INVITED ARTICLE

Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation β-Lactam/β-Lactamase Inhibitor Combinations

David van Duin[1] and Robert A. Bonomo[2,3,4,5]

[1]Division of Infectious Diseases, University of North Carolina, Chapel Hill; [2]Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, [3]Division of Infectious Diseases and HIV Medicine, Department of Medicine, [4]Department of Molecular Biology and Microbiology, and [5]Department of Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio

Ceftolozane/tazobactam and ceftazidime/avibactam are 2 novel β-lactam/β-lactamase combination antibiotics. The antimicrobial spectrum of activity of these antibiotics includes multidrug-resistant (MDR) gram-negative bacteria (GNB), including *Pseudomonas aeruginosa*. Ceftazidime/avibactam is also active against carbapenem-resistant Enterobacteriaceae that produce *Klebsiella pneumoniae* carbapenemases. However, avibactam does not inactivate metallo-β-lactamases such as New Delhi metallo-β-lactamases. Both ceftolozane/tazobactam and ceftazidime/avibactam are only available as intravenous formulations and are dosed 3 times daily in patients with normal renal function. Clinical trials showed noninferiority to comparators of both agents when used in the treatment of complicated urinary tract infections and complicated intra-abdominal infections (when used with metronidazole). Results from pneumonia studies have not yet been reported. In summary, ceftolozane/tazobactam and ceftazidime/avibactam are 2 new second-generation cephalosporin/β-lactamase inhibitor combinations. After appropriate trials are conducted, they may prove useful in the treatment of MDR GNB infections. Antimicrobial stewardship will be essential to preserve the activity of these agents.

Keywords. ceftolozane/tazobactam; ceftazidime/avibactam; multidrug resistance; *Pseudomonas*; Enterobacteriaceae.

A number of important initiatives have been introduced to address the issue of multidrug-resistant (MDR) bacteria. In addition to the "bad bugs, no drugs" and the "10 × '20" initiatives of the Infectious Disease Society of America, a comprehensive plan to combat the rise of antibiotic-resistant bacteria called Combating Antibiotic-Resistant Bacteria was recently released [1–3]. This plan describes the need to develop "at least 2 new antibiotic drug candidates, non-traditional therapeutics, and/or vaccines from pre-clinical testing to clinical trials for treatment or prevention of human disease" by 2020.

The concerns regarding antibacterial resistance, especially in clinically important gram-negative bacteria (GNB), are continuing to increase worldwide [4, 5]. A better understanding of the epidemiology of this multifaceted epidemic is needed. In the long term, prevention of spread of MDR GNB is most important. Meanwhile, however, patients will continue to present with difficult-to-treat infections caused by MDR GNB. Treatment choices for these infections have been limited, especially for infections caused by bacteria that produce carbapenemases and/or extended-spectrum β-lactamases (ESBLs) [6–8].

Ceftolozane/tazobactam and ceftazidime/avibactam are 2 antibiotics with anti-GNB activity that were recently approved for the treatment of complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) by the US Food and Drug Administration (FDA). Their characteristics will be reviewed, with a focus on their respective antimicrobial spectra and currently available clinical trial data.

CHEMISTRY AND MODE OF ACTION

Ceftolozane/tazobactam combines a novel cephalosporin with an established β-lactam β-lactamase inhibitor, whereas ceftazidime/avibactam couples a well-known cephalosporin with a novel non-β-lactam β-lactamase inhibitor. Both tazobactam and avibactam target the active site of serine β-lactamases (Table 1). Tazobactam, a β-lactam sulfone, binds irreversibly to the active site of β-lactamases. The details of the process are quite complex as there is also a small amount of hydrolysis of tazobactam by certain class A β-lactamases such as SHV-1. In contrast, avibactam is a diazabicyclooctane non-β-lactam that binds covalently and reversibly to β-lactamases [9]. This reversibility is a unique feature that allows avibactam to undergo recyclization to inactivate another β-lactamase. The crucial advantage of avibactam is its ability to inhibit ESBLs, AmpC β-lactamases (as expressed in *Pseudomonas aeruginosa* and Enterobacteriaceae), and class A carbapenemases of the *Klebsiella pneumoniae* carbapenemase (KPC and OXA-48) family [10].

Table 1. Comparative In Vitro Inhibitory Activity of Tazobactam and Avibactam Against Selected β-Lactamases

Enzymes	Class	Substrates	Inhibited by	
			Tazobactam	Avibactam
TEM-1, TEM-2, SHV-1	A	Penicillins, early cephalosporins	Yes	Yes
TEM-3, SHV-2 CTX-M-14	A	Extended-spectrum cephalosporins, monobactams	Yes	Yes
KPC-2, KPC-3	A	Broad spectrum including carbapenems	No	Yes
IMP-1, NDM-1, VIM-1	B	Broad spectrum including carbapenems, but not monobactams	No	No
Escherichia coli AmpC	C	Cephalosporins	High concentrations	Yes
OXA-48	D	Carbapenems	No	Yes

Abbreviation: KPC, Klebsiella pneumoniae carbapenemase

Ceftolozane and ceftazidime are structurally similar cephalosporins (Figure 1). Ceftolozane is an oxyimino-aminothiazolyl cephalosporin with a pyrazole substituent at the 3-position side chain instead of the lighter pyridium present in ceftazidime. This heavier side-chain provides improved steric hindrance to prevent hydrolysis mediated through AmpC β-lactamases [11]. Porin loss significantly increases in vitro minimum inhibitory concentration (MIC) values of ceftazidime, but appears to have no effect on the efficacy of ceftolozane [12]. This porin loss

is described in a minority of clinical isolates and results in low-level resistance to ceftazidime/avibactam (MIC = ~8 mg/L).

