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REVIEW ARTICLE

Ceftazidime-Avibactam: a Novel Cephalosporin/β-lactamase Inhibitor Combination

George G. Zhanel · Christopher D. Lawson · Heather Adam · Frank Schweizer · Sheryl Zelenitsky · Philippe R. S. Lagacé-Wiens · Andrew Denisuik · Ethan Rubinstein · Alfred S. Gin · Daryl J. Hoban · Joseph P. Lynch 3rd · James A. Karlowsky

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Abstract Avibactam (formerly NXL104, AVE1330A) is a synthetic non-β-lactam, β-lactamase inhibitor that inhibits the activities of Ambler class A and C β-lactamases and some Ambler class D enzymes. This review summarizes the existing data published for ceftazidime-avibactam, including relevant chemistry, mechanisms of action and resistance, microbiology, pharmacokinetics, pharmacodynamics, and efficacy and safety data from animal and human trials. Although not a β-lactam, the chemical structure of avibactam closely resembles portions of the cephem bicyclic ring system, and avibactam has been shown to bond covalently to β-lactamases. Very little is known about the potential for avibactam to select for resistance. The addition of avibactam greatly (4-1024-fold minimum inhibitory concentration [MIC] reduction) improves the activity of ceftazidime versus most species of Enterobacteriaceae depending on the presence or absence of β-lactamase enzyme(s). Against *Pseudomonas aeruginosa*, the addition of avibactam also improves the activity of ceftazidime (~fourfold MIC reduction). Limited data suggest that the addition of avibactam does not improve the activity of ceftazidime versus *Acinetobacter* species or most anaerobic bacteria (exceptions: *Bacteroides fragilis*, *Clostridium perfringens*, *Prevotella* spp. and *Porphyromonas* spp.). The pharmacokinetics of avibactam follow a two-compartment model and do not appear to be altered by the co-administration of ceftazidime. The maximum plasma drug concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of avibactam increase linearly with doses ranging from 50 mg to

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2,000 mg. The mean volume of distribution and half-life of 22 L (~0.3 L/kg) and ~2 hours, respectively, are similar to ceftazidime. Like ceftazidime, avibactam is primarily renally excreted, and clearance correlates with creatinine clearance. Pharmacodynamic data suggest that ceftazidime-avibactam is rapidly bactericidal versus β-lactamase-producing Gram-negative bacilli that are not inhibited by ceftazidime alone.

Clinical trials to date have reported that ceftazidime-avibactam is as effective as standard carbapenem therapy in complicated intra-abdominal infection and complicated urinary tract infection, including infection caused by cephalosporin-resistant Gram-negative isolates. The safety and tolerability of ceftazidime-avibactam has been reported in three phase I pharmacokinetic studies and two phase II clinical studies. Ceftazidime-avibactam appears to be well tolerated in healthy subjects and hospitalized patients, with few serious drug-related treatment-emergent adverse events reported to date.

In conclusion, avibactam serves to broaden the spectrum of ceftazidime versus ß-lactamase-producing Gram-negative bacilli. The exact roles for ceftazidime-avibactam will be defined by efficacy and safety data from further clinical trials. Potential future roles for ceftazidime-avibactam include the treatment of suspected or documented infections caused by resistant Gram-negative-bacilli producing extended-spectrum ß-lactamase (ESBL), *Klebsiella pneumoniae* carbapenemases (KPCs) and/or AmpC ß-lactamases. In addition, ceftazidime-avibactam may be used in combination (with metronidazole) for suspected polymicrobial infections. Finally, the increased activity of ceftazidime-avibactam versus *P. aeruginosa* may be of clinical benefit in patients with suspected or documented *P. aeruginosa* infections.

1 Introduction

Broad-spectrum activity, well characterized pharmacokinetic and pharmacodynamic properties, and proven efficacy and safety have made cephalosporins an important part of the antimicrobial armamentarium for decades [1]. However, the worldwide spread of extended-spectrum β-lactamases (ESBLs) [2], *Klebsiella pneumoniae* carbapenemases (KPCs) [3], metallo-β-lactamases (MBLs) [3] as well as the presence of chromosomal AmpC β-lactamases [4] in Gram-negative bacilli has reduced the utility of the cephalosporins and contributed to the increase in difficult-to-treat multidrug-resistant (MDR) organisms [5]. Ceftazidime is a well described third-generation cephalosporin with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *Pseudomonas aeruginosa*; however, resistance—especially with Gram-negative bacilli—is increasing globally [6–8].

Avibactam (NXL104, AVE1330A), patented in 2011, is a non-β-lactam (diazabicyclooctane) [10] β-lactamase inhibitor, is active in vitro against Ambler class A and C β-lactamases and possesses activity versus some Ambler class D enzymes [9, 10]. Avibactam is being developed in combination with ceftazidime as well as in combination with ceftaroline, with the aim of broadening the spectra of these cephalosporins by inhibiting Ambler class A and C β-lactamases. Ceftazidime-avibactam is currently in phase III clinical trials for treatment of complicated urinary tract infection and complicated intra-abdominal infection (http://clinicaltrials.gov, identifiers NCT01595438, NCT01599806, NCT01499290 and NCT01500239).

This article reviews the existing published data for ceftazidime-avibactam, including relevant chemistry, mechanisms of action, mechanisms of resistance, microbiology, pharmacokinetics, pharmacodynamics, and efficacy and safety data from animal and human trials. Literature for this review was obtained via a comprehensive search of MEDLINE, SCOPUS and databases of scientific meetings from 2005 to September 2012 for all materials containing the name 'ceftazidime' and any of 'avibactam', 'NXL104' or 'AVE1330A'. These results were supplemented by bibliographies obtained from Novexel (http://www.novexel.com/NXL104.htm) and AstraZeneca.

2 Chemistry

The cephem nucleus is a bicyclic ring system composed of a four-member β-lactam ring fused with a six-member dihydrothiazine ring, with a sulfur atom at position 1, a double-bond between carbon 2 and carbon 3, and a carboxylic acid at position 4 [1, 11]. The distinct properties of individual cephalosporins arise from side-chains attached to the cephem nucleus at positions 3 and 7. The properties conferred by particular cephalosporin side-chains have been extensively reviewed [12–14].

