described above, Kullar et al. reported higher risk for clinical failure in patients aged 65 years and older treated with TOL-TAZ for cUTI or cIAI (157).

TABLE 11 Studies evaluating ceftolozane-tazobactam for *Enterobacterales* infections

Study ID; main pathogen tested (reference)[a]	Design[b]	No. included (p/i)[c]	Source of infection[d]	No. of isolates by type	No. of isolates by susceptibility	Combination treatment?	Outcomes (no. [%])[e]
Huntington 2016; Levo[r] pathogens (148)	*Post hoc* analysis of RCT (143) (C-T vs Levo)	212 p, 225 i (mMITT)	212 UTI, 7 BSI	186 *Enterobacterales*, 12 *P. aeruginosa*, 27 Gram positive	212 p Levo nonsusceptible, 85 p ESBL	No	Clinical response TOC: C-T, 90/100 (90.0); comp, 86/112 (76.8) Microbiol response TOC: C-T, 63/100 (63.0); comp, 49/112 (43.8)
Popejoy 2017; ESBL-producing *Enterobacterales* (322)	*Post hoc* analysis of 2 RCTs (142, 143)	150 p, 159 i	UTI: 54 C-T, 46 Levo IAI: 24 C-T, 26 Mero	UTI: *E coli*: 36 C-T, 36 Levo; *K. pneumoniae*: 10 C-T, 7 Levo IAI: *E. coli*: 14 C-T, 20 Levo; *K. pneumoniae*; 8 C-T, 4 Levo	All ESBL	No	Clinical cure TOC: C-T, 76/78 (97.4); Levo, 38/46 (82.6); Mero, 23/26 (88.5) Microbiol cure TOC: C-T, 62/78 (79.5); Levo/Mero, 45/72 (62.5)
Arakawa 2019; ESBL-producing *Enterobacterales* (149)	Nonrandomized single group	Overall 115 p: evaluable, 90 p 94 i	90 UTI, 24 BSI	93 *Enterobacterales*, 1 *P. aeruginosa*,	13/94 ESBL	No	(For all patients) Mortality: 0/114 Clinical response TOC: 86/89 (96.6) Microbiol response TOC: 71/88 (80.7) (For ESBL) Mortality: 0/13 Microbiol response TOC: 5/13 (38.5)
Mikamo 2019; ESBL producing *Enterobacterales* (150)	Nonrandomized single group	Overall 100 p, 130 i	130 i IAI	58 *Enterobacterales*, 9 *P. aeruginosa*, 27 Gram positive, 36 anaerobes	5/130 ESBL	No	(For all patients) Mortality: 1/100 (1) Clinical response TOC: 81/88 (92.0) Microbiol response TOC: 55/61 (90.2) (For ESBL) Mortality: 0/5 Clinical response TOC: 5/5 (100) Microbiol response TOC: 5/5 (100)

[a]Levo[r], levofloxacin resistant; ESBL, extended spectrum β-lactamase.
[b]RCT, randomized controlled trial; C-T, ceftolozane-tazobactam.
[c]p, patients; i, isolates; mMITT, microbiologically modified intention to treat.
[d]UTI, urinary tract infection; BSI, bloodstream infection; IAI, intra-abdominal infection.
[e]Microbiol, microbiological; TOC, test of cure.

Clinical use of TOL-TAZ for specific bacteria. No clinical studies tested TOL-TAZ against *Burkholderia* spp.; however, some *in vitro* data are available.

(i) *In vitro* activity against specific bacteria. TOL-TAZ has good *in vitro* activity against *Burkholderia cepacia* spp., with 89% of the strains susceptible based on CLSI breakpoints for *P. aeruginosa* in one study (105). In the same study, TOL-TAZ was shown to be less active against *B. gladioli* spp., and have some activity against *S. maltophilia*, with an advantage over ceftazidime for this pathogen (105). No advantage over ceftazidime was demonstrated against *Acinetobacter* spp. or *Elizabethkingia* spp. (162).

Safety data. In RCTs assessing TOL-TAZ, rates of AEs in general were similar between TOL-TAZ and the comparator. Most common AEs included gastrointestinal AEs, *C. difficile* infection, headaches, pyrexia, and abnormal liver function tests. In the only trial using high-dose TOL-TAZ for pneumonia (3 g every 8 h), there was a trend for higher rate of SAEs (140).

In two prospective studies using usual dose of TOL-TAZ (1.5 g every 8 h), any AEs were reported in 58% to 62%, and drug-related AEs were reported in 17.5% to 19%. Most common AEs were gastrointestinal events, insomnia, and abnormal liver function tests (149, 150).

Pogue et al. (145) reported use of high-dose TOL-TAZ in 63% of 100 patients with MDR/XDR *P. aeruginosa* infections. Safety data were not separately addressed; however, among clinical outcomes, six cases of acute kidney injury and four cases of *C. difficile* infection during therapy were reported (145). Bassetti et al. (158) reported, overall, three drug-related AEs (ash, gastrointestinal symptoms, and liver function test abnormalities) among 101 patients; ~30% of them received high-dose TOL-TAZ.

Emergence of resistance to TOL-TAZ during treatment. RCTs evaluating TOL-TAZ reported baseline resistance to TOL-TAZ, but none tested for emergence of resistance. Several nonrandomized studies reported resistance development during or after TOL-TAZ therapy, with various rates. Among 101 patients treated with TOL-TAZ for various *P. aeruginosa* infections, TOL-TAZ resistance was detected in 3 patients (3.0%) during or following treatment (158). Xipell et al. demonstrated similar rates with 1 of 23 patients developing a resistant strain (163). In contrast, other studies reported higher rates of resistance emergence during or in subsequent cultures, up to 11% to 17% (130, 164–166). Mutations leading to such resistance involved overexpression or structural modification of AmpC (including T96I, E247K, and Ω-loop deletions, amino acid replacement in residue E247 [E247G], and F147L mutation) or involved the OXA-10 enzyme (132, 165). Factors suggested to be associated with selection of resistant strains include time above MIC of 10% to 30%, clinical failure, and microbiological failure (163, 165).

Future clinical studies evaluating TOL-TAZ. In addition to two ongoing trials evaluating TOL-TAZ in pediatric populations (152, 153), two other trials are currently recruiting participants. A phase II RCT evaluates TOL-TAZ versus standard therapy as empirical therapy for 100 neutropenic febrile patients (167). Another RCT is planned to recruit 268 patients with cIAI for the comparison of TOL-TAZ plus metronidazole versus meropenem (168). An additional trial was posted on ClinicalTrials.gov in January 2020. This is an open label randomized controlled trial comparing ceftolozane-tazobactam versus meropenem for the treatment of bloodstream infections caused by ESBL- and AmpC-producing *Enterobacterales*. The sample size is calculated at 630 patients and the primary outcome is 30-day mortality (169).

As in the case of CAZ-AVI, data regarding the use of TOL-TAZ for MDR infections are limited by design, selection of patients for treatment with the new drug, and number of patients included. Further observational studies are needed.

MEROPENEM-VABORBACTAM

Spectrum of Activity

Vaborbactam was developed to restore the activity of β-lactams against β-lactamase-producing Gram-negative bacteria, particularly to inactivate *K. pneumoniae* carbapenemases (KPCs). (170) A combination of meropenem-vaborbactam

(MER-VAB) has documented activity against class C β-lactamases, a variety of class A β-lactamases, including CTX-M, SHV, TEM, SME, and NMC-A, KPC-producing isolates, and FRI-1 as well as BKC-1 carbapenemases found in *K. pneumoniae* and *E. cloacae* (170–178). Vaborbactam also restored the activity of meropenem against class A and class C β-lactamase-producing *K. pneumoniae* strains with reduced permeability due to porin mutations. MER-VAB does not inhibit class D (OXA-48) or class B carbapenemases (174–176, 179). The activity of vaborbactam against β-lactamases is summarized in Table 1.

Addressing particular data, in a study by Lapuebla et al. evaluating MER-VAB activity against KPC-producing *Enterobacterales*, the combination inhibited 98.5% (131/133) of isolates at the meropenem concentration of 1 mg/liter (174). It should be noted that in all studies, a fixed vaborbactam concentration of 8 mg/liter was used if not stated differently. A study by Castanheira et al. (171) including 315 serine carbapenemase-producing *Enterobacterales* showed that meropenem alone at ≤1 mg/liter and ≤2 mg/liter inhibited only 2.2% and 7.3% of the bacteria, respectively. The combination (≤2 mg/liter of MER-VAB) inhibited ≥96.5% of the isolates (171).