ANTIMICROBIAL ACTIVITY

Overall Spectrum of Activity

Ceftolozane/tazobactam and ceftazidime/avibactam have similar spectra of antimicrobial activity, but with some important differences. Their primary activity is against aerobic GNB. For gram-positive bacteria, both cephalosporin combinations have
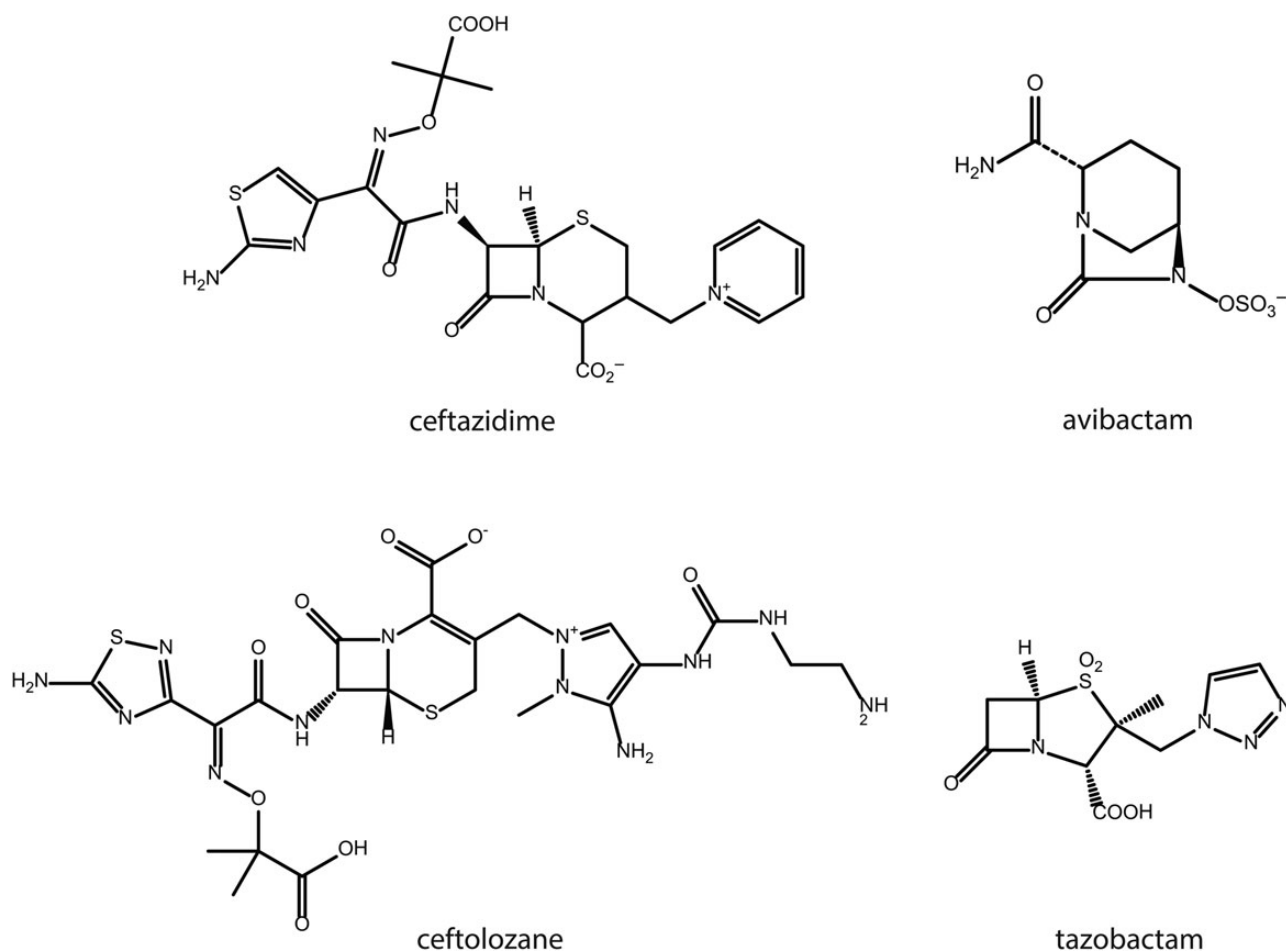

Figure 1. Chemical structures of ceftolozane, tazobactam, ceftazidime, and avibactam.

some antistreptococcal, very limited antistaphylococcal, and no antienterococcal activity. Both agents have in vitro activity against selected anaerobic bacteria, including *Fusobacterium* species and *Propionibacterium* species. However, activity against *Bacteroides* species is less predictable, and *Clostridium* species are resistant [13, 14]. Consequently, in clinical trials evaluating the use of ceftolozane/tazobactam and ceftazidime/avibactam in cIAI, metronidazole was added [15–17].

Importantly, both ceftolozane/tazobactam and ceftazidime/avibactam are active against *P. aeruginosa*. In contrast, *Acinetobacter* and *Stenotrophomonas* species are generally resistant [18–20]. Pending appropriate clinical trials, both combinations have most promise for use in infections caused by MDR *Pseudomonas* species and MDR Enterobacteriaceae.

Spectrum of Activity Against Selected MDR GNB

Studies outlining the in vitro activity of ceftazidime/avibactam and ceftolozane/tazobactam against *Escherichia coli*, *K. pneumoniae*, and *P. aeruginosa* are summarized in Tables 2 and 3. Clinically, the key microbiologic difference between ceftazidime/avibactam and ceftolozane/tazobactam is that avibactam inhibits carbapenemases of the KPC family [10].

In a large in vitro study, ceftazidime/avibactam was tested against >20 000 clinical US Enterobacteriaceae isolates [36]. Only 11 isolates displayed a ceftazidime/avibactam MIC > 8 μg/mL.