Ceftazidime's position 7 side-chain is an amino-acyl group with an aminothiadiazole ring and a carboxypropyl-oxyimino chain attached at the α-carbon (Fig. 1). The aminothiadiazole ring, common to many extended-spectrum cephalosporins, confers increased activity against Gram-negative bacilli. In comparison with the methoxy-imino group frequently found in other third-generation cephalosporins, the carboxypropyl-oxyimino group confers similar stability to many β-lactamases, slightly decreased activity towards the *Enterobacteriaceae*, but much-increased activity versus *P. aeruginosa* [13–15]. The methyl-pyridinium group at position 3 enhances activity versus *P. aeruginosa* [12], and provides ceftazidime with zwitterionic properties that enhance its water solubility [11].

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The chemical structure of avibactam is (1R,2S,5R)-7-oxo-6-(sulfoxy)-1,6-diazabicyclo[3.2.1]octan-2-carboxamide [9] (Fig. 2) and it has a molecular weight of 265.25 Da. Avibactam is a synthetic compound produced by an enantio-selective process [9, 16]. Although not a β-lactam, avibactam closely resembles β-lactams in key areas: the carbonyl at avibactam position 7 mimics the β-lactam carbonyl of a cephalosporin such as ceftazidime; the sulfate at position 6 of avibactam takes the place of the carboxyl group at ceftazidime position 4; and the carboxamide at position 2 of avibactam aligns with the amino-acyl side-chain at ceftazidime position 7 (Fig. 3). Avibactam is synthesized as a sodium salt that is water soluble and stable in aqueous solution at room temperature [17], but detailed chemical data have not been published to date.

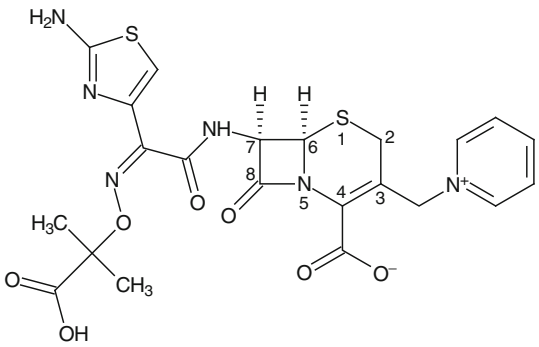

Fig. 1 Chemical structure of ceftazidime

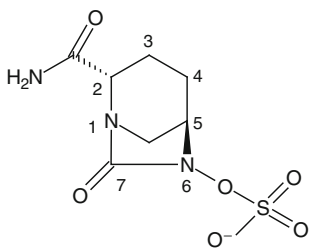

Fig. 2 Chemical structure of avibactam

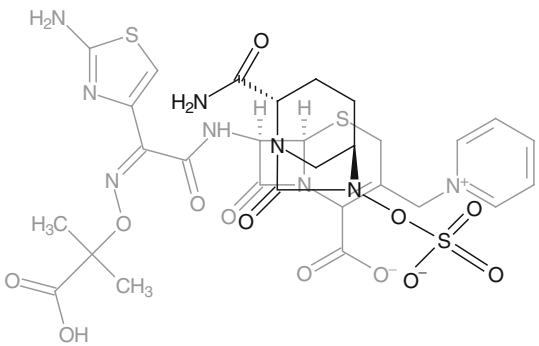

Fig. 3 Structural comparison of avibactam to ceftazidime

3 Mechanism of Action

Ceftazidime, like other β-lactams, inhibits peptidoglycan synthesis by inhibiting penicillin-binding proteins (PBPs) [18–20]. Inactivation of a sufficient fraction of the PBPs leads to an unstable peptidoglycan cell wall, ultimately resulting in cell death. Ceftazidime, by inhibiting peptidoglycan synthesis, inhibits growth of *Escherichia coli* and *P. aeruginosa* at low concentrations and induces rapid lysis in both species at higher concentrations [21].

β-lactamases are the most widespread and clinically important contributor toward β-lactam resistance, particularly among Gram-negative bacilli [4, 22, 23]. The β-lactamases are commonly classified into groups A, B, C and D based on similarity and difference in primary amino acid sequence as described by Ambler and colleagues [24–27]. A second system that classifies the β-lactamases by spectrum of activity and resistance to β-lactamase inhibitors was described by Bush and colleagues [28, 29], though the molecular (Ambler) classification system is referred to in this paper. The basic mechanism of action of β-lactamases has been well described [30–32]. A common strategy to inactivate β-lactamase activity is alteration of side-chains to create a molecule for which the β-lactamase has poor affinity (e.g. the 3 and 7 side-chains of the cephem nucleus). A second effective strategy is the pairing of a β-lactam with a β-lactamase inhibitor, a mechanistic or suicide substrate that inactivates the β-lactamase in much the same manner as the PBP is inactivated by a β-lactam. As new β-lactams and β-lactamase inhibitors have been introduced, selective pressure on clinical species expressing β-lactamases has driven their evolution such that for any given β-lactam, a β-lactamase now exists that is capable of inactivating it [28, 29]. A wide variety of mutations alter the spectrum of existing β-lactamases to increase their affinity for previously unaffected β-lactams or render them resistant to existing β-lactamase inhibitors [30, 33] (http://www.lahey.org/Studies/).

Avibactam has been shown to bond covalently to β-lactamases through the formation of a carbamate bond between avibactam's position 7 carbonyl carbon and the same active-site serine that participates in acyl bonding with β-lactam substrates. The covalent nature of the bond has been confirmed via determination of the x-ray crystal structure of avibactam bound to a variety of β-lactamases [34–38], representing all three molecular classes of serine active site β-lactamases. Mass spectroscopy studies provide evidence that avibactam/β-lactamase binding involves a simple reaction mechanism with no rearrangement like that observed for molecules containing a β-lactam moiety [39–41].