Data from a study analyzing 10,426 *Enterobacterales* collected worldwide during 2014 showed that MER-VAB inhibited 99.3% of isolates at a meropenem MIC of ≤2 mg/liter (172). In a subsequent study on 11,559 *Enterobacterales* isolates collected during 2015, MER-VAB inhibited 99.3% of all strains and 99.5% of KPC producers at the FDA susceptibility breakpoint of ≤4/8 mg/liter. The combination had limited activity against MBL-producing bacteria (including 49 NDM, 1 IMP-64, and 2 VIM) and/or carbapenem-hydrolyzing class D enzymes (47 OXA-48/-232), which is consistent with the previously reported data (178). In an *in vitro* study by Hackel et al. (180), 99.0% (981/991) of KPC-positive (OXA-48- and MBL-negative) *Enterobacterales* had MER-VAB MICs of ≤4 μg/ml. Vaborbactam lowered the MIC_{90} of meropenem from >32 to 1 mg/liter (180). Kinn et al. (181), assessing *in vitro* activity of MER-VAB against carbapenem-resistant *Enterobacterales* (CRE) isolates, reported that MIC decreased by 128-fold on average compared with that for exposure to meropenem alone. The authors also highlighted that vaborbactam significantly decreased meropenem MIC in both non-KPC-producing and KPC-producing CRE despite that previous studies have demonstrated decreased vaborbactam activity in non-KPC-producing CRE. The authors assume that this finding is due to the absence of NDM and OXA-48 isolates in the study sample population (181).

In a recently published study assessing the activity of MER-VAB against pneumonia-causing bacteria (3,193 *P. aeruginosa* and 4,790 *Enterobacterales*) isolated between 2014 and 2018 from patients in U.S. hospitals, 99.9% of *Enterobacterales* (including CRE) and 89.5% of *P. aeruginosa* were susceptible to MER-VAB (182). Evaluating activity against carbapenem-resistant *Enterobacterales* in an *in vitro* hollow-fiber model during >32-h exposure, MER-VAB (2 g/2 g) showed bactericidal activity against *K. pneumoniae*, *E. cloacae*, and *E. coli* strains, MICs were up to 8 mg/liter (183).

Data from the clinical practice are limited, but in 2019, Athans et al. (184) reported a clinical case of a liver transplant recipient developing bacteremia with a KPC-producing *K. pneumoniae* isolate becoming resistant to CAZ-AVI after 33 days of CAZ-AVI monotherapy; the isolate harbored a D179Y mutant bla_{KPC-2} gene. The infection resolved after treatment with MER-VAB, indicating that this combination could be important under conditions of emerging CAZ-AVI resistance (184). The respective EUCAST-, FDA-, and CLSI-approved breakpoints for the interpretation of the susceptibility of particular pathogens to MER-VAB are summarized in Table 2. For antimicrobial susceptibility data of various pathogens to MER-VAB, see Table 4.

Resistance Rates and Mechanisms

Several studies have reported that the MER-VAB combination is not active against bacteria producing MBL or OXA carbapenemases (174–176). Vaborbactam also lacked the activity against Gram-negative bacteria with porin mutations combined with overexpression of efflux pumps. A decreased potency of vaborbactam against strains

affected by the inactivation of OmpK35 and OmpK36 and strains overexpressing AcrA have been documented (170, 176, 178, 185). In a previously mentioned study by Castanheira et al., MER-VAB-resistant isolates produced MBL (MIC, 16 to ≥64 mg/liter) or had decreased expression of *ompK37* porin and/or hyperexpression of the AcrAB-TolC efflux system (MIC, 16 mg/liter) (171). A study by Lapuebla et al. also identified bacteria resistant to MER-VAB due to diminished OmpK35 and OmpK36 expression, where MICs for MER-VAB were 8- to 16-fold higher than for isolates with the same β-lactamases but without porin changes (174). A surveillance study by Castanheira et al. described increased MER-VAB MIC (>8 mg/liter) in bacteria with a mutation in *ompK35* or harboring bla_{KPC} with $bla_{OXA\text{-}48\text{-}like}$ or $bla_{NDM\text{-}1}$ (186).

PK-PD Characteristics

Both vaborbactam and meropenem display low plasma protein binding (~33% and ~2%, respectively) and comparable volumes of distribution at steady state (V_{ss}) and half-lives (Table 5). Approximately 28% of meropenem is hepatically hydrolyzed to an inactive open lactam metabolite; both the parent and metabolite are excreted renally. Vaborbactam is also excreted unchanged in urine (187, 188).

The PK-PD targets for both meropenem and vaborbactam were defined based on meropenem MICs with a fixed concentration of 8 mg/liter vaborbactam. The magnitude of $\%fT_{>MIC}$ required for maximal meropenem efficacy was determined for KPC-producing *Enterobacterales* as 30% to 45% $fT_{>MIC}$. For vaborbactam, $f\text{AUC}_{0-24}$/MIC was the index identified to describe the inhibitory activity of vaborbactam in preclinical studies against a fixed exposure of meropenem (i.e., the human-equivalent dose of 2 g infused over 3 h every 8 h). A target $f\text{AUC}_{0-24}$/MIC of 38 derived in murine thigh infection models using KPC-producing *Enterobacterales* was subsequently used in PTA analyses to support the proposed dosing and susceptibility breakpoints (14).

While the highest approved dose for meropenem is 1 g every 8 h administered as a 15- to 30- min infusion, a 2-g meropenem dose and a longer duration of infusion (3 h) were evaluated in a PTA analysis and a preclinical hollow-fiber infection model (183). The use of high-dose meropenem delivered over an extended infusion is supported by clinical experience in the treatment of infections due to carbapenem-resistant *Enterobacterales* and other meropenem-resistant strains (14). Consequently, the approved dose for this combination is 2 g each of meropenem and vaborbactam infused over 3 h every 8 h. Renal impairment status was the only intrinsic factor warranting dosage adjustment based on estimated glomerular filtration rate (eGFR; ml/min/1.73 m^2). Currently, there are no recommendations for the use of this combination in pediatrics.

Clinical Data

Approval date and indications. MER-VAB is EMA and FDA approved. It was first approved by FDA in 2017 for use in adults with cUTI, including pyelonephritis. The dosage approved for these indications was 4 g every 8 h. It has not yet been approved for use in pediatric patients (187).

Randomized controlled trials evaluating MER-VAB for any infection. The TANGO I phase 3 RCT randomized 550 adult patients to either MER-VAB or piperacillin-tazobactam (PIP-TAZ) for the treatment of cUTI, including pyelonephritis (189). Patients with severe renal or hepatic impairment, septic shock, or immunosuppression were excluded. Three hundred seventy-four patients were included in the microbiological intention-to-treat population (MITT); 85% of them had *Enterobacterales* as the causative pathogen. For the MITT population, overall success at end of intravenous treatment, defined as clinical cure or improvement and microbial eradication, was 189/192 (98.4%) in the MER-VAB arm versus 171/182 (94.0%) in the PIP-TAZ arm, with a significant advantage to MER-VAB (risk difference [RD], 4.5; 95% confidence interval [CI], 0.7 to 9.1). No significant difference was demonstrated for the outcome of clinical cure alone (RD, 2.8; 95% CI, −0.7 to 7.1). At test of cure, no difference between MER-VAB and PIP-TAZ was demonstrated in either overall success or clinical cure. Microbiological eradication was significantly better with MER-VAB at end of intravenous treatment but not at test

of cure. Subgroup analysis for the outcome of overall success at the end of intravenous treatment showed significantly higher success rates with MER-VAB in patients aged 65 years and older, women, patients without sepsis or bacteremia, and patients with higher Charlson comorbidity scores (≥3).

No difference between MER-VAB and PIP-TAZ was demonstrated for any AEs (106/272 [39.0%] MER-VAB versus 97/273 [35.5%] PIP-TAZ group) or SAEs (11/272 [4.0%] MER-VAB versus 12/273 [4.4%] PIP-TAZ); however, AEs resulting in drug discontinuation were more common with PIP-TAZ (7/272 [2.6%] MER-VAB versus 14/273 [5.1%] PIP-TAZ). Two patients in each group died. Most common AEs with MER-VAB were headache, diarrhea, phlebitis, and abnormal liver function tests (189).

MER-VAB in specific populations. (i) Pediatric population. A phase 1 study for dose finding, pharmacokinetics, and safety of MER-VAB in children with serious bacterial infections is currently ongoing (190). It is planned to enroll 60 patients, who will be receiving a single dose MER-VAB infused over 3 h, at the following dosage regimens: age 12 to <18 years, 40 mg/kg meropenem and 40 mg/kg vaborbactam, or 2 g meropenem 2 g vaborbactam for subjects ≥50 kg in weight; for age 2 to <6 years, 60 mg/kg, or 2 g meropenem 2 g vaborbactam for subjects >33 kg in weight (190).

A single case report described a 4-year-old child with KPC-producing *K. pneumoniae* bacteremia treated with MER-VAB at a dose of 40 mg/kg every 6 h infused over 3 h (191). The patient received this therapy as monotherapy for 14 days with no evidence of treatment emergent adverse events and with good clinical outcome and clearance of bacteremia. The pharmacodynamic target of time above MIC of ≥40% was achieved for 100% of the dosing interval (191).