Two of these 11 isolates expressed metallo-β-lactamases (MBLs), which are known to be resistant to avibactam-mediated inhibition [36]. These data suggest that ceftazidime/avibactam will be a very useful addition to the quite limited number of antibiotics currently available to treat KPC-producing carbapenem-resistant Enterobacteriaceae (CRE). A concern to note is that avibactam-resistant variants of SHV-1 and KPC-2 containing single point mutations are known. These avibactam-resistant variants have amino acid changes that are described in inhibitor-resistant SHVs and TEMs. However, these KPC-2 variants also display decreased carbapenemase activity [37]. Fortunately, the combination of ceftazidime/avibactam still maintains activity as the inhibitor-resistant β-lactamases are less able to hydrolyze the oxyimono-cephalosporin partner. Of greater concern are New Delhi metallo-β-lactamase 1–producing Enterobacteriaceae, which are increasingly common in the Indian subcontinent and the Balkan countries [38].

Noncarbapenemase β-lactamases that are inhibited by avibactam include class A, class C, and some class D β-lactamases. Ceftazidime/avibactam has excellent in vitro activity against ESBL-producing Enterobacteriaceae [36, 39]. In contrast, only 58% of ESBL-producing *K. pneumoniae* isolates from patients with pneumonia had a ceftolozane/tazobactam MIC ≤ 8 μg/mL [19]. Around 78% of abdominal and urinary clinical ESBL-producing *K. pneumoniae* isolates demonstrated a ceftolozane/tazobactam MIC ≤ 8 μg/mL [18]. Ceftolozane/tazobactam has reliable

Table 2. In Vitro Susceptibility of Selected Subsets of *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* to Ceftazidime/Avibactam

Isolates (No.)	Ceftazidime/Avibactam			
	MIC$_{50}$	MIC$_{90}$	% S	Reference
KPC-producing Enterobacteriaceae (129)	0.5	2	100	[21]
KPC-producing Enterobacteriaceae (120)	0.25	1	97.5	[22]
Escherichia coli (6486)	0.06	0.12	100	[22]
E. coli (375)	0.06	0.12	100	[23]
ESBL-producing *E. coli* (90)	0.12	0.25	100	[23]
Gentamicin-resistant *E. coli* (166)	0.12	0.25	100	[24]
Klebsiella pneumoniae (4421)	0.12	0.25	99.9	[22]
K. pneumoniae (254)	0.12	0.5	100	[23]
ESBL-producing *K. pneumoniae* (84)	0.25	1	100	[23]
Pseudomonas aeruginosa (5328)	2	4	96.8	[25]
Meropenem-nonsusceptible[a] *P. aeruginosa* (396)	8	32	67.4	[25]
Non-ICU *P. aeruginosa* (2240)	2	4	97.5	[21]
ICU *P. aeruginosa* (842)	2	8	95.6	[21]
Meropenem-nonsusceptible *P. aeruginosa* (537)	4	16	87.0	[21]
Ceftazidime-nonsusceptible *P. aeruginosa* (482)	4	16	80.7	[21]
P. aeruginosa (3902)	2	4	97	[26]
MDR *P. aeruginosa* (580)	4	16	81	[26]
XDR *P. aeruginosa* (338)	8	32	74	[26]
P. aeruginosa (1743)	2	8	96.3	[27]
P. aeruginosa (881)[b]	2	8	95.8	[28]
Gentamicin-resistant *P. aeruginosa* (131)	4	16	88	[24]
β-lactam–resistant *P. aeruginosa* (55)	2	32	84	[29]

Abbreviations: ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug resistant; MIC$_{50}$, minimal inhibitory concentration that inhibits growth of 50% of the test population; MIC$_{90}$, minimal inhibitory concentration that inhibits growth of 50% of the test population; S, susceptible; XDR, extensively drug resistant.

[a] These isolates were also nonsusceptible to ceftazidime, cefepime, and piperacillin/tazobactam.

Table 3. In Vitro Susceptibility of Selected Subsets of *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* to Ceftolozane/Tazobactam

Isolates (No.)	Ceftolozane/Tazobactam			
	MIC_{50}	MIC_{90}	% S	Reference
Escherichia coli (3843)	0.25	0.5	99.2	[30]
ESBL-producing *E. coli* (715)	0.5	4	95.7	[30]
E. coli (2691)	0.25	0.5	99.3	[31]
ESBL-producing *E. coli* (327)	0.5	4	94.5	[31]
E. coli (1306)	NR	0.5	98	[32]
E. coli (368)	0.25	1	98.6	[19]
ESBL-producing *E. coli* (76)	0.5	4	93.4	[19]
E. coli (341)	0.25	0.5	98.5	[18]
CTX-M-15–producing *E. coli* (219)	<0.25	0.5	100	[33]
E. coli (250)	0.25	0.5	100	[34]
Klebsiella pneumoniae (1408)	0.5	>32	82.7	[30]
ESBL-producing *K. pneumoniae* (493)	2	>32	78.7	[30]
Meropenem-nonsusceptible *K. pneumoniae* (140)	>32	>32	1.4	[30]
K. pneumoniae (1298)	0.25	16	89.1	[31]
ESBL-producing *K. pneumoniae* (244)	32	>32	41.8	[31]
Meropenem-nonsusceptible *K. pneumoniae* (100)	>32	>32	4	[31]
K. pneumoniae (1205)	NR	4	89	[32]
K. pneumoniae (370)	0.25	>32	84.9	[19]
ESBL-producing *K. pneumoniae* (132)	4	>32	57.6	[19]
K. pneumoniae (126)	0.25	16	88.9	[18]
Pseudomonas aeruginosa (2435)	0.5	1	99	[35]
Ceftazidime-nonsusceptible *P. aeruginosa* (398)	1	4	94.5	[35]
Meropenem-nonsusceptible *P. aeruginosa* (401)	1	4	96.5	[35]
P. aeruginosa (2191)	1	>32	86.3	[30]
MDR *P. aeruginosa* (698)	4	>32	57.4	[30]
XDR *P. aeruginosa* (538)	32	>32	46.3	[30]
P. aeruginosa (1971)	0.5	2	98.5	[31]
Ceftazidime-nonsusceptible *P. aeruginosa* (338)	4	8	91.1	[31]
Meropenem-nonsusceptible *P. aeruginosa* (388)	1	8	92.8	[31]
P. aeruginosa (1257)	NR	2	97	[32]
P. aeruginosa (1019)	0.5	4	94.1	[19]
Ceftazidime-nonsusceptible *P. aeruginosa* (269)	4	>32	77.7	[19]
Meropenem-nonsusceptible *P. aeruginosa* (268)	2	>32	78	[19]
P. aeruginosa (500)	0.5	4	94.4	[34]
Ceftazidime-nonsusceptible *P. aeruginosa* (120)	2	>64	80.8	[34]
Meropenem-nonsusceptible *P. aeruginosa* (177)	2	32	85.3	[34]
P. aeruginosa (212)	0.5	4	93.4	[18]

Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant; MIC_{50}, minimal inhibitory concentration that inhibits growth of 50% of the test population; MIC_{90}, minimal inhibitory concentration that inhibits growth of 90% of the test population; NR, not reported; S, susceptible; XDR, extensively drug resistant.

activity against Enterobacteriaceae that produce the globally important ESBLs CTX-M-14 and CTX-M-15 [33].

However, when considering these in vitro susceptibilities, previous reports of treatment failures of piperacillin/tazobactam in serious infections caused by ESBL-producing organisms suggest that caution should be used when considering treatment of such infections with ceftolozane/tazobactam until clinical data become available [40].

Ceftolozane/tazobactam shows potent in vitro activity against *Pseudomonas* species, although baseline resistance is already detectable. Between 86% and 95% of clinical *P. aeruginosa* isolates show a ceftolozane/tazobactam MIC ≤ 8 µg/mL [18, 19, 30]. When evaluating specifically more resistant strains, 60%–80%

ceftazidime-resistant and meropenem-resistant pseudomonal isolates displayed MICs to ceftolozane/tazobactam of ≤8 µg/mL [18, 19, 30].

Similarly, ceftazidime/avibactam has potent in vitro antipseudomonal activity; 84%–97% of clinical isolates had a ceftazidime/avibactam MIC ≤ 8 µg/mL in several large studies [20, 41, 42]. Of note, in a study on archived *Pseudomonas* isolates—collected >10 years before the release of avibactam—a resistance rate of 18% was found [29]. Resistance was found to be mediated by decreased cell wall permeability and increased efflux, rather than changes in penicillin-binding protein or novel β-lactamases. This further emphasizes the ongoing struggle of treating infections caused by MDR *Pseudomonas* species. The mechanism of

efflux and decreased cell wall permeability can pose a significant threat to all future drug development.

PHARMACOKINETICS

Dosing
Both ceftolozane/tazobactam and ceftazidime/avibactam are available for intravenous use only. The currently approved dosages for adult patients with an estimated creatinine clearance >50 mL/minute are ceftolozane 1 g with tazobactam 500 mg every 8 hours and ceftazidime 2 g with avibactam 500 mg every 8 hours. Both drugs are primarily cleared through the kidneys, and the dosages have to be renally adjusted (Table 4). Both are dialyzable and the dose that is scheduled near hemodialysis should be given after hemodialysis in patients with end-stage renal disease.

Ceftolozane/Tazobactam
The maximum plasma concentration of ceftolozane occurs at around an hour after the start of infusion. The mean plasma half-life of ceftolozane is 2.7 hours in healthy, uninfected adults, and significant accumulation does not occur after multiple doses [43]. This relatively short half-life accounts for the need to administer a dose every 8 hours. Ceftolozane is excreted through the kidneys with minimal metabolism and appears as parent compound in the urine. The clearance of tazobactam, which has been extensively previously reviewed, does not appear to be influenced when coadministering ceftolozane [44]. This is in contrast to coadministration with piperacillin, which leads to a decrease in clearance of tazobactam with a corresponding increase in the area under the curve (AUC) [43, 45]. The steady-state volume of distribution of ceftolozane is 12.9 L, which is close to the average extracellular volume, suggesting potential therapeutic levels at extracellular sites of infection. The volume of distribution was found to be increased in patients with obesity, and further increased in patients with infection [46].

Ceftolozane/tazobactam is currently being studied for use in pneumonia. In this context, the pharmacokinetics in the lung were evaluated in healthy volunteers and compared to those of piperacillin/tazobactam [47]. The ratio of epithelial lining fluid (ELF) to plasma AUC of ceftolozane was comparable to that of piperacillin (0.48 vs 0.26, respectively). The ELF concentrations of ceftolozane exceeded 8 mg/L for >60% of the dosing interval, suggesting that the growth of susceptible *Pseudomonas* species should be inhibited in the lungs. Of note, the tazobactam concentration was 2-fold higher in ELF when given with piperacillin as compared to ceftolozane. This is unlikely to be of much importance in lower respiratory tract infections caused by *Pseudomonas* species—as tazobactam adds little to the antipseudomonal effect of ceftolozane—but it may be important when treating β-lactamase–producing Enterobacteriaceae in the lungs.