Studies assessing the half maximal inhibitory concentration (IC_{50}) values for avibactam have been measured and

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Table 1 Half maximal inhibitory concentration values for avibactam and comparator β-lactamase inhibitors determined after 5 min of incubation with different β-lactamases

	β-lactamase inhibitor IC_{50} (nM)			Reference
	Avibactam	Clavulanic acid	Tazobactam	
Class A				
TEM-1	8	130	40	[42]
TEM-1	8	58	32	[41]
SHV-4	1.5	5	120	[79]
SHV-4	3	4	55	[41]
KPC-2	38	6,500	80,000	[82]
KPC-2	37.5 ± 2.6	6,500 ± 400	9,200 ± 4,100	[78]
KPC-2	170	>100,000	50,000	[41]
CTX-M-15	4.5 ± 0.9	12.5 ± 2.8	5.8 ± 2.7	[78]
CTX-M-15	5	12	6	[34]
CTX-M-15	5	12	6	[41]
Class C				
P99	80	1×10^6	5,000	[42]
P99	100	>100,000	1,300	[41]
AmpC	128	>100,000	4,600	[41]

IC_{50} Half maximal inhibitory concentration

compared with clavulanic acid and tazobactam for a variety of class A and C β-lactamases (Table 1) [40]. Although IC_{50} values are time dependent [40], the values compiled in Table 1 originate from experiments using similar methodology, allowing for useful comparison. Avibactam has activity similar to that of clavulanic acid against SHV-4 and similar to that of both clavulanic acid and tazobactam against CTX-M-15, but shows greater activity than (i.e. is a more potent inhibitor) comparator inhibitors in all other cases, particularly against the carbapenemase KPC-2 and the class C β-lactamases.

A turnover value (indicating the number of inhibitor molecules required to deactivate a single enzyme) of 1 has been uniformly reported for avibactam (with one exception [42]). The turnover rate of clavulanic acid is greater than 100-fold that of avibactam against TEM-1 [40], while that of tazobactam is more than tenfold that of avibactam against P99, and 50-fold that of avibactam when inhibiting TEM-1 [40–42]. Initial studies reported an enzyme kinetic model where inactivation of the β-lactamase enzyme involved two binding steps: non-covalent association of avibactam with the binding site followed by covalent acylation of avibactam to the enzyme (along with opening of the 5-member urea ring) [34, 40–42].

A recent paper by Ehmann et al. proposes that the enzyme kinetics of avibactam are in fact that of a covalently-binding reversible inhibitor with a two-step binding process (as described above) and a slow deacylation phase that restores avibactam's 5-membered urea ring [39]. The work of Ehmann et al. supports the notion that avibactam is released from the β-lactam in its original form. This experiment was repeated with each of CTX-M-15, KPC-2, P99 and the chromosomal AmpC of *P. aeruginosa* inhibited by avibactam serving as a donor to uninhibited TEM-1, with similar results [39]. Details of reaction mechanism leading to the restoration of avibactam as it is cleaved from the β-lactamase active site remain to be discovered.

4 Mechanism of Resistance

Limited data exist regarding the potential for avibactam to select for resistance and no data are available for ceftazidime-avibactam. Avibactam has been reported to not induce chromosomal *ampC* expression in *Enterobacter cloacae* [43]. Livermore et al. [44] studied the consequences of exposing Enterobacteriaceae to varying concentrations of avibactam when used along with ceftaroline (an oxyimino-cephalosporin). Single- and multi-step selection (where the concentration of ceftaroline was doubled each step) was performed and mutations were characterized by polymerase chain reaction (PCR), DNA sequencing and SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis). Minimum inhibitory concentrations (MICs) of the pre- and post-selection organisms were compared for a large panel of β-lactam antibacterials. Single-step selection experiments found that isolated colonies occurred at a frequency of $<10^{-9}$. An *E. coli* expressing a mutant CTX-M-15 was found to have gained resistance to ceftaroline-avibactam but lost resistance to all non-ceftaroline oxyimino cephalosporins through a point mutation in $bla_{\text{CTX-M-15}}$ leading to a Lys237Gln substitution. Two AmpC-derepressed *E. cloacae* isolates were found to have identical deletions in *ampC*, gaining resistance to ceftaroline-avibactam with no loss of resistance to other agents. The MICs for three derepressed-AmpC *E. cloacae* were doubled six times against ceftaroline plus 1 mg/L avibactam, and four or five times against ceftaroline plus 4 mg/L avibactam. One *E. cloacae* mutant lacked the porins OmpC and OmpF but showed no other mutation, while the remaining mutants showed point mutations at the same location in *ampC* leading to Asn366His (in a mutant also showing reduced porin expression) and Asn366Ile substitutions. In experiments assessing the activity of several β-lactamase inhibitors against functional CMY-2 β-lactamase mutants, the affinity of avibactam for mutant enzymes was found to decrease, but this did not result in a reduction of in vitro antimicrobial activity [45, 46]. Clearly, information on potential mechanisms of resistance to avibactam are limited and no data exist with ceftazidime-avibactam, thus work is required in this area.

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5 Microbiology

The MIC_{50}, MIC_{90} and MIC range values (mg/L) presented in Tables 2, 3 and 4 are modal values derived from a review of available published literature for ceftazidime-avibactam and comparators to date. Table 2 shows the activity of ceftazidime-avibactam and comparators against Gram-negative bacteria [47–66]. These data demonstrate that the addition of avibactam greatly improves (4-1024-fold MIC reduction) the activity of ceftazidime versus most *Enterobacteriaceae* species depending on the presence or absence of a β-lactamase enzyme(s). Against *P. aeruginosa*, the addition of avibactam improves the activity of ceftazidime (~fourfold MIC_{90} reduction) [Table 2]. Limited data suggest that the addition of avibactam does not improve the activity of ceftazidime versus *Acinetobacter* species (Table 2).

Table 3 shows the activity of ceftazidime-avibactam compared with ceftazidime alone against *E. coli* and *K. pneumoniae* isolates producing specific β-lactamase enzymes [42, 47, 57, 58, 67–83]. It should be noted that, except where indicated, MIC values are based on results from fewer than ten isolates. Although the effect of avibactam was consistent when larger sample sizes were available, results derived from smaller numbers of isolates should be interpreted cautiously. Avibactam significantly improved the activity of ceftazidime against both *E. coli* and *K. pneumoniae*-producing ESBLs from Ambler classes A (4-1024-fold MIC reduction) and D (2-512-fold MIC reduction), KPC carbapenemases (32-8192-fold MIC reduction) and both chromosomal and mobile Ambler class C β-lactamases (2-512-fold MIC reduction). As expected, given its mechanism of action, avibactam does not improve the activity of ceftazidime against organisms producing MBLs such as New Delhi MBL (NDM) [Table 3]. It needs to be stated that the majority of Enterobacteriaceae with elevated ceftazidime-avibactam MIC values will likely contain multiple resistance mechanisms, which may include β-lactamases not inhibited by avibactam (i.e. some OXA-types and MBLs), porin alterations and overexpression of efflux pumps.