(ii) Cancer patients. Viale et al. (192) performed a subgroup analysis of 15 cancer patients with CRE infection who were included in the TANGO II trial (193) (MER-VAB versus BAT for suspected CRE infections). Among these patients, 8 patients that were treated with MER-VAB (versus 7 with BAT) had significantly lower mortality, fewer AEs, and higher clinical and microbiological cure rates (192).

Clinical use of MER-VAB for specific bacteria. (i) CRE. The TANGO II phase 3 RCT randomized 77 adult patients with CRE infections to receive either MER-VAB (52 patients [p]) versus BAT (25 p) (193). Patients with confirmed infection due to Ambler class B or D *Enterobacterales* were excluded. The population with a confirmed CRE isolate included 32 MER-VAB patients and 15 BAT patients (most of them treated with various combinations, including 2 to 3 of carbapenem, polymyxin, aminoglycoside, and/or tigecycline). More than one-half of the patients in each group had either bacteremia or cUTI; other included sources were cIAI and HABP/VABP. Thirty four percent of patients in the MER-VAB arm and 53% in the BAT arm were immunocompromised; 22% and 27%, respectively, had baseline CrCLs of <50 ml/min. *K. pneumoniae* was the most common pathogen (87%), mostly KPC-producing species (73%). Clinical cure at EOT and TOC was significantly higher with MER-VAB than with BAT. The microbiological cure was nonsignificantly higher in the MER-VAB group and mortality was nonsignificantly lower (193) (see Table 12).

Subgroup analysis showed improved clinical cure with MER-VAB in patients aged 65 years and older, patients with a Charlson score of ≥4, and immunocompromised patients. Any AEs were less frequent with MER-VAB (42/50 [84.0%] MER-VAB versus 23/25 [92.0%] BAT), and a similar trend was observed for SAEs (17/50 [34.0%] versus 11/25 [44.0%]). Decreased nephrotoxicity was shown with MER-VAB. The most common AEs with MER-VAB were diarrhea, hypotension, anemia, and hypokalemia (193).

Bassetti et al. (194) performed a *post hoc* analysis of this RCT (193), analyzing 22 MER-VAB patients and 15 BAT patients without prior antimicrobial failure. Significantly lower mortality and higher rates of clinical and microbiological cure were demonstrated with MER-VAB (Table 13).

Lai et al. (195) compiled the two TANGO trials (189, 193) in a meta-analysis and found no difference between MER-VAB and comparator for any of the efficacy or safety outcomes. Shields et al. (196) conducted a prospective noncomparative study, using MER-VAB as treatment of choice for 20 consecutive patients with confirmed or sus-

TABLE 12 Randomized trials assessing meropenem-vaborbactam

Trial ID (reference)	Comparator[a]	Phase	Design[b]	No. of patients randomized	Indication[c]	Exclusion of immunocompromised patients	Outcomes[d]	
							No. (%)	Risk difference (95% CIs)
Wunderink 2018 (193)	BAT	3	Noninferential	77	CRE infections: cUTI, cIAI, BSI, or NP	Immunocompromised allowed	Mortality: 1/32 (3.1) vs 5/15 (33.3)	−29.0 (−54.3 to −3.7)
							Clinical cure TOC: 19/32 (59.4) vs 4/15 (26.7)	32.7 (4.6 to 60.8)
							Microbiol cure TOC: 17/32 (53.1) vs 5/15 (33.3)	19.8 (−9.7 to 49.3)
Kaye 2018 (189)	PIP-TAZ	3	NI	550	cUTI	Organ transplant; HIV (CD4 <200/mm$^{3)}$; chemotherapy; immunosuppressive therapy; neutropenia <1,000/mm^3	Mortality: 2/272 (0.7) vs 2/273 (0.7)	
							Clinical cure TOC: 174/192 (90.6) vs 157/182 (86.3)	4.4 (−2.2 to 11.1)
							Microbiol response TOC: 132/192 (68.8) vs 113/182 (62.1)	6.7 (−3.0 to 16.2)

[a]BAT, best available therapy, including monotherapy or any combination of carbapenem, aminoglycoside, polymyxin B, colistin, tigecycline, or ceftazidime-avibactam; PIP-TAZ, piperacillin-tazobactam.
[b]NI, noninferiority.
[c]CRE, carbapenem resistant *Enterobacterales*; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; NP, nosocomial pneumonia; BSI, bloodstream infection.
[d]TOC, test of cure; microbiol, microbiological.

TABLE 13 Nonrandomized trials assessing meropenem-vaborbactam

Study ID; main pathogen tested (reference)	Design	No. included (p/i)[a]	Source of infection[b]	No. of isolates by type	No. of isolates by susceptibility[c]	No. with combination treatment	Outcomes[d]	
							No. (%)	Risk difference (95% CIs)
Bassetti 2019; CRE, patients without prior antimicrobial failure (194)	*Post hoc* analysis of RCT (193)	23 p M-V vs 15 p BAT	M-V: 10 BSI, 9 UTI, 3 LRTI, 1 IAI; BAT: 8 BSI, 4 LRTI, 1 UTI, 2 IAI	*K. pneumoniae*: 22 M-V, 12 BAT; *E. coli*: 2 M-V, 1 BAT; *E. cloacae*: 0 M-V, 2 BAT 2; *P. mirabilis*: 0 M-V, 2 BAT; *S. marcescens*: 1 M-V, 1 BAT	CRE	0	Mortality: M-V 1/23 (4.3) vs BAT 5/15 (33.3)	−29.0 (−54.3 to −3.7)
							Clinical cure TOC: M-V 16/23 (69.6) vs BAT 4/15 (26.7)	42.9 (13.7 to 72.1)
							Microbiol cure TOC: M-V 16/23 (69.6) vs BAT 5/15 (33.3)	36.2 (5.9 to 66.6)
Shields 2019; CRE (196)	Prospective observational study	20 p	8 BSI, 8 LRTI, 4 others	14 *K. pneumoniae*, 2 *K. oxytoca*, 2 *E. coli*, 1 *E. cloacae*, 1 *C. freundii*	18 KPC (10 KPC3, 7 KPC2, 1 KPC31)	4	Mortality: 30 days, 2/20 (10); 90 days, 4/20 (20)	
							Clinical success 30 days: 13/20 (65)	
							Microbiol response ≥7 days: 14/20 (65)	

[a]BAT, best available therapy; M-V, meropenem-vaborbactam; p, patients; i, isolates.
[b]BSI, bloodstream infection; LRTI, lower respiratory tract infection; UTI, urinary tract infection; IAI, intra-abdominal infection.
[c]KPC, *Klebsiella pneumoniae* carbapenemase producing.
[d]TOC, test of cure; CI, confidence interval; microbiol, microbiological.

pected CRE infections. These patents were mostly intensive care unit (ICU) patients (70%), with 35% of them requiring renal replacement therapy at infection onset (6 intermittent hemodialysis, 1 continuous renal replacement therapy [CRRT]). Dosages of the drug used were according to the manufacturer, with 2 g every 8 h administered for CRRT patients. Mortality at 30 and 90 days was 2/20 and 4/20, respectively, clinical cure was 65% at 30 days, and after ≥7 days of treatment, microbiological failure was reported in 6 patients (35%). Higher APACHE II scores were associated with clinical failure. Need for RRT and type of infection did not influence cure rates (196).

A recent case report described an HIV patient with KPC-producing *Serratia marcescens* and *Enterobacter aerogenes* bacteremia. The patient failed treatment with CAZ-AVI and was switched to MER-VAB and also underwent a source control procedure. He was successfully treated with MER-VAB for 14 days and discharged from hospital (197). Kufel et al. (198) reported on a patient with a carbapenem-resistant *K. pneumoniae* prosthetic joint infection who was treated as first line with MER-VAB (2 g over 3 h every 8 h adjusted for CRRT). The patient died after 12 days of MER-VAB therapy, without a source control procedure (198). *In vitro* activity of MER-VAB was demonstrated against *S. marcescens* enzyme (SME)-positive isolates, with bactericidal activity against all four isolates tested (199).

(ii) *In vitro* activity against specific bacteria. MER-VAB has good *in vitro* activity against *Burkholderia* spp., including *B. cepacia* and *B. gladioli*, with most isolates demonstrating MICs below CLSI breakpoints for *P. aeruginosa* in one study. Among BLBLIs, MER-VAB and PIP-TAZ showed the greatest activity against *Achromobacter* spp. (105).