Ceftazidime/Avibactam
The pharmacokinetics of ceftazidime/avibactam are similar to those of ceftolozane/tazobactam. The primary route of elimination is renal excretion for both ceftazidime and avibactam, resulting in high levels of the parent compounds in the urine. The pharmacokinetics of ceftazidime are known for most patient populations [48]. In brief, the steady-state volume of distribution is around 15 L, and only 10%–17% of drug is protein-bound. The half-life is around 1.5 hours, and peak plasma concentrations occur 30 minutes after intravenous infusion of ceftazidime [48, 49].

Similarly, avibactam plasma concentrations also peak shortly after infusion with a maximum noted at 30–60 minutes after start of infusion, followed by a biphasic decrease [50]. In the same study of 32 healthy volunteers, elderly (defined as age ≥65 years) men but not elderly women were found to have a lower maximum concentration (C_{max}) of avibactam compared with young adults (defined as age 18–45 years); elderly men had a mean C_{max} of 26 μg/mL compared with 34–38 μg/mL in the young and elderly female cohorts [50]. As this was a small study in healthy volunteers, the clinical relevance of this finding remains to be determined. The half-life of avibactam ranged from 1.7 to 3.2 hours; this tended to be somewhat longer in the elderly adults. The volume of distribution of avibactam ranged from 15 L to 24 L [50].

Even in supratherapeutic doses, ceftazidime/avibactam did not increase QT duration in healthy male volunteers [51]. Adverse events were observed in 30% of volunteers who received the supratherapeutic dose of ceftazidime 3000 mg with avibactam 2000 mg. Most were mild and included nausea, vomiting, and headache [51].

CLINICAL EXPERIENCE

Ceftolozane/Tazobactam
In a phase II cUTI study, 86 patients received ceftolozane dosed at 1 g every 8 hours and 43 patients were treated with ceftazidime. Microbiological cure rates in the ceftolozane (83%) and ceftazidime (76%) arms were comparable. Adverse events in the ceftolozane vs ceftazidime arms included constipation (9% vs 5%), sleep disorder (7% vs 5%), and diarrhea (4 vs 7%) [52].

Table 4. Recommended Dosing for Ceftolozane/Tazobactam and Ceftazidime/Avibactam

Estimated Creatinine Clearance, mL/min	Ceftolozane/ Tazobactam, mg	Estimated Creatinine Clearance, mL/min	Ceftazidime/ Avibactam, mg
>50	1000/500 q8h	>50	2000/500 q8h
30–50	500/250 q8h	31–50	1000/250 q8h
15–29	250/125 q8h	16–30	750/190 q12h
ESRD on hemodialysis[a]	500/250 × 1 loading dose, followed by 100/50 q8h	6–15	750/190 q24h
		<6[a]	750/190 q48h

Abbreviation: ESRD, end-stage renal disease.

[a] Give after completion of hemodialysis on hemodialysis days.

In phase III cUTI trials, ceftolozane/tazobactam (n = 398) was compared to levofloxacin (n = 402) [53]. Of note, in vitro fluoroquinolone resistance at baseline was seen in more than a quarter of uropathogens, whereas baseline resistance to ceftolozane/tazobactam was only found in 2.7% of isolates. Clinical cure and microbiological eradication were required for the composite cure outcome. Superiority of ceftolozane/tazobactam compared with levofloxacin was found in both the modified intention-to-treat (mITT) analysis (77% vs 68%), as well as in the per-protocol (83% vs 75%) analysis. In contrast, outcomes were similar when only patients with baseline levofloxacin-susceptible pathogens were analyzed. Rates of adverse events were similar; headache occurred in 6% vs 5%, constipation in 4% vs 3% [53].

In a phase II cIAI study, 83 patients were randomized to ceftolozane/tazobactam plus metronidazole vs 39 patients to meropenem [15]. While not statistically significant, the clinical cure rate in the microbiologically mITT (m-mITT) population—those patients who received at least 1 dose of study medication and had a bacterial pathogen isolated from cultures—was numerically lower in the patients treated with ceftolozane/tazobactam plus metronidazole; clinical cure was observed in 51 of 61 (84%) patients vs 24 of 25 (96%) patients in the meropenem arm (difference, −12%; 95% confidence interval [CI], −35% to 11%). Adverse event rates were similar [15].

In 2 large multicenter phase 3 cIAI randomized controlled trials, patients were randomized to ceftolozane/tazobactam plus metronidazole (n = 389) vs meropenem (n = 417) [16]. A numerically lower cure rate was again observed in the m-mITT analysis: 83% vs 87% (weighted difference, −4.2%; 95% CI, −9% to 0.5%) in patients treated with ceftolozane/tazobactam plus metronidazole vs meropenem, respectively. However, this difference was not statistically significant and the 95% CI did not include the a priori noninferiority boundary of a 10% difference. Of note, in patients with moderate renal failure (creatinine clearance, 30–50 mL/minute), a numerically lower cure rate was noted in the phase 3 intra-abdominal infection trial: 11 of 23 (48%) in the ceftolozane/tazobactam plus metronidazole arm vs 9 of 13 (69.2) in the meropenem arm. The decreased cure rate in the patients aged ≥65 years (69% vs 82%) was also thought to be secondary to changes in renal clearance. These findings prompted the FDA to include a warning in the package insert of ceftolozane/tazobactam to monitor renal function at least daily in patients with changing renal function and to change ceftolozane/tazobactam dosing as needed.

Reported adverse events included hypokalemia (2.9%), headache (2.5%), and increased alanine aminotransferase (2.5%) and aspartate aminotransferase (1.6%) levels [16].