The activity of ceftazidime-avibactam and comparators against anaerobic bacteria is presented in Table 4 [84–86]. Versus *Bacteroides fragilis*, *Clostridium perfringens* and organisms from the *Prevotella* and *Porphyromonas* genera, ceftazidime-avibactam significantly increased the activity compared with ceftazidime alone. For other anaerobes, ceftazidime-avibactam showed little or no improvement over that of ceftazidime alone; most MIC_{50} values and all MIC_{90} values remained above the Clinical and Laboratory Standards Institute (CLSI) resistant breakpoint for ceftazidime (≥32 mg/L). No data have been published on the activity of ceftazidime-avibactam versus Gram-positive bacteria.

6 Pharmacokinetics

The pharmacokinetics of ceftazidime are well known. Following a 1 g dose (infused over 30 min), the concentration profile is best described by a two-compartment model with a rapid distribution phase, a maximum plasma drug concentration (C_{max}) of ~100 mg/L, and a volume of distribution (V_d) of ~0.3 L/kg [1, 87]. Ceftazidime is approximately 17 % protein bound, is 80–90 % renally cleared with an elimination half-life ($t_{½}$) of approximately 1.8 h in patients with normal renal function [1, 87]. Data on the interaction of ceftazidime with avibactam was published for 16 healthy volunteers [88]. Two cohorts of eight subjects were administered single doses of 250 mg or 500 mg of avibactam, followed (after a 7-day washout period) by a ceftazidime-avibactam dose of 1,000/250 mg and 2,000/500 mg, respectively. The presence of ceftazidime was not found to affect the pharmacokinetics of avibactam and, in the presence of avibactam, the pharmacokinetics of ceftazidime were unchanged.

The results of three phase I trials examining the single-dose pharmacokinetics of avibactam ranging from 50 mg to 2,000 mg are summarized in Table 5. In a single dose escalation study involving 70 subjects, the pharmacokinetics of avibactam were reported as linear for doses from 50 mg to 2,000 mg (Table 5) [88, 89, 91]. Following a 100-mg dose (infused over 30 min), the concentration profile of avibactam is best described by a two-compartment model with a rapid distribution phase, a C_{max} of ~5.0 mg/L and a V_d at steady state (V_{ss}) of ~22.5 L [88, 91]. To date, the protein binding of avibactam is unknown; avibactam, like ceftazidime, is primarily (95 %) renally cleared, with clearance correlating well with creatinine clearance (CL_{CR}) [89]. The phase I studies in healthy volunteers describe an average half-life of 1.7–2.1 h. The study of avibactam in complicated intra-abdominal infection reported a 62 % increase in avibactam clearance compared with healthy subjects [90].

In six anuric patients, a pharmacokinetic study of 100 mg of avibactam administered over 30 mins prior to haemodialysis (4-h session) found a mean extraction coefficient of 0.77, with a total clearance of 9.29 L/h (155 mL/min), and approximately 54 % of the drug removed during dialysis, which is similar to ceftazidime [91]. In the same patient cohort, the average clearance off-dialysis was 1.02 L/h (17 mL/min) with a $t_{½}$ of 22.2 h.

In summary, the pharmacokinetics of avibactam and ceftazidime appear to be very complementary, with similar

Table 2 In vitro activity[a] of ceftazidime-avibactam and comparators against Gram-negative aerobes [47–66]

Gram negative aerobe	Ceftazidime			Ceftazidime-avibactam[a]			Ceftazidime-avibactam MIC_{90} reduction (fold)	Cefepime		Ceftriaxone	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Citrobacter freundii	0.5	>32	≤0.25–>64	0.25	0.5	≤0.06–2	>64	≤1	≤1	≤1	32
Citrobacter spp.	0.25	>32	NA	0.12	0.5	≤0.06–4	>64	≤0.12	4	NA	NA
Ceftazidime non-susceptible	32	>32	NA	0.25	1	≤0.06–4	>32	1	>16	NA	NA
Enterobacter aerogenes	≤0.5	>32	≤0.25–>32	0.25	0.5	≤0.06–2	>64	≤1	≤1	≤1	16
Enterobacter cloacae	0.5	>32	≤0.25–>32	0.25	1	≤0.06–2	>32	≤1	1	≤0.25	64
Enterobacter spp.	0.25	>32	NA	0.25	1	≤0.03–>32	>32	≤0.12	2	NA	NA
Ceftazidime-resistant[b]	32	>32	NA	0.5	2	0.06–>32	>16	2	>16	NA	NA
AmpC producing + porin loss	256	256	64–256	1	1	0.25–1	256	NA	NA	NA	NA
Escherichia coli	0.25	2	≤0.03–>32	0.12	0.25	≤0.03–2	8	≤0.12	1	≤0.25	≤0.25
ESBL producing	16	32	0.5–>64	0.12	0.25	<0.008–2	128	8	32	64	>64
AmpC hyper-producing	16	64	0.12–>64	0.12	0.5	≤0.004–4	128	0.25	0.5	8	32
ESBL producing and AmpC hyper-producing	32	>64	2–>64	0.12	0.12	0.015–0.12	>512	16	32	>64	>64
Klebsiella oxytoca	≤0.25	0.5	≤0.25–>64	0.12	0.5	≤0.06–1	1	≤1	≤1	≤0.25	0.5
Klebsiella pneumoniae	≤0.25	1	≤0.5–>32	0.12	0.5	≤0.06–2	2	≤1	≤1	≤0.25	≤0.25
ESBL producing	64	>64	0.12–256	0.5	1	0.06–2	>64	8	64	>64	>64
OXA-48 carbapenemase-producing	256	512	≤0.12–512	0.25	0.5	<0.008–1	1024	32	512	NA	NA
KPC-producing	≥512	≥512	32–≥512	0.25	1	≤0.06–1	≥512	32	128	NA	NA
ESBL-producing plus porin loss	256	512	126–512	1	1	0.5–2	512	NA	NA	NA	NA
Klebsiella spp.	0.12	32	NA	0.12	0.5	≤0.03–32	64	≤0.12	16	0.06	32
ESBL	>32	>32	NA	0.5	2	≤0.03–32	>16	>16	>16	NA	NA
Carbapenem non-susceptible[c]	>32	>32	NA	0.5	2	≤0.03–32	>16	>16	>16	NA	NA
Morganella morganii	0.12	8	NA	0.06	0.12	≤0.06–8	64	≤0.12	0.25	0.12	8
Proteus mirabilis	0.06	0.12	≤0.25–32	0.06	0.12	≤0.03–0.25	1	≤0.12	0.25	≤0.25	≤0.25
Indole-positive *Proteus* spp.	0.12	8	NA	0.06	0.25	≤0.03–2	32	≤0.12	0.25	NA	NA
Salmonella spp.	0.25	0.5	NA	0.25	0.5	≤0.03–0.5	1	≤0.12	0.25	0.06	0.125
Serratia marcescens	0.12	2	≤0.25–16	0.25	0.5	≤0.06–>8	4	≤0.12	2	≤0.25	1
Serratia spp.	0.25	0.5	N	0.25	0.5	0.06–8	1	≤0.12	0.5	NA	NA
Burkholderia cepacia	64	>128	8–>128	8	>128	≤1–>128	1	NA	NA	NA	NA
Pseudomonas aeruginosa	4	32	≤0.25–256	2	8	≤0.06–>128	4	4	16	32	>64
MDR[d]			NA	8	32	≤1–>128	NA	NA	NA	NA	NA
AmpC-derepressed	64	>128	8–>128	4	8	≤1–64	>16	NA	NA	NA	NA
Intrinsic MexA/OprM	4	8	≤1–16	4	8	≤1–16	1	NA	NA	NA	NA
Acinetobacter baumannii	8	32	1–>512	8	>16	1–256	NA	64	128	8	64
OXA carbapenemase-producing	128	>128	4–>128	8	>128	4–>128	1	NA	NA	NA	NA