Emergence of resistance to MER-VAB during treatment. Assessing the development of the resistance during exposure to MER-VAB, an *in vitro* study by Sun et al. (200) on 18 KPC-producing *K. pneumoniae* strains reported that after exposure to low drug concentrations, resistance was emerging due to an increase in the bla_{KPC} copy number and *ompK36* inactivation. Thereby, the authors concluded that the development of the resistance to MER-VAB could be prevented by the optimal drug concentrations (200). In the study described above by Shields et al. (196), 20 patients with CRE infections were treated with MER-VAB for >48 h. Within 90 days, microbiological failures (isolation of the same bacterial species following ≥7 days of MER-VAB treatment) were noted in 35% (6/20) of cases. One-half of the recurrent isolates demonstrated a ≥8-fold MER-VAB MIC increase, and one was categorized as nonsusceptible to MER-VAB (MIC = 8 mg/liter). Addressing the resistant isolate, it occurred in a patient with bacteremia due to a CAZ-AVI-resistant *K. pneumoniae* harboring KPC-31. Therapy with MER-VAB was initiated (MER-VAB, MIC of 0.12 mg/liter), but after 12 days of treatment, the patient developed an abdominal wall abscess caused by *K. pneumoniae* nonsusceptible to MER-VAB (MIC = 8 mg/liter). Whole-genome sequencing identified a new IS*5* insertion in the *ompK36* promoter of the recurrent isolate (196). However, data regarding emerging resistance after the exposure to MER-VAB are limited, and new resistance mechanisms may arise when MER-VAB becomes more widely used in the clinical practice.

Future clinical studies evaluating MER-VAB. No clinical trial is currently registered for MER-VAB at ClinicalTrials.gov. One trial was withdrawn by the sponsor in January 2019. This trial was registered in 2016 and was planned to compare MER-VAB versus PIP-TAZ for the treatment of HABP/VABP (201).

Data to support the use of MER-VAB in CRE infections are encouraging; however, they are limited to one small RCT and one small observational study.

IMIPENEM-RELEBACTAM

Spectrum of Activity

Imipenem-cilastatin is combined with relebactam mainly to restore the activity against KPC and other carbapenemase-producing *Enterobacterales* and *P. aeruginosa* isolates (202–204). The most common mechanisms of imipenem resistance in *P. aeruginosa* are decreased expression of OprD and overproduction of AmpC

β-lactamases. Relebactam inhibits AmpC, thereby improving the activity of imipenem (202, 205). Several studies have reported that the combination of imipenem/cilastatin-relebactam (IMI-REL) is effective against bacteria carrying class A and class C β-lactamases, while the activity against bla_{OXA-48}-expressing carbapenem-resistant *Enterobacterales* (CRE) is limited, and no activity against MBL (including IMP, VIM, and NDM)-producing isolates is demonstrated (202, 206–212). A recent study by Biagi et al. reported that IMI-REL had no activity against the carbapenem-resistant *Serratia marcescens* (199). The activity of relebactam against β-lactamases is summarized in Table 1.

A global surveillance program (SMART [Study for Monitoring Antimicrobial Resistance Trends]) including 21 clinical laboratories in the United States in 2015 reported that relebactam restored susceptibility to imipenem in 80.5%, 100%, and 74.1% of imipenem-nonsusceptible *P. aeruginosa*, *Enterobacter* spp., and *K. pneumoniae*, respectively. Relebactam at fixed concentration of 4 mg/liter in combination with doubling dilutions of imipenem was used and IMI-REL MIC interpreted according to CLSI imipenem breakpoints. Isolates producing OXA-48-type carbapenemases, metallo-β-lactamases (VIM), or the class A carbapenemase GES-20 were resistant to IMI-REL (213). The data from SMART surveillance between 2015 and 2017 assessing IMI-REL *in vitro* activity in isolates causing lower respiratory tract infections showed that 92.2% of *P. aeruginosa*, including 77.2% of imipenem-nonsusceptible and 79.6% of MDR isolates, were susceptible to IMI-REL (214). Similar results were reported in isolates from the intra-abdominal and urinary tract infections, where 96.7% and 96.4% of *P. aeruginosa* isolates, respectively, were susceptible to IMI-REL. When analyzing imipenem nonsusceptible and MDR *P. aeruginosa*, 85.0%, and 87.3%, respectively, were susceptible to the combination (215). It should be noted that the data are limited by the interpretation according to CLSI imipenem breakpoints, while currently, there are EUCAST-specific IMI-REL breakpoints (Table 2).

In a study by Livermore et al. (202), IMI-REL was active against AmpC- or ESBL-producing *Enterobacterales* with impermeability phenotypes (e.g., loss of porins). In the case of OprD-deficient *P. aeruginosa* strains, the MIC of imipenem dropped from 16 to 64 mg/liter to 1 to 4 mg/liter (202). In a study investigating bacterial isolates from 11 hospitals in New York (November 2013 to January 2014), the addition of relebactam decreased the MIC values of imipenem in *P. aeruginosa* isolates approximately 4-fold (216). Nevertheless, relebactam did not improve the activity of imipenem against *A. baumannii* harboring $bla_{OXA-23-like}$ or with overexpression of AmpC and/or OXA-51 β-lactamase (213, 216). In a recent study by Tooke et al., IMI-REL was reported as active against bacteria producing class A β-lactamases, both chromosomal and plasmid-borne enzymes, i.e., ESBLs L2 and CTX-M-15 (211).

Evidence that IMI-REL inhibits Bla_{Mab} has been observed in a study evaluating *in vitro* activity of IMI-REL against *Mycobacterium abscessus* complex when relebactam reduced the MIC_{50} and MIC_{90} of imipenem from 16 to 8 and from 32 to 16, respectively (217). A study by Papp-Wallace et al. including 101 clinical isolates of KPC-producing *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*), *Enterobacter cloacae*, *Citrobacter freundii*, *Citrobacter koseri*, and *Escherichia coli* reported that all of the isolates were highly susceptible to IMI-REL (MICs $\leq$ 2 mg/liter) (218). Similar results were documented in a study by Carpenter et al., where IMI-REL was the most potent agent combination tested against CRE: MIC_{50}/MIC_{90} values of IMI-REL were $\leq$0.25/0.5 mg/liter (219). Another study published in 2019 including *P. aeruginosa* clinical isolates showed IMI-REL susceptibility rates of 97.3%, and MICs remained $\leq$2 mg/liter, including for all isogenic PAO1 mutants and XDR clinical strains with mutations in OXA-10 or AmpC (220). The respective EUCAST-, FDA-, and CLSI-approved breakpoints for the interpretation of the susceptibility of particular pathogens to IMI-REL are summarized in Table 2. For antimicrobial susceptibility data of various pathogens to IMI-REL, see Table 4.

Resistance Rates and Mechanisms

The pathogens resistant to IMI-REL are mostly those producing class B metallo-β-

lactamases and some of the OXA class D β-lactamases. There is also an intrinsic resistance to carbapenems, where adding β-lactamase inhibitor does not increase the sensitivity, i.e., for *Enterococcus faecium* producing PBP5 (175, 179). Other resistance mechanisms are the decreased expression of OmpK porin proteins in *K. pneumoniae*, OmpC and OmpF in *Enterobacter* spp., and downregulation or mutations in OmpK36 porin (179, 209, 216). Tested against *E. cloacae*, *P. aeruginosa*, and *C. freundii* strains, relebactam did not result in AmpC induction for any of the strains (58).

Neither imipenem nor relebactam is a substrate of *P. aeruginosa* efflux (204). In a study by Haidar et al. published in 2017, OmpK36 porin mutations in carbapenem-resistant *Enterobacterales* were independently associated with higher MICs of IMI-REL (209). Assessing the development of the resistance during exposure, in a study by Noel et al. (221) using *in vitro* simulations of 7- or 14-day human exposures to IMI-REL on aerobic Gram-negative bacilli, there were no changes in MICs after the first 7 days of exposure. Meanwhile, in *P. aeruginosa*, there was increase in MIC and regrowth in the 14-day model using monotherapy with IMI-REL. The addition of amikacin increased the clearance of *P. aeruginosa* and prevented the development of resistance. The authors concluded that IMI-REL was effective and there was no emergence of resistance in *Enterobacterales*. The drug was active against *P. aeruginosa*, but in a 14-day model, regrowth and resistance were detected and were prevented with the addition of amikacin (221).

PK-PD Characteristics

Like other BLBLIs, imipenem and relebactam exhibit very similar plasma protein binding, half-lives, V_{ss} values (as summarized in Table 5), and routes of elimination (222). Consistent with other β-lactams and β-lactamase inhibitors, both drugs are predominantly excreted unchanged in urine. Wu et al. modeled data from checkerboard assays to describe a dynamic PK-PD index (time above dynamic MIC [$T_{>\mathrm{MICdynamic}}$]) that simultaneously accounted for the activities of both imipenem and relebactam (223). Unlike traditional MIC assessments, the dynamic MIC describes the MIC of imipenem as a function dependent on various relebactam concentrations encountered over a typical dosing interval. Hollow-fiber experiments were used to derive a target $\%fT_{>\mathrm{MIC}}$ dynamic predictive of the efficacy of the combination. FDA approval for the current indications (cIAI and cUTI) relied on assessment of target attainment for relebactam alone, as $\%fT_{>\mathrm{MICdynamic}}$ may not be readily amenable to traditional PTA analyses. As with other inhibitors, the PK-PD index of relebactam was characterized using a fixed imipenem exposure (15). A target $f\mathrm{AUC}_{0-24}$/MIC of 14.4 for 1-$\log_{10}$ reduction in baseline inoculum (for β-lactam-expressing isolates) obtained from murine thigh infection experiments was evaluated in PTA analysis and used to support the approved dose of 0.25 g relebactam with 1 g imipenem/cilastatin (15).