Ceftazidime/Avibactam

In a phase 2 trial on cUTIs, 68 patients received ceftazidime/avibactam and 67 were randomized to imipenem/cilastatin [54]. The dosing was 500 mg of ceftazidime and 125 mg of avibactam every 8 hours. More than 90% of patients were infected with *E. coli*. In the clinically evaluable population (n = 64), a favorable clinical response was observed in 24 of 28 (86%) of patients in the ceftazidime/avibactam arm vs 29 of 36 (81%) in the imipenem/cilastatin arm. Microbiological responses were evaluated in the microbiologically evaluable population (n = 62); 19 of 27 (70%) patients had a favorable microbiological response in the ceftazidime/avibactam arm vs 25 of 35 (71%) in the imipenem/cilastatin arm. Drug-related serious adverse events were uncommon: 1 of the 68 (1.5%) patients treated with ceftazidime/avibactam developed acute renal failure and another patient developed diarrhea.

A cIAI phase 2 trial compared ceftazidime/avibactam plus metronidazole (n = 101) vs meropenem (n = 102) [17]. Note that the dosing for this trial was 4 times higher than the dosing in the UTI study; 2 g of ceftazidime was given with 500 mg of avibactam every 8 hours. This is also the dose that is recommended in the package insert for patients with normal renal function. Clinical response rates were comparable in the m-mITT population: 82% (70/85 patients) in the ceftazidime/avibactam plus metronidazole arm vs 88% (79/89 patients) in the meropenem arm (difference, −6.4%; 95% CI, −23.8% to 6.0%). In this trial the predominant pathogen was also *E. coli*, which represented 69% of GNB. Gastrointestinal side effects such as nausea (10% vs 6%), vomiting (14% vs 5%), and abdominal pain (8% vs 3%) were more common in the ceftazidime/avibactam plus metronidazole group compared with the meropenem group [17]. This was likely due to the metronidazole component of the therapy. The pooled results of 2 phase 3 trials comparing ceftazidime/avibactam plus metronidazole vs meropenem in adult hospitalized patients with cIAI were recently presented [55]. Again, noninferiority to meropenem was established. In the mITT analysis, 83% of 520 patients in the ceftazidime/avibactam plus metronidazole arm had a clinical cure, compared to 85% of 523 patients receiving meropenem. In the clinically evaluable population, clinical cure rates were higher: 92% vs 93% in the ceftazidime/avibactam plus metronidazole vs meropenem arms, respectively [55]. Notably, subgroup analysis indicated that patients with moderate renal impairment (estimated creatinine clearance between 30 and 50 mL/minute) had lower cure rates in the ceftazidime/avibactam plus metronidazole arm (45%) vs the meropenem arm (74%). This may have been secondary to an observed delay in dose readjustment back to full dosing in patients with recovery of renal function [56]. Importantly, the dosing strategy used in these phase 3 cIAI trials for moderate renal failure was 1000/250 mg ceftazidime/avibactam every 12 hours. The current package insert recommendations are to give 1000/250 mg ceftazidime/avibactam every 8 hours to patients with moderate renal failure.

FORMULARY CONSIDERATIONS

Both ceftolozane/tazobactam and ceftazidime/avibactam will be most useful in the treatment of infections caused by MDR GNB.

The need for these agents is limited in patients with cUTI and cIAI caused by bacteria with a more favorable susceptibility pattern. However, the incidence of MDR GNB is increasing at an alarming pace, and these 2 agents represent important additions to currently available antibiotics.

For both drugs there is an issue of preexisting in vitro resistance. The percentages of Enterobacteriaceae and *Pseudomonas* species that are resistant to these antibiotics is likely to dramatically increase following their widespread clinical use, as it has for virtually any other antibiotic. We are in need of reliable clinical data to evaluate the role of ceftazidime/avibactam in the treatment of CRE. However, extrapolating from its in vitro activity, its safety profile, and the known clinical efficacy of β-lactam antibiotics, there is great promise that the outcomes of patients infected with KPC-producing CRE will improve. It would be terrible if we were to lose the opportunity to treat future critically ill patients because of overuse in patients with infections caused by more susceptible organisms. Therefore, the introduction into hospital formularies should be considered with great care and the appropriate restrictions should be put in place.

The need for either ceftolozane/tazobactam or ceftazidime/avibactam will vary greatly from hospital to hospital, depending on the population that they serve and specifically on their local antibiogram. Hospitals that have low rates of multidrug resistance in their isolates of *P. aeruginosa* and Enterobacteriaceae will have a limited need for these drugs.

In summary, ceftolozane/tazobactam and ceftazidime/avibactam are second-generation cephalosporin/β-lactamase inhibitor combinations with potential to improve outcomes of patients infected with MDR GNB. Pathogen-specific randomized trials are needed to determine the efficacy in those settings. If overused, widespread resistance is likely to evolve rapidly by the selection of resistant strains.