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Table 2 continued

Gram negative aerobe	Ceftazidime			Ceftazidime-avibactam[a]			Ceftazidime-avibactam MIC_{90} reduction (fold)	Cefepime		Ceftriaxone	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Acinetobacter spp.	>32	>32	NA	16	>32	≤0.03–>32	1	>16	>16	16	>32
Imipenem-resistant[e]	>32	>32	NA	32	>32	0.25–>32	1	>16	>16	NA	NA

[a] Fixed avibactam concentration of 4 mg/L

[b] Ceftazidime MIC ≥32 mg/L

[c] Meropenem MIC ≥8 mg/L; imipenem MIC ≥8 mg/L

[d] MDR defined as concomitant resistance to three or more different antimicrobial classes

[e] Imipenem MIC ≥16 mg/L

ESBL extended-spectrum ß-lactamase, *KPC Klebsiella pneumoniae* carbapenemases, *MDR* multidrug resistant, MIC_{50} minimum concentration to inhibit growth of 50 % of isolates, MIC_{90} minimum concentration to inhibit growth of 90 % of isolates

V_d, $t_{½}$ and clearance. The administration of ceftazidime does not impact the pharmacokinetics of avibactam.

7 Pharmacodynamics

The comparative results of an in vitro time kill study examining the bactericidal activity of ceftazidime in combination with avibactam against a variety of β-lactamase-producing genotypes are summarized in Table 6 [70]. In this study, ceftazidime alone was not bactericidal except at 256 mg/L against the *K. pneumoniae* expressing SHV-11, a non-ESBL. The comparator ceftazidime-clavulanic acid (ratio of 4:1) was only bactericidal against one *E. cloacae* isolate (at 32 mg/L), while the comparator piperacillin/tazobactam (ratio 8:1) was not bactericidal against any isolate at concentrations between 16 mg/L and 256 mg/L. In contrast, ceftazidime-avibactam proved to be bactericidal versus all strains at concentrations ranging from 2 to 8 mg/L (Table 6).

The bactericidal activity of two ceftazidime-avibactam dosing regimens was studied against a variety of β-lactamase-producing genotypes, in an in vitro pharmacodynamic hollow-fibre model [67]. Both regimens maintained a continuous infusion of ceftazidime at 16 mg/L, with regimen 1 adding a continuous infusion of avibactam at 4 mg/L, while regimen 2 added a single dose of avibactam (both with a 2-h half-life). Both regimens were tested against an *E. cloacae* isolate expressing AmpC, a *K. pneumoniae* isolate expressing CTX-M-15, and two *K. pneumoniae* isolates expressing SHV-5 and TEM-10, respectively. With ceftazidime alone, all four isolates demonstrated MICs >128 mg/L, ceftazidime-avibactam MICs were ≤4 mg/L for all isolates. For all isolates, the total area under the plasma concentration-time curve (AUC) of avibactam was either similar for both regimens or higher in regimen 2. Versus all isolates studied, both combinations of ceftazidime-avibactam were bactericidal (>3 $\log_{10}$ bacterial kill) within 2 h. Regarding regrowth, no regrowth was observed with regimen 1; however, regrowth was observed for all four isolates with regimen 2 after the concentration of avibactam dropped below the limit of detection of 0.5 mg/L. No change in pre- and post-experiment MIC occurred with any isolate treated with ceftazidime-avibactam.