Clinical Data

Approval date and indications. IMI-REL is FDA and EMA approved. It was first approved by the FDA in July 2019 for use in adults with cUTI and cIAI. The dosage approved for these indications was 1.25 g (500 mg imipenem, 500 mg cilastatin, and 250 mg relebactam infused over 30 min every 6 h). It has not yet been approved for use in pediatric patients (222, 224).

Randomized controlled trials evaluating IMI-REL for any infection. Three RCTs have been published so far evaluating IMI-REL for various infections. Sims et al. (225), in a phase 2 RCT, compared two different doses of IMI-REL versus imipenem alone for cUTI. Study arm dosing included high-dose relebactam (imipenem/cilastatin 500 mg plus relebactam 250 mg) versus low-dose relebactam (imipenem/cilastatin 500 mg plus relebactam 125 mg) versus imipenem/cilastatin 500 mg alone (plus placebo). All drugs were administered over 30 min intravenously every 6 h. Overall, 302 patients were randomized. Among 230 patients who had a baseline pathogen, most common was *E. coli* (62%); 50.2% had multidrug-resistant bacteria, and 11% of all pathogens were imipenem nonsusceptible at baseline. No cases of mortality were documented and no

differences between study arms were demonstrated for either clinical or microbiological response at EOT, early follow-up at 5 to 9 days after completion of treatment, or long-term follow-up, 28 to 42 days after completion of all study therapy. No differences in microbiological response were demonstrated between study arms for the subgroups of bacteremia, elderly patients (age, ≥65 years), or patients with abnormal renal function. AEs were reported in the investigational arms in 28% to 29% of patients, most commonly, gastrointestinal side effects, headaches, hypertension, and liver function test abnormalities. SAEs and AEs requiring drug discontinuation were not common and without a significant difference between IMI-REL arms and imipenem (225) (Table 14).

Lucasti et al. (226) conducted a similar phase 2 dose-ranging study in patients with cIAI. Three hundred fifty-one patients were enrolled, and only 21% were elderly (age, ≥65 years), 4% had bacteremia, and 4% had an APACHE II score of >15. Among 250 patients who had a baseline pathogen, most common was *E. coli* (65%), and 13% of patients had an imipenem-nonsusceptible pathogen at baseline. No differences between study arms were demonstrated for either the clinical or microbiological response at EOT, early follow-up at 5 to 9 days after completion of treatment, or long-term follow-up, 28 to 42 days after completion of all study therapy. Any AEs were reported in the investigational arms in 47% to 48% of patients, most commonly, gastrointestinal side effects and liver function test abnormalities. No significant difference between IMI-REL arms and imipenem was demonstrated in rates of SAEs, AEs requiring drug discontinuation, and mortality, though all were more common in the low-dose IMI-REL arm (226) (Table 14).

The RESTORE-IMI 1 was a phase 3 RCT, comparing IMI-REL alone versus imipenem combined with colistin for imipenem-nonsusceptible infections (227). The dosage of IMI-REL was 500 and 250 mg every 6 h; the dosages of imipenem and colistin were 500 mg every 6 h and 4.5 MU every 12 h, respectively. The infections included were HABP/VABP, cIAI, and cUTI. Overall, 31 patients were included in the IMI-REL arm and 16 in the comparator arm (imipenem plus colistin). Including both arms, overall, 31 patients had a baseline pathogen, 24 patients had *P. aeruginosa*, and 7 had various *Enterobacterales*, 6 of them KPC or OXA-48 producing. Of the 31 microbiologically evaluable patients, 11 (35.5%) were 65 years and older, more commonly in the comparator arm (50% versus 28%), 9 had an APACHE II score of >15 (7 IMI-REL and 2 comparator), and 7 had CrCL of <60 ml/min (4 IMI-REL and 3 comparator). The primary outcome was overall response, defined differently for each type of infection (Table 14). There was no significant difference between study arms for the primary outcome (71.4% versus 70%). Twenty-eight-day all-cause mortality was lower with IMI-REL (2/21 [9.5%] versus 3/10 [30%]), and clinical response at 28 days was significantly higher with IMI-REL (71% versus 40%) (Table 14). AEs occurred in 71.0% of patients treated with IMI-REL compared to 81% with comparator. Most common AEs were pyrexia, nausea, decreased creatinine renal clearance, and abnormal liver function tests, all of which were more common in the comparator arm. Specifically, nephrotoxicity was significantly more common in the comparator arm (10% versus 56%). SAEs and AEs requiring drug discontinuation were more common with the comparator (227) (Table 14).

Other clinical studies for IMI-REL. (i) IMI-REL in pediatric populations. Currently, a phase 2/3 RCT comparing IMI-REL versus active control for Gram-negative infections in pediatric population is ongoing (228).

(ii) Other clinical studies. NCT03293485 is an ongoing, interventional single-arm study evaluating IMI-REL for the treatment of cIAI and cUTI in Japanese participants. Results from 83 included participants were posted on ClinicalTrials.gov, showing an overall low mortality of 1 of 83 patients, clinical response of 82% (28/34) for cIAI, and 100% microbiological response for cUTI (229) (Table 14).

Future clinical studies evaluating IMI-REL. Two phase 3 RCTs evaluating IMI-REL versus PIP-TAZ for HABP/VABP in adults are ongoing. One is currently recruiting patients, aiming for a sample size of 270 patients (230), and the other has been completed and awaiting results for 537 enrolled participants (231).

TABLE 14 Clinical studies assessing imipenem-relebactam

Trial ID (reference)	Comparator[a]	Phase	Design[b]	No. of patients[c]	Indication[d]	Exclusion of immunocompromised patients	Bacteria[e]	Outcomes[f]	
								No. (%) interventions vs control	Risk difference (95% CIs)
Motsch 2019 (227)	Col+Imi	3	RCT, Noninferential	47 p (31 I-R, 16 Col+Imi)	NP, cUTI, cIAI	Immunocompromised allowed	*P. aeruginosa*: 31p (77%), 24 i (42% ceftazidime^r, 54% Mero^r)	Mortality: 2/21 (9.5) vs 3/10 (30)	−17.3 (−46.4 to 6.7)
								Overall response[g]: 15/21 (71.4) vs 7/10 (70.0)	−7.3 (−27.5 to 21.4)
								Clinical response 28 days: 15/21 (71.4) vs 4/10 (40.0)	31.4 (1.3 to 51.5)
								Microbiol response 5−9 days after EOT (cUTI): 8/11 (72.7) vs 5/5 (100)	−27.4 (−52.8 to 12.8)
Sims 2017 (225)	Imi	2	RCT, NI	302 (3 arms: high dose, low dose, control)[h]	cUTI	No	*E. coli*, 62%; *K. pneumoniae*, 15; MDR, 50.2%	Mortality: 0/99 vs 0/99 vs 0/100	
								Clinical response EOT: 69/71 (97.1) vs 78/79 (98.7) vs 79/80 (98.8)	High dose vs control: −1.6 (−8.9 to 4.2); low dose vs control: −0.0 (−5.8 to 5.6)
								Clinical response 5–9 days after EOT: 89.1% vs 91.8% vs 93.4%	High dose vs control: −4.4 (−15.2 to 5.3); low dose vs control: −1.6 (−11.2 to 7.5)
								Microbiol response 5–9 days after EOT: 61.5% vs 68.1% vs 70.4%	High dose vs control: −8.9 (−24.6 to 7.1); low dose vs control: −2.4 (−17.4 to 12.8)
Lucasti 2016 (226)	Imi	2	RCT, NI	351 (3 arms: high dose, low dose, control)[h]	cIAI	No	*E. coli*, 65%; *K. pneumoniae*, 14%; *P. aeruginosa*, 14%; Imi nonsusceptible, 13%	Mortality: 0/117 (0.0) vs 3/116 (2.6) vs 0/114 (0.0)	High dose vs control: 0.0 (−3.3 to 3.2); low dose vs control: 2.6 (−0.7 to 7.3)
								Clinical response EOT: 80/89 (89.9) vs 88/96 (91.7) vs 83/92 (90.2)	High dose vs control: 0.3 (−9.6 to 8.9); low dose vs control: 1.4 (−7.2 to 10.3)
								Clinical response 5–9 days after EOT: 77/89 (86.5) vs 85/96 (88.5) vs 82/92 (89.1)	High dose vs control: −2.6 (−12.7 to 7.2); low dose vs control: −0.6 (−10.0 to 8.9)
								Microbiol response EOT: 81/83 (97.6) vs 86/86 (100) vs 82/84 (97.6)	High dose vs control: 0 (−6.3 to 6.2); low dose vs control: 2.4 (−2.0 to 8.3)
								Microbiol response 5–9 days after EOT: 76/78 (97.4) vs 80/82 (97.6) vs 78/80 (97.5)	High dose vs control: −0.1 (−6.7 to 6.4); low dose vs control: 0.1 (−6.3 to 6.5)
NCT03293485 (229)	Single group	NA[i]	Nonrandomized	83 Japanese p (cIAI 39, cUTI 44)	cIAI, cUTI	Immunosuppressive therapy, including high-dose corticosteroids	NS	Mortality: 1/81 (1.23)	
								Clinical response TOC for cIAI: 28/34 (82.1)	
								Microbiol response TOC for cUTI: 39/39 (100)	