Notes

References

1. White House Office of the Press Secretary. Fact sheet: Obama administration releases national action plan to combat antibiotic-resistant bacteria. The White House, **2015**. Available at: https://www.whitehouse.gov/the-press-office/2015/03/27/fact-sheet-obama-administration-releases-national-action-plan-combat-ant. Accessed 5 November 2015.
2. Boucher HW, Talbot GH, Benjamin DK Jr, et al. 10×'20 Progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis **2013**; 56:1685–94.
3. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis **2009**; 48:1–12.
4. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis **2013**; 13:785–96.
5. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009–2012. Int J Antimicrob Agents **2014**; 43:328–34.
6. van Duin D, Kaye KS, Neuner EA, Bonomo RA. Carbapenem-resistant Enterobacteriaceae: a review of treatment and outcomes. Diagn Microbiol Infect Dis **2013**; 75:115–20.
7. Han JH, Bilker WB, Nachamkin I, et al. The effect of a hospital-wide urine culture screening intervention on the incidence of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species. Infect Control Hosp Epidemiol **2013**; 34:1160–6.
8. Andes D, Craig WA. Treatment of infections with ESBL-producing organisms: pharmacokinetic and pharmacodynamic considerations. Clin Microbiol Infect **2005**; 11(suppl 6):10–7.
9. Ehmann DE, Jahic H, Ross PL, et al. Avibactam is a covalent, reversible, non-beta-lactam beta-lactamase inhibitor. Proc Natl Acad Sci U S A **2012**; 109:11663–8.
10. Stachyra T, Levasseur P, Pechereau MC, et al. In vitro activity of the {beta}-lactamase inhibitor NXL104 against KPC-2 carbapenemase and Enterobacteriaceae expressing KPC carbapenemases. J Antimicrob Chemother **2009**; 64:326–9.
11. Murano K, Yamanaka T, Toda A, et al. Structural requirements for the stability of novel cephalosporins to AmpC beta-lactamase based on 3D-structure. Bioorg Med Chem **2008**; 16:2261–75.
12. Castanheira M, Mills JC, Farrell DJ, Jones RN. Mutation-driven beta-lactam resistance mechanisms among contemporary ceftazidime-nonsusceptible *Pseudomonas aeruginosa* isolates from U.S. hospitals. Antimicrob Agents Chemother **2014**; 58:6844–50.
13. Snydman DR, McDermott LA, Jacobus NV. Activity of ceftolozane-tazobactam against a broad spectrum of recent clinical anaerobic isolates. Antimicrob Agents Chemother **2014**; 58:1218–23.
14. Dubreuil LJ, Mahieux S, Neut C, Miossec C, Pace J. Anti-anaerobic activity of a new beta-lactamase inhibitor NXL104 in combination with beta-lactams and metronidazole. Int J Antimicrob Agents **2012**; 39:500–4.
15. Lucasti C, Hershberger E, Miller B, et al. Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Antimicrob Agents Chemother **2014**; 58:5350–7.
16. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis **2015**; 60:1462–71.
17. Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. J Antimicrob Chemother **2013**; 68:1183–92.
18. Sader HS, Farrell DJ, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against aerobic gram-negative organisms isolated from intra-abdominal and urinary tract infections in European and United States hospitals (2012). J Infect **2014**; 69:266–77.
19. Farrell DJ, Sader HS, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against gram-negative bacterial isolates from hospitalised patients with pneumonia in US and European medical centres (2012). Int J Antimicrob Agents **2014**; 43:533–9.
20. Sader HS, Castanheira M, Flamm RK, Farrell DJ, Jones RN. Antimicrobial activity of ceftazidime-avibactam against gram-negative organisms collected from U.S. medical centers in 2012. Antimicrob Agents Chemother **2014**; 58:1684–92.
21. Sader HS, Castanheira M, Flamm RK, Mendes RE, Farrell DJ, Jones RN. Ceftazidime/avibactam tested against gram-negative bacteria from intensive care unit

(ICU) and non-ICU patients, including those with ventilator-associated pneumonia. Int J Antimicrob Agents **2015**; 46:53–9.

22. Castanheira M, Mills JC, Costello SE, Jones RN, Sader HS. Ceftazidime-avibactam activity tested against Enterobacteriaceae isolates from U.S. hospitals (2011 to 2013) and characterization of beta-lactamase-producing strains. Antimicrob Agents Chemother **2015**; 59:3509–17.

23. Flamm RK, Sader HS, Farrell DJ, Jones RN. Ceftazidime-avibactam and comparator agents tested against urinary tract isolates from a global surveillance program (2011). Diagn Microbiol Infect Dis **2014**; 80:233–8.

24. Denisuik AJ, Karlowsky JA, Denisuik T, et al. In vitro activity of ceftazidime-avibactam against 338 molecularly characterized gentamicin-nonsusceptible gram-negative clinical isolates obtained from patients in Canadian hospitals. Antimicrob Agents Chemother **2015**; 59:3623–6.

25. Sader HS, Castanheira M, Farrell DJ, Flamm RK, Jones RN. Ceftazidime-avibactam activity when tested against ceftazidime-nonsusceptible *Citrobacter* spp., *Enterobacter* spp., *Serratia marcescens*, and *Pseudomonas aeruginosa* from United States medical centers (2011–2014). Diagn Microbiol Infect Dis **2015**; 83:389–94.

26. Sader HS, Castanheira M, Mendes RE, Flamm RK, Farrell DJ, Jones RN. Ceftazidime-avibactam activity against multidrug-resistant *Pseudomonas aeruginosa* isolated in U.S. medical centers in 2012 and 2013. Antimicrob Agents Chemother **2015**; 59: 3656–9.

27. Huband MD, Castanheira M, Flamm RK, Farrell DJ, Jones RN, Sader HS. In vitro activity of ceftazidime-avibactam against contemporary *Pseudomonas aeruginosa* isolates from United States medical centers by census region (2014). Antimicrob Agents Chemother **2016**; 60:2537–41.

28. Flamm RK, Farrell DJ, Sader HS, Jones RN. Ceftazidime/avibactam activity tested against gram-negative bacteria isolated from bloodstream, pneumonia, intra-abdominal and urinary tract infections in US medical centres (2012). J Antimicrob Chemother **2014**; 69:1589–98.

29. Winkler ML, Papp-Wallace KM, Hujer AM, et al. Unexpected challenges in treating multidrug-resistant gram-negative bacteria: resistance to ceftazidime-avibactam in archived isolates of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother **2015**; 59:1020–9.

30. Sader HS, Farrell DJ, Castanheira M, Flamm RK, Jones RN. Antimicrobial activity of ceftolozane/tazobactam tested against *Pseudomonas aeruginosa* and Enterobacteriaceae with various resistance patterns isolated in European hospitals (2011–12). J Antimicrob Chemother **2014**; 69:2713–22.

31. Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. hospitals (2011–2012). Antimicrob Agents Chemother **2013**; 57:6305–10.

32. Sutherland CA, Nicolau DP. Susceptibility profile of ceftolozane/tazobactam and other parenteral antimicrobials against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* from US hospitals. Clin Ther **2015**; 37:1564–71.

33. Estabrook M, Bussell B, Clugston SL, Bush K. In vitro activity of ceftolozane-tazobactam as determined by broth dilution and agar diffusion assays against recent U.S. *Escherichia coli* isolates from 2010 to 2011 carrying CTX-M-type extended-spectrum beta-lactamases. J Clin Microbiol **2014**; 52:4049–52.

34. Tato M, Garcia-Castillo M, Bofarull AM, Canton R, Group CS. In vitro activity of ceftolozane/tazobactam against clinical isolates of *Pseudomonas aeruginosa* and Enterobacteriaceae recovered in Spanish medical centres: results of the CENIT study. Int J Antimicrob Agents **2015**; 46:502–10.

35. Walkty A, Karlowsky JA, Adam H, et al. In vitro activity of ceftolozane-tazobactam against *Pseudomonas aeruginosa* isolates obtained from patients in Canadian hospitals in the CANWARD study, 2007 to 2012. Antimicrob Agents Chemother **2013**; 57:5707–9.

36. Castanheira M, Mills JC, Costello SE, Jones RN, Sader HS. Ceftazidime-avibactam activity tested against Enterobacteriaceae from United States hospitals (2011–2013) and characterization of beta-lactamase producing strains. Antimicrob Agents Chemother **2015**; 59:3509–17.

37. Papp-Wallace KM, Winkler ML, Taracila MA, Bonomo RA. Variants of the KPC-2 beta-lactamase which are resistant to inhibition by avibactam. Antimicrob Agents Chemother **2015**; 59:3710–7.

38. Berrazeg M, Diene S, Medjahed L, et al. New Delhi metallo-beta-lactamase around the world: an eReview using Google Maps. Euro Surveill **2014**; 19.

39. Li H, Estabrook M, Jacoby GA, Nichols WW, Testa RT, Bush K. In vitro susceptibility of characterized beta-lactamase-producing strains tested with avibactam combinations. Antimicrob Agents Chemother **2015**; 59:1789–93.

40. Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. Clin Infect Dis **2004**; 39:31–7.

41. Walkty A, DeCorby M, Lagace-Wiens PR, Karlowsky JA, Hoban DJ, Zhanel GG. In vitro activity of ceftazidime combined with NXL104 versus *Pseudomonas aeruginosa* isolates obtained from patients in Canadian hospitals (CANWARD 2009 study). Antimicrob Agents Chemother **2011**; 55:2992–4.

42. Levasseur P, Girard AM, Claudon M, et al. In vitro antibacterial activity of the ceftazidime-avibactam (NXL104) combination against *Pseudomonas aeruginosa* clinical isolates. Antimicrob Agents Chemother **2012**; 56:1606–8.

43. Miller B, Hershberger E, Benziger D, Trinh M, Friedland I. Pharmacokinetics and safety of intravenous ceftolozane-tazobactam in healthy adult subjects following single and multiple ascending doses. Antimicrob Agents Chemother **2012**; 56:3086–91.

44. Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. J Antimicrob Chemother **1993**; 31 suppl A:39–60.

45. Wise R, Logan M, Cooper M, Andrews JM. Pharmacokinetics and tissue penetration of tazobactam administered alone and with piperacillin. Antimicrob Agents Chemother **1991**; 35:1081–4.

46. Chandorkar G, Xiao A, Mouksassi MS, Hershberger E, Krishna G. Population pharmacokinetics of ceftolozane/tazobactam in healthy volunteers, subjects with varying degrees of renal function and patients with bacterial infections. J Clin Pharmacol **2015**; 55:230–9.

47. Chandorkar G, Huntington JA, Gotfried MH, Rodvold KA, Umeh O. Intrapulmonary penetration of ceftolozane/tazobactam and piperacillin/tazobactam in healthy adult subjects. J Antimicrob Chemother **2012**; 67:2463–9.

48. Rains CP, Bryson HM, Peters DH. Ceftazidime. An update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. Drugs **1995**; 49: 577–617.

49. Leroy A, Leguy F, Borsa F, Spencer GR, Fillastre JP, Humbert G. Pharmacokinetics of ceftazidime in normal and uremic subjects. Antimicrob Agents Chemother **1984**; 25:638–42.

50. Tarral A, Merdjan H. Effect of age and sex on the pharmacokinetics and safety of avibactam in healthy volunteers. Clinical Ther **2015**; 37:877–86.

51. Das S, Armstrong J, Mathews D, Li J, Edeki T. Randomized, placebo-controlled study to assess the impact on QT/QTc interval of supratherapeutic doses of ceftazidime-avibactam or ceftaroline fosamil-avibactam. J Clin Pharmacol **2014**; 54:331–40.

52. Umeh O, Cebrik D, Friedland I. A double-blind, randomized, phase 2 study to compare the safety and efficacy of intravenous CXA-101 (CXA) and intravenous ceftazidime (CTZ) in complicated urinary tract infections (cUTI). In: 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, **2010**.

53. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet **2015**; 385:1949–56.

54. Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin **2012**; 28:1921–31.

55. Mazuski JE, Gasnik L, Broadhurst H, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection—results from a phase III programme. In: 25th European Congress on Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, **2015**.

56. Food and Drug Administration. Briefing package NDA 206494 ceftazidime-avibactam. Silver Spring, Maryland: FDA, **2014**:1–55.