An in vitro study examined the bactericidal activity of 2,000 mg ceftazidime dosed three times per day plus avibactam dosed as a continuous infusion with concentrations of 0.5, 1, 2, 4, 6, 8 or 10 mg/L over the course of 72 h versus a strain of Amp-C hyperproducing *E. cloacae* (ceftazidime-avibactam MIC of 0.5 mg/L, avibactam fixed at 2 mg/L) [92]. Bactericidal activity was monitored by change in viable colony counts and area under the bacterial kill curve. Ceftazidime-avibactam was bactericidal

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Table 3 In vitro activity of ceftazidime-avibactam and comparators against bacteria expressing specific β-lactamase enzymes [42, 47, 57, 58, 67–83]

	β-lactamase enzyme[a]	MIC		MIC reduction (fold)
		Ceftazidime	Ceftazidime-avibactam[b]	
Escherichia coli				
Extended-spectrum β-lactamases	CTX-M-9	2	0.25	8
	CTX-M-14	2	0.06	32
	CTX-M-15[c]	32	0.12	256
	PER-1	256	1	256
	SHV-3	32	0.06	512
	SHV-4	128	0.25	512
	SHV-5	64	0.25	256
	TEM-3	64	0.25	256
	TEM-5	32	0.06	512
	TEM-6	>128	0.5	>256
	TEM-7	16	1	16
	TEM-8	256	0.25	1024
	TEM-9	>128	0.5	>256
	TEM-10	128	0.5	256
	TEM-12	16	0.25	64
	TEM-16	256	0.5	512
	TEM-24	>64	4	>16
	TEM-43	4	0.25	16
	OXA-2	0.25	0.12	2
	OXA-48	4	≤0.008	≥512
	CTX-M-2, TEM-1	32	0.5	64
	CTX-M-15, TEM-1[c]	32	0.12	256
	CTX-M-15, OXA-1[c]	16	0.25	64
	CTX-M-16, TEM-1[c]	>128	1	>128
	SHV-12, TEM-1	16	0.06	256
	CTX-M-15, TEM-1, OXA-1[c]	128	0.25	512
Carbapenemases	KPC-2	64	0.25	256
	KPC-2, TEM-1	128	0.5	256
	KPC-3	64	2	32
	GES-3	128	0.25	512
	GES-4	128	1	128
Metallo-β-lactamases	NMC-A	0.25	≤0.015	≥16
	PER-1	>64	4	>16
	VEB-1	2	0.5	4
	IMP-1	256	64	4
	NDM	>256	>256	>1
	VIM-1	>512	512	>1
Ambler class C β-lactamases	AmpC	16	1	16
	AmpC, CTX-M-15	>32	0.12	>56
	AmpC, CTX-M-15, OXA-1, TEM-1	>32	0.25	>128
	ACC-1	>64	4	>16
	CMY-2, VEB-2	256	128	2
	CMY-2, CTX-M-14, TEM-1	128	1	128
	CMY-2, CTX-M-15, OXA-1	32	0.06	512
	FOX-1	32	4	8

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Table 3 continued

	β-lactamase enzyme[a]	MIC		MIC reduction (fold)
		Ceftazidime	Ceftazidime-avibactam[b]	
Klebsiella pneumoniae				
Extended-spectrum β-lactamases	CTX-M-3	16	0.5	32
	CTX-M-14	16	1	16
	CTX-M-15[c]	>128	1	>128
	SHV-2	>64	0.5	>128
	SHV-3	>64	0.5	>128
	SHV-4	>256	4	>64
	SHV-5	64	0.5	128
	SHV-6	4	1	4
	SHV-18	64	2	32
	SHV-38	8	2	4
	TEM-4	32	0.5	64
	CTX-M-2, TEM-1B	128	2	64
	CTX-M-16, OXA-1	256	1	256
	SHV-5, TEM-10	>128	2	>64
	CTX-M-2, SHV-5, TEM-12	>128	2	>64
	CTX-M-2, SHV-2, TEM-12	>128	4	>32
	CTX-M-3, SHV-1, TEM-1B	256	2	128
	CTX-M-15, TEM-1, OXA-1	256	2	128
	SHV-1, TEM-2, PER	256	4	64
Carbapenemases	KPC-2[c]	>128	1	>128
	KPC-3[c]	256	0.5	512
	KPC-2, SHV-11, SHV-12, TEM-1	512	≤0.06	≥8192
Metallo-β-lactamases	VIM-1, SHV-5	256	256	1
Ambler class C β-lactamases	AmpC + SHV-11	64	2	32
	DHA-2	256	2	128
	ACC-1, TEM-1	128	1	128
	LAT-4, SHV-11 variant	32	1	32
	CMY-4, TEM-1	256	0.5	512
	DHA-1, SHV-2a, TEM-1	>128	1	>128
	MOX-2, SHV-5, TEM-1	256	1	256

[a] Isolates may contain genes encoding other β-lactamases

[b] Fixed avibactam concentration of 4 mg/L

[c] Modal MIC values derived from MIC data for ten or more unique isolates

MIC minimum inhibitory concentration

(≥3 $\log_{10}$) for all concentrations of avibactam. Regrowth was observed with all concentrations of avibactam. Whether this was due to low ceftazidime or avibactam concentrations was unknown; however, sigmoid curves fit at 12, 24, 48 and 72 h for change in viable colony count, and at 24, 48 and 72 h for area under the bacterial kill curve (r^2 0.67 to 0.99), indicated that no additional benefit was gained from avibactam concentrations >2 mg/L.

Human plasma samples containing ceftazidime-avibactam were collected from a phase I pharmacokinetic and safety evaluation study and assessed in vitro for bactericidal activity against 5×10^5 colony-forming units (CFUs) of two *K. pneumoniae* strains: one ceftazidime-susceptible and one ceftazidime-resistant expressing AmpC and SHV-11 β-lactamases [88]. Plasma samples from eight subjects dosed with 1,000/250 mg ceftazidime-avibactam and eight subjects dosed with 2,000/500 mg ceftazidime-avibactam were found to be bactericidal (minimum of 3 $\log_{10}$ reduction from the initial inoculum count) versus both strains.

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Table 4 In vitro activity of ceftazidime-avibactam and comparators versus anaerobic bacteria [84–86]

Anaerobic bacteria	Ceftazidime			Ceftazidime-avibactam[a]			Ceftazidime-avibactam MIC_{90} reduction (fold)	Ceftriaxone	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range		MIC_{50}	MIC_{90}
Bacteroides caccae	>128	>128	8–>128	32	>128	4–>128	1	NA	NA
Bacteroides fragilis	64	>128	0.5–>128	4	32	≤0.06–>64	>4	16	128
Bacteroides ovatus	>128	>128	8–>128	128	>128	32–>128	1	>64	>64
Bacteroides stercoris/uniformis/salyersiae	>128	>128	32–>128	64	128	4–>128	>1	32	>128
Bacteroides thetaiotaomicron	>128	>128	>128	128	>128	16–>128	1	>64	>64
Bacteroides vulgatus	>128	>128	32–>128	32	128	16–128	>1	16	>64
Bacteroides spp.	128	>128	0.5–>128	8	64	≤0.06–>64	>2	64	>128
Parabacteroides spp.	>128	>128	8–>128	16	64	4–>128	>2	NA	NA
Clostridium difficile	128	>128	64–>128	32	64	32–>128	>2	32	128
Clostridium perfringens	64	>128	0.5–>128	≤0.06	2	≤0.06–4	>64	0.5	2
Fusobacterium spp.	NA	NA	0.125–32	NA	NA	≤0.06–2	NA	NA	NA
Prevotella/Porphyromonas spp.	32	>128	0.5–>128	2	4	≤0.125–8	>32	NA	NA
Gram-positive anaerobes	1	64	≤0.06–32	0.25	32	≤0.06–16	2	1	64