[a]Imi, imipenem; Col, colistin.
[b]NI, noninferiority.
[c]I-R, imipenem-relebactam; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection.
[d]NP, nosocomial pneumonia.
[e]Mero^r, meropenem resistant; MDR, multidrug resistant; NS, nonspecified.
[f]EOT, end of therapy; TOC, test of cure; CI, confidence interval; microbiol, microbiological.
[g]Definition of overall response: for hospital-acquired or ventilator-associated pneumonia, 28-day all-cause mortality: for cIAI, day 28 clinical response; and for cUTI, composite clinical and microbiologic response at end of follow-up. Favorable clinical response was defined as resolution of baseline signs and symptoms, and favorable microbiologic response was defined as eradication of baseline uropathogens. Death or missing data were considered treatment failures.
[h]For the three arms: imipenem/cilastatin+relebactam 250 mg, imipenem/cilastatin+relebactam 125 mg, and imipenem/cilastatin alone, all administered four times daily.
[i]NA, nonapplicable.

No future RCTs to evaluate the use of IMI-REL for MDR infections are registered, and further data are needed.

BLBLIs IN DEVELOPMENT PROCESS

The BLBLIs in development are summarized in Table 15.

β-Lactam–Sulfone β-Lactamase Inhibitor Combinations

Cefepime-tazobactam. Cefepime-tazobactam is licensed for clinical use by the Drugs Controller General of India. The preparations used in India are 8:1 cefepime-tazobactam (maximum 1,000 mg/250 mg per vial). A 1:1 preparation has been tested in a phase 1 study and was shown to be well tolerated at a dose of up to 2 g and 2 g intravenously every 8 h for up to 7 days. The spectrum of activity includes *Enterobacterales* that are AmpC, ESBL, K1, or OXA-48 β-lactamase producing, with coverage similar to that of meropenem for these pathogens. KPC- and NDM-producing *Enterobacterales* are mostly resistant, though susceptibility of ~75% of isolates with VIM has been demonstrated. The latter was explained by the weak activity of VIM against cefepime specifically, supported by activity of tazobactam against coproduction of ESBLs. For *P. aeruginosa* and other nonfermenters, the addition of tazobactam results in minimal changes in MIC, and the activity of cefepime-tazobactam is comparable to that of other antipseudomonal β-lactams (meropenem, piperacillin-tazobactam, and ceftazidime) (232, 233).

Clinical experience is reported only from India. In a retrospective study from India, 154 patients were treated with cefepime-tazobactam, mainly for pneumonia (31%) or UTI (23%) caused by ESBL-producing *Klebsiella pneumoniae* or *E. coli* (234). Twenty-nine percent of patients were admitted to an ICU. Clinical improvement was documented in 142 patients (92.2%), and 2 patients died. No adverse events were reported other than diarrhea in 6 patients (234). Ghafur et al. (235) included in a retrospective study 32 patients, adults and children, who were treated with cefepime-tazobactam in an Indian hospital with endemic occurrence of ESBL producers. The effectiveness analysis was limited to 15 patients who received the drug for a clear-source (12 respiratory infections) monomicrobial infection (5 *P. aeruginosa*, 3 *Acinetobacter* spp., and 7 *Enterobacterales*) treated with cefepime-tazobactam alone. All 15 patients improved clinically and were discharged from the hospital. The safety analysis included all 32 patients, and none of them experienced a serious adverse event (235).

An interventional RCT comparing cefepime-tazobactam (2 g and 2 g) versus meropenem for cUTI is ongoing (236).

Cefepime-enmetazobactam (AAI101). Enmetazobactam is a penicillanic acid sulfone β-lactamase inhibitor with no intrinsic activity against Gram-negative bacteria. It has a similar structure to that of tazobactam, with a difference in a single methyl group that gives the drug a net neutral charge, promoting bacterial wall penetration. This structural difference enables enmetazobactam to form more hydrogen bonds in the active site of class A β-lactamases than tazobactam, resulting in possibly delayed turnover of enmetazobactam (237). The combination was shown to be as effective as carbapenems against ESBLs *in vitro*. In addition, cefepime itself is relatively stable against hydrolysis by AmpC and OXA β-lactamases; thus, the combination is active against class A, C, and D β-lactamases (237). Broth microdilution and disk diffusion quality control ranges for cefepime-enmetazobactam were recently set by CLSI (238). Testing the drug against a panel of 1,696 *Enterobacterales* isolates, the addition of enmetazobactam to cefepime lowered the MIC_{90} by seven doubling dilutions (from 32 to 0.25 μg/ml) compared to that of cefepime alone. The effect was substantial for ESBLs (all but one turned from resistant to susceptible) but limited for KPC- and VIM-producing *Enterobacterales*. This was not shown for *P. aeruginosa*, for which enmetazobactam did not enhance the potency of cefepime. Using a cefepime breakpoint of 8 mg/liter, the addition of enmetazobactam to cefepime rendered 82.8% of isolates susceptible (239).

An ongoing phase 3, randomized, controlled, double-blind noninferiority trial is

TABLE 15 β-Lactam–β-lactamase inhibitor combinations in development process[a]

Drug	Spectrum of activity (references)	Limitations in spectrum (reference[s])[b]	Tested for:[c]	Dose[d]
Cefepime-tazobactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, K1; class B, VIM (~75%); class C, AmpC; class D, OXA-48 (232, 233)	No activity against class B except VIM; KPC mostly R; For *P. aeruginosa*, same activity as meropenem (232, 233)	cUTI	2 g/2 g every 8 h
Cefepime-enmetazobactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, some KPC (limited evidence); class C, AmpC; class D, OXA-48 (limited evidence) (239, 323)	No activity against class B; no additional coverage for *P. aeruginosa* over cefepime (239, 323)	cUTI	2 g/500 mg every 8 h
Cefepime-zidebactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, MBLs (IMP, VIM, NDM); class C, AmpC; class D, OXA-48; highly active against *P. aeruginosa*, including carbapenem R (243, 244, 324)	Activity against *Acinetobacter* spp. probably limited (244)	NA	NA
Aztreonam-avibactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, any MBL; class C, AmpC; class D, OXA-48 (248–250)	No enhanced activity over aztreonam alone for *P. aeruginosa*; no *in vitro* activity against *A. baumannii* (248–250)	HABP/VABP, cUTI	CrCL >50 ml/min: LD, 500 mg/167 mg; ELD, 1,500 mg/500 mg; MD, 1,500 mg/500 mg every 6 h CrCL 31–50 ml/min: LD, 500 mg/167 mg; ELD, 1,500 mg/500 mg; MD, 750 mg/250 mg every 6 h CrCL 16–30 ml/min: LD, 675 mg/225 mg; ELD, 675 mg/225 mg; MD, 675 mg/225 mg every 8 h
Sulbactam-durlobactam	*Acinetobacter baumannii*, including carbapenem R (256)	Limited data on potential activity against *Enterobacterales* (255)	Any UTI; HABP/VABP, BSI caused by *A. baumannii*	1 g/1 g every 6 h
Meropenem-nacubactam	Potential activity against *Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, NDM; class C, AmpC; class D, OXA-48 (259, 262, 264)	For *Pseudomonas* and *Acinetobacter* spp., similar activity to meropenem (264)	NA	NA
Cefpodoxime proxetil-ETX0282	Potential activity against *Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class C, AmpC; class D, OXA-48 (265–267)	No activity described for *P. aeruginosa* or *A. baumannii* (265–267)	NA	NA
Cefepime-taniborbactam (VNRX-5133)	Potential activity against *Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, VIM, NDM, SPM-1, and GIM-1 (but not IMP-1); class C, AmpC; class D, OXA-48; *P. aeruginosa*, cefepime and carbapenem R (268–270)		cUTI	NA

[a]Data are limited by the fact that there are few available studies to date.
[b]R, resistant.
[c]cUTI, complicated urinary tract infection; HABP/VABP, hospital-acquired and ventilator-associated bacterial pneumonia; BSI, bloodstream infection; NA, nonapplicable.
[d]LD, loading dose; ELD, extended loading dose; MD, maintenance dose; CrCL, creatinine clearance.

currently recruiting adult patients with cUTI for treatment with cefepime 2 g/AAI101 500 mg every 8 h (q8h) versus piperacillin 4 g/tazobactam 500 mg q8h. The primary outcome is overall treatment success at test of cure, and the trial is planned to include 1,040 patients (240).

β-Lactam–Diazabicyclooctane β-Lactamase Inhibitor Combinations

Diazabicyclooctanes (DBOs) are a class of β-lactamase inhibitors that includes older DBOs (avibactam and relebactam) and newer DBOs (zidebactam, nacubactam, durlobactam, and ETX0282). The latter ones possess the ability to inhibit PBPs and are thus considered β-lactam enhancers, acting synergistically with the partner β-lactam on different PBPs in addition to the β-lactamase inhibitor activity (241).

Cefepime-zidebactam (WCK 5107). Zidebactam is a non-β-lactam that inhibits class A and metallo-β lactamases (MBLs). In addition, it also inhibits PBP2. The four approved new BLBLIs described above do not provide *in vitro* activity against MBL. Cefepime-zidebactam, not yet approved for clinical use, has demonstrated promising *in vitro* activity against MBL-positive pathogens. Recent studies have demonstrated 90% to 100% susceptibility to cefepime-zidebactam among 35 MBL-positive CPE strains, including coproducers of serine β-lactamases. Cefepime-zidebactam was also demonstrated to have *in vitro* activity against *P. aeruginosa* with AmpC overexpression and MBLs, with activity against 78% to 98% of meropenem-nonsusceptible strains and 97% of ceftazidime-nonsusceptible strains. It has also documented moderate activity against OXA-23/24/58-producing *Acinetobacter baumannii*, with 4-fold higher activity than cefepime or ceftazidime for this pathogen. In one study, 85% of isolates and 34% of carbapenem-resistant isolates had MICs below the susceptible-dose-dependent breakpoint of cefepime (242–244). Breakpoints and recommended testing methods are still pending, and no clinical trial is yet registered for this drug (245).

Kaushik et al. (246) demonstrated that addition of zidebactam to cefepime reduced the latter compound's MIC_{50} to *Mycobacterium abscessus* 2-fold, from 32 to 16 mg/liter. These results are limited by the fact that there are no established breakpoints for cefepime against *Mycobacterium abscessus*, and the results were determined considering CLSI cefepime breakpoints for *P. aeruginosa* (246).

Aztreonam-avibactam. The combination of the monobactam aztreonam together with avibactam has been shown as having *in vitro* activity against *Enterobacterales* with class B, A, C, and some D β-lactamases. Aztreonam is stable for hydrolysis by MBLs but not by most serine β-lactamases. The addition of avibactam has the potential to inhibit other classes and provide coverage for MBL-producing isolates, which usually coproduce serine β-lactamases. Kazmierczak et al. tested 333 *Enterobacterales* isolates carrying bla_{OXA-48} and $bla_{OXA-48-like}$ genes and found >99.6% susceptibility to aztreonam-avibactam (247). Sader et al. reported aztreonam-avibactam to be highly active against >10,000 *Enterobacterales* isolates, including ~100 KPC isolates, ~60 OXA-48-like producers, and ~60 MBL-positive isolates (248). An additional large study demonstrated similar results for >50,000 *Enterobacterales* isolates tested, with potent activity of aztreonam-avibactam against these isolates, including meropenem-nonsusceptible and MBL-positive isolates. In this study, the *in vitro* activity of aztreonam-avibactam against *P. aeruginosa* was less potent (MIC_{90}, 32 mg/liter), with avibactam addition not improving the activity of aztreonam. The authors concluded that resistance was probably caused, at least partially, by mechanisms other than β-lactamases (249). Neither aztreonam alone nor the combination of aztreonam-avibactam has *in vitro* activity against *A. baumannii* (250).

First posted in 2017, a phase 3 randomized controlled trial comparing aztreonam-avibactam with or without metronidazole versus meropenem with or without colistin for the treatment of HABP/VABP and cIAI is ongoing. Clinical cure at 28 days is the primary outcome in this trial, which plans to include 375 patients (251).

A phase 2a, prospective single-arm study recently evaluated 34 adults treated with aztreonam-avibactam plus metronidazole for cIAI. Twenty-three had microbiologically documented infection, and none of them had either ESBL- or MBL-positive isolates. The

PK-PD assessment demonstrated that mean exposures of the drug components were consistent with those predicted to achieve PTA in >90% of patients. Twenty-three patients (67%) had any AE, most commonly, liver function abnormalities and diarrhea. Clinical cure rate at day 25 was overall 20/34 (58.8%). Dosage data from this study supported the regimen selected for the phase 3 trial (loading dose of 500/167 mg administered over 30 min, followed by 1,500/500 mg administered over 3 h every 6 h regimen [in patients with CrCL >50 ml/min]) (252).

Decreased susceptibility to aztreonam-avibactam has been reported to be due to PBP3 alteration by a 4-amino-acid insertion in *E. coli* strains (253).

The combination of aztreonam with avibactam was also tested for *in vitro activity* against *Stenotrophomonas maltophilia*, using CLSI breakpoints for *P. aeruginosa* as reference. Aztreonam-avibactam reduced the MIC compared to that for aztreonam alone from >128 to 8 mg/liter for most isolates tested in one study (254).

Sulbactam-durlobactam (ETX2514). Sulbactam is a β-lactam with intrinsic activity against *A. baumannii* (through affinity to PBP1 and PBP3) and is also known as a β-lactamase inhibitor with activity against class A β-lactamases. Its activity as a single agent against *A. baumannii* is limited due to its hydrolysis by various β-lactamases produced by the bacteria, in particular, those of class D. Durlobactam (ETX2514) is a β-lactamase inhibitor that inhibits class A, C, and D β-lactamases. It also presents β-lactam properties, inhibiting PBP2 and thus having activity against some *Enterobacterales* (255). The antibacterial activity of the combination sulbactam-durlobactam was recently tested against 1,722 clinical isolates of *Acinetobacter* sp., predominantly, *A. baumannii*. Among these isolates, ~50% were carbapenem resistant, and durlobactam added to sulbactam lowered the MIC_{90} by 32-fold compared to that of sulbactam alone, from 64 mg/liter to 2 mg/liter. This level of activity was consistent among susceptible and resistant strains. Among strains with a sulbactam-durlobactam MIC of >4 mg/liter, either NDM-1 or PBP3 alteration was demonstrated (256).

Results from a double-blind, randomized controlled trial comparing sulbactam-durlobactam plus imipenem versus placebo plus imipenem for UTI were published recently (257). Fifty-three patients were randomized to receive 1 g durlobactam/1 g sulbactam infused over 3 h q6h plus 500 mg imipenem q6h, and 27 patients were randomized to receive same dose of imipenem with placebo. Overall success (clinical cure and microbiologic eradication) at 21 days was achieved in 76.6% (36/47) in the intervention arm versus 81.0% (17/21) in the control arm. None of the patients died during the study, and no SAEs were reported. The most common adverse events with the drug were headache, nausea, and diarrhea. The PK profile was consistent with that demonstrated in health volunteers (257).

A phase 3 evaluating sulbactam-durlobactam plus imipenem versus colistin plus imipenem for HABP/VABP and bacteremia caused by *A. baumannii* is currently recruiting patients (258).

Meropenem-nacubactam (FPI-1465). Nacubactam is a non-β-lactam β-lactamase inhibitor with *in vitro* activity against class A, C, and some class D β-lactamases. In addition, it has affinity to PBP2 and hence acts as an enhancer, conferring activity against MBL-producing *Enterobacterales* (259). The combination meropenem-nacubactam has been tested against seven meropenem-resistant *P. aeruginosa* clinical isolates in a neutropenic murine lung infection model, showing substantial reductions of bacterial burden (260). Similarly, enhanced activity of the combination was demonstrated in animal models against class A serine carbapenemase-producing *Enterobacterales* isolates and other MDR *Enterobacterales*, including NDM-, KPC-, OXA-, CTX-M-, SHV-, and TEM-producing isolates (261, 262). Nacubactam, with its intrinsic PBP2 activity, may be a potential agent for strains with ceftazidime-avibactam resistance due to mutation in the Ω-loop (263). In a large *in vitro* study, meropenem-nacubactam inhibited >99.5% of 3,306 *Enterobacterales* isolates tested (264). Among 117 meropenem-nonsusceptible or MDR *Enterobacterales*, 87.2%, 92.3%, and 96.6% were inhibited at ≤2, ≤4, and ≤8 mg/liter, respectively. In addition, for 33 of 37 ceftazidime-avibactam-resistant *Enterobacterales*, meropenem-nacubactam displayed an MIC of ≤8 mg/liter. In the same study, for 960 *Pseudomonas* spp. and 429 *Acinetobacter*

spp., the combination had similar activity to meropenem alone (264). In an evaluation of *in vitro* activities of meropenem-nacubactam against clinical isolates of *Mycobacterium abscessus* complex, addition of nacubactam lowered the MIC_{50} of meropenem from 16 to 2 mg/liter in Middlebrook 7H9 medium (246).