[a] Fixed avibactam concentration of 4 mg/L

MIC_{50} minimum concentration to inhibit growth of 50 % of isolates, *MIC_{90}* minimum concentration to inhibit growth of 90 % of isolates, *NA* No data available

8 Animal Studies

Two studies have reported the efficacy of ceftazidime-avibactam in murine septicaemia. In the first study, female CD-1 mice were infected with 3.3 to 3.6 × 10^5 CFU of two strains of KPC-producing *K. pneumoniae* (strain VA-361 expressing KPC-2, TEM-1 and SHV-11 with ceftazidime MIC 256 mg/L, or strain VA-406 expressing KPC-2, TEM-1, SHV-11 and SHV-12 with ceftazidime MIC ≥512 mg/L) via intraperitoneal injection [93]. Single doses of ceftazidime-avibactam (ratios of 2:1, 4:1, 8:1 and 16:1; ceftazidime doses, depending on strain and ratio, from 1 to 64 mg/kg by twofold steps) or ceftazidime alone (512, 1,024 or 2,048 mg/kg) were administered subcutaneously 30 minutes after infection. Five mice were tested per dose, survival rate was monitored twice daily for 5 days, and all tests were performed in triplicate. Untreated mice died within 24 to 48 hours. For ceftazidime alone, effective dose in 50% (ED_{50}) was 1,578 mg/kg for strain VA-261 and 709 mg/kg for strain VA-406, whereas for ceftazidime-avibactam, ED_{50} values were significantly reduced at 8.1, 15.1, 16.9 and 29.5 mg/kg (ceftazidime component) for strain VA-261, and 3.5, 3.8, 7.2 and 12.1 mg/kg for strain VA-406 for ceftazidime-avibactam ratios of 2:1, 4:1, 8:1 and 16:1, respectively. At any given dose, animal survival was observed to increase as the proportion of avibactam in ceftazidime-avibactam increased.

In the second septicaemia study, male CD-1 mice were infected with 10^8 CFU of one of four ceftazidime-resistant strains (*E. coli* expressing CTX-M-16 and TEM-1; *E. coli* expressing CTX-M-2 and TEM-1; *K. pneumoniae* expressing CTX-M-2, SHV-2 and TEM-12; *K. pneumoniae* expressing CTX-M-2 and TEM-1B, all with ceftazidime MICs from 32 to >128 mg/L) by intraperitoneal injection [71]. Infected mice were administered subcutaneous doses at 1 and 4 h post-infection with one of ceftazidime-avibactam (4:1 ratio, ceftazidime doses 3, 10 and 30 mg/kg), ceftazidime (doses 3, 10, 30 and 60 mg/kg), cefotaxime (doses 3, 10, 30, 60 and 90 mg/kg) or piperacillin/tazobactam (4:1 ratio, piperacillin doses 30, 60 and 90 mg/kg). Ten to twenty mice were infected per strain per dose regimen, and survival was monitored for 5 days. Untreated mice died within 2 days. For ceftazidime-avibactam, ED_{50} values were reported as 11 mg/kg/dose (for the ceftazidime component) for the *E. coli* strain expressing CTX-M-16 and TEM-1, 27 mg/kg/dose for the *E. coli* strain expressing CTX-M-2 and TEM-1, 27 mg/kg/dose for the *K. pneumoniae* strain expressing CTX-M-2, SHV-2 and TEM-12, and 18 mg/kg/dose for the *K. pneumoniae* strain expressing CTX-M-2 and TEM-1B. ED_{50} values for all comparators for all strains were >90 mg/kg/dose except for ceftazidime alone against the *E. coli* strain expressing CTX-M-16 and TEM-1, with an ED_{50} of 74 mg/kg/dose.

In a murine kidney infection model study, male CD-1 mice were infected with approximately 10^4 CFU of one of six ceftazidime-resistant strains (*E. coli* expressing SHV-4, *E. coli* expressing AmpC, *E. cloacae* expressing AmpC, *K. pneumoniae* expressing AmpC and SHV-11, *Morganella morganii* expressing AmpC, or *Citrobacter freundii* expressing AmpC, all with ceftazidime MICs from 16 to >128 mg/L) via direct injection to the left kidney [68]. Infected mice were treated at 4, 8, 24 and 32 h after

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Table 5 Results from phase I pharmacokinetic studies of avibactam in healthy human subjects

Subject Demographics	n	Type of study	Dose (mg)	C_{max} (mg/L)[a]	AUC (mg · h/L)[a]	V_{ss} (L)[a]	$t_{1/2}$ (h)[a]	CL (mL/min)[a]	Reference
Young healthy adult males[b]	70	Single escalating dose[e]	50	2.67 ± 0.37	3.72 ± 0.41	22.5 ± 2.0	1.99 ± 0.42	206.9 ± 19.9	[88]
			100	5.09 ± 1.68	8.36 ± 1.67				
			250[c]	12.1 ± 2.4	19.7 ± 2.2				
			500[d]	29.0 ± 16.8	38.5 ± 10.4				
			1,000	49.6 ± 10.9	87.1 ± 13.9				
			1,500	101 ± 21	146 ± 15				
			2,000	124 ± 29	186 ± 28				
Healthy males, mean age 28.7 years (range 20–37)	8	Single dose[e]	500	33.83 ± 4.24	49.86 ± 6.27	NR	2.09 ± 0.64	169.3 ± 20.5	[88]
Healthy females, mean age 20.9 years (range 23–44)	8	Single dose[e]	500	36.86 ± 9.31	49.75 ± 9.10	NR	1.71 ± 0.09	172.3 ± 30.3	[88]
Healthy males[b]	6	Single dose[e]	100	4.66 ± 0.36	6.89 ± 0.56	NR	1.79 ± 0.32	243.3 ± 19.2	[91]