No clinical trials aiming to assess the efficacy of meropenem-nacubactam are yet registered at ClinicalTrials.gov.

Cefpodoxime proxetil-ETX0282 (active compound ETX1317). Cefpodoxime proxetil-ETX0282 is the only orally administered β-lactam β-lactamase inhibitor under clinical development to date. ETX0282 is a prodrug of ETX1317, a β-lactamase inhibitor with activity against serine β-lactamases of class A, C, and a selection of class D. In addition, it has intrinsic antibacterial activity against some species. ETX1317 is combined with a β-lactam prodrug, cefpodoxime proxetil, hydrolyzed *in vivo* to cefpodoxime. It was found that cefpodoxime-ETX1317 in a 1:2 fixed ratio has the most potent activity and probably the best correlation to *in vivo* efficacy (265). This combination has been tested *in vivo* on 1,875 *Enterobacterales* urinary clinical isolates. In this study, addition of ETX1317 lowered cefpodoxime MIC_{50} and MIC_{90} from of 0.5 and >16 mg/liter to 0.06 and 0.12 mg/liter, regardless of the resistance phenotypes and type of bacteria (265). It has also been tested *in vitro* on 30 isolates of *Enterobacterales* with various resistance genes and phenotypic resistance to carbapenems or colistin and showed potent antibacterial activity (265, 266). In addition, isolates of KPC3 with resistance mutations to ceftazidime-avibactam (V240G, D179Y, and D179Y/T243M) were inhibited by the combination. MICs for cefpodoxime proxetil-ETX0282 were 0.12 to 0.25 mg/liter both for wild-type and for mutant KPC-3 isolates (267).

β-Lactam–Boronate β-Lactamase Inhibitor Combinations

Cefepime-taniborbactam (VNRX-5133). Taniborbactam is a boronic-acid-containing β-lactamase inhibitor that inhibits class A, C, D, and even class B β-lactamases, including VIM, NDM, SPM-1, and GIM-1 (but not IMP). The inhibition of serine β-lactamases occurs while the drug covalently binds to the site serine residue, producing enzyme-mediated hydrolysis. The inhibition of metallo-β-lactamases involves interaction of the boron moiety with the active zinc site, inducing narrowing of the active site cleft (268). The combination cefepime-taniborbactam has been demonstrated to provide potent activity against strains with an elevated MIC to ceftazidime-avibactam (producing 171KPC-3 Ω-loop variants D179Y, V240G, A177E/D179Y and D179Y/T243M). It was recently demonstrated to have potent *in vitro* activity against *Enterobacterales* and *P. aeruginosa*. Among 817 *P. aeruginosa* isolates nonsusceptible to cefepime, meropenem, or both, 70% were inhibited at the susceptible breakpoint of 8 mg/liter, and overall, 85% were inhibited at 16 mg/liter (268–270). A phase 3, randomized, double-blind noninferiority study is currently recruiting patients to evaluate cefepime-taniborbactam versus meropenem for the treatment of cUTI in adults (271). The primary outcome is a composite of microbiological eradication and symptomatic clinical success at test of cure.

QPX7728. QPX7728 is an additional boronic-acid-containing β-lactamase inhibitor, with ability to inhibit class A ESBLs and carbapenemases (KPC) in class B (NDM, VIM, IMP), class C, and class D (OXA-48 in *Enterobacterales* and OXA-23 in *A. baumannii*). This compound was tested against carbapenem-resistant *A. baumannii* and *P. aeruginosa* isolates, combined with several β-lactams. Meropenem, ceftolozane, piperacillin, and cefepime all demonstrated increased potency with the addition of QPX7728 (272). Similarly, combinations of several β-lactams with QPX7728 restored their activity against CRE producing either KPC, OXA-48-like, or metallo-β-lactamases (273). It was also tested against CAZ-AVI-resistant KPC-producing isolates, with retained activity attributed to their different binding sites (274). The potency of the drug is also retained in *P. aeruginosa* with inactivation of the OprD porin, and it is also minimally affected by efflux pumps. There is currently no fixed combination of this compound with a

TABLE 16 Different resistance mechanisms among *Enterobacterales* and *P. aeruginosa* against four approved new BLBLIs[a]

Drug[b]	Resistance mechanisms
CAZ-AVI	Class B MBLs Hyperexpression of efflux pumps Porin alterations Increased expression of the bla_{KPC} gene or mutations on Ω-loop of KPC enzymes Mutations in PBPs (rare)
TOL-TAZ	Class A β-lactamases (some of ESBLs, mainly *K. pneumoniae*, most of KPCs) Class B MBLs Hyperproduction of AmpC (not in *P. aeruginosa*) Class D carbapenemases (OXA-48-like)
MER-VAB	Class B MBLs Class D carbapenemases (OXA-48-like) Porin alterations Hyperexpression of efflux pumps
IMI-REL	Class B MBLs Class D carbapenemases (OXA-48-like) Specific class A carbapenemases (e.g., GES) Hyperexpression of KPC Porin alterations

[a]See references 325 to 329.
[b]CAZ-AVI, ceftazidime-avibactam; TOL-TAZ, ceftolozane-tazobactam; MER-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam.

β-lactam, and it has been suggested as a "stand-alone" drug, though the latter approach is still debated (275).

INSIGHTS FROM THE EXPERTS

Novel BLBLIs enable new options of treatment for carbapenem-resistant *Enterobacterales*, *P. aeruginosa*, *A. baumannii*, and other bacteria with limited treatment options, including mycobacteria. They also constitute a carbapenem-sparing option for the treatment of common infections, including those caused by ESBL/AmpC-producing *Enterobacterales* and non-carbapenem-resistant *P. aeruginosa*. Nevertheless, currently, this alternative is limited by the high cost of novel BLBLIs.

Current use of the four approved BLBLIs should probably be as definitive therapy for isolates resistant to other treatment options. CAZ-AVI could be an option for most resistant *Enterobacterales*, including ESBL-, KPC-, AmpC-, and OXA-48-producing isolates. It may also be used for CAZ-AVI-susceptible *P. aeruginosa* carbapenem-resistant isolates. TOL-TAZ and, to some extent, ESBLs, could be used mainly for carbapenem-resistant *P. aeruginosa*. MER-VAB and IMI-REL, similarly to CAZ-AVI, could be used for various resistant *Enterobacterales*, however, with no coverage for class D β-lactamase-producing pathogens. For *P. aeruginosa*, the activity is of MER-VAB is similar to that of meropenem alone. Relebactam restores imipenem's activity in ~80% of resistant *P. aeruginosa* strains. None of these drugs is active against MBL-producing bacteria or carbapenemase-producing *A. baumannii*. For resistance mechanisms for each of the four drugs, see Table 16.

Most clinical data on new BLBIs come from two types of studies.

1. Randomized controlled trials, with a noninferiority design, conducted mostly for cUTI or cIAI in patients with no immunosuppression and nonsevere infection and including mostly nonresistant bacteria. These trials have limited external validity for use of these drugs to treat MDR pneumonia or bacteremia. Exceptions are the TANGO II trial (193), evaluating MER-VAB exclusively in CRE infections, and the RESTORE-IMI 1 (227), evaluating IMI-REL for imipenem-nonsusceptible bacterial infections. Postmarketing trials including patients with carbapenem-resistant bacterial infections are not listed at ClinicalTrials.gov. One trial in an immuno-

compromised population is registered for TOL-TAZ (for neutropenic fever); another trial is registered for treating ESBL and AmpC producers.
2. Real-life small retrospective studies focusing on treating CRE infections with CAZ-AVI and MER-VAB, with few data addressing MDR/XDR *P. aeruginosa* for these drugs, and on treating MDR/XDR *P. aeruginosa* with TOL-TAZ, with limited data on *Enterobacterales* for this drug.

Future randomized controlled trials would best define the role of different novel BLBLIs in the treatment of carbapenem-resistant and other MDR infections. Since such studies are difficult to conduct and none are currently registered at ClinicalTrials.gov, observational data are needed to further define efficacy and the magnitude of resistance emergence.

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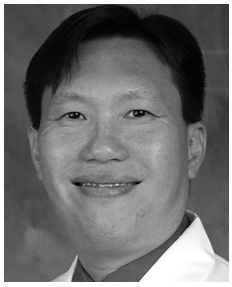

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