[a] Mean ± standard deviation

[b] Demographic details not available

[c] Administered alone and separately with 1,000 mg of ceftazidime

[d] Administered alone and separately with 2,000 mg of ceftazidime

[e] 30-minute intravenous infusion

AUC area under the plasma concentration-time curve, *CL* clearance, C_{max} maximum plasma drug concentration, *NR* value not reported, $t_{½}$ elimination half-life, V_{ss} volume of distribution at steady state

Table 6 In vitro bactericidal activity of ceftazidime/avibactam by time kill assay [70]

Species	Resistance phenotype	Ceftazidime MIC (mg/L)	Ceftazidime/avibactam[a] MIC (mg/L)	Minimum bactericidal concentration of ceftazidime/avibactam[b] (mg/L)
Citrobacter freundii	TEM-1 and AmpC	64	2	2
C. freundii	Derepressed AmpC	>32	2	4
Enterobacter cloacae	Derepressed AmpC	>64	4	4
E. cloacae	Derepressed AmpC	>128	4	4
E. cloacae	Derepressed AmpC	>64	4	8
Klebsiella pneumoniae	DHA-2	>256	4	4
K. pneumoniae	LAT-4 and SHV-11 variant	32	1	4
K. pneumoniae	SHV-4	>256	4	2
K. pneumoniae	SHV-11	32	4	2

[a] 4:1 ratio ceftazidime/avibactam

[b] A 3 $\log_{10}$ reduction of the initial colony count was considered bactericidal

MIC minimum inhibitory concentration

infection with one of ceftazidime-avibactam (ratio 4:1), ceftazidime alone, ceftazidime/clavulanic acid (ration 4:1, 10 or 25 mg/kg/dose for all ceftazidime components) or imipenem (10 or 25 mg/kg/dose). Four mice were infected per dose group or control group, control groups were euthanized at 4 and 48 h, and test mice were euthanized at 48 h. At 10 mg/kg/dose, ceftazidime was ineffective at eradicating the pathogen from the kidney versus the *E. coli* strain expressing AmpC and the *C. freundii* strain. Ceftazidime-avibactam (10 mg/kg/dose) was significantly more effective than ceftazidime alone against the AmpC-expressing *E. coli*. Ceftazidime-avibactam (10 mg/kg/dose) and imipenem (10 mg/kg/dose) were significantly more effective than ceftazidime alone against the *C. freundii* strain. At 25 mg/kg/dose, ceftazidime was ineffective against the SHV-4-expressing *E. coli* strain and the *E. cloacae*, *K. pneumoniae* and *M. morganii* strains. Ceftazidime/clavulanic acid (25 mg/kg/dose) was significantly more effective than ceftazidime alone against the SHV-4-expressing *E. coli* strain and the *M. morganii* strain, and both

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ceftazidime-avibactam (25 mg/kg/dose) and imipenem (25 mg/kg/dose) were significantly more effective than ceftazidime alone against all four strains. Bacterial load in the kidney in mice receiving ceftazidime-avibactam was 2.6 to 4.5 $\log_{10}$ lower than the bacterial load in mice receiving ceftazidime alone.

In a neutropenic murine thigh infection model study, female CD-1 mice were infected with 10^6 CFU of two strains of KPC-producing *K. pneumoniae* (strain VA-361 expressing KPC-2, TEM-1 and SHV-11 with ceftazidime MIC 256 mg/L, and strain VA-406 expressing KPC-2, TEM-1, SHV-11 and SHV-12 with ceftazidime MIC ≥512 mg/L) via intramuscular injection in the right thigh [93]. Mice were treated 1.5 hours after infection with a single subcutaneous dose of ceftazidime-avibactam (4:1 ratio with doses of the ceftazidime component ranging by twofold steps from 32 to 1,024 mg/kg for strain VA-361, and 8 to 1,024 mg/kg for strain VA-406) or ceftazidime alone (1,024 mg/kg or 2,048 mg/kg). Three mice were tested per dose and control group, treatment mice were euthanized and analysed 24 h after infection, and control mice were euthanized and analysed 1.5 and 24 h after infection. Doses resulting in bacteriostasis using ceftazidime-avibactam were 216/54 mg for strain VA-361 and 116/29 mg for strain VA-406.

In a second human-simulated study of murine thigh infection in both immunocompromised (cyclophosphamide-induced neutropenia) and immunocompetent mice, immunocompromised mice were infected with one of 27 strains of *P. aeruginosa* in triplicate, and immunocompetent mice were infected with one of 15 strains in triplicate [94]. Ceftazidime-avibactam MICs ranged from 4 to 32 mg/L and all but one isolate was non-susceptible to ceftazidime alone (MICs ranging from 8 to >128 mg/L). Human simulated regimens of ceftazidime or ceftazidime-avibactam beginning 2 h after inoculation were administered. Simulated regimens were pharmacokinetically assessed to closely match human dosing of 2 g ceftazidime or 2 g ceftazidime plus 500 mg avibactam every 8 h. By analysis of post-treatment bacterial loads, the authors reported that the in vivo activity was pharmacodynamically predictable based on the MIC of the strain to the drug tested. Ceftazidime decreased bacterial counts by ≥0.5 $\log_{10}$ in only 10/27 isolates; while ceftazidime avibactam did so in 22/27 of the *P. aeruginosa* strains. In the immunocompetent mice, ceftazidime achieved reductions of ≥0.3 $\log_{10}$ in 10/15 isolates, while ceftazidime-avibactam did so against all 15 isolates [94].

In a murine pneumonia model study, immunosuppressed female Swiss OF1 mice were infected intratracheally with 10^8 to 10^9 CFU of a LAT-4 and SHV-11-producing strain of *K. pneumoniae* [75]. Mice were treated twice per day for 2 days with subcutaneous doses of 2:1 ceftazidime-avibactam (150/75 mg/kg), 4:1 ceftazidime-avibactam (150/37.5 mg/kg), ceftazidime (150 mg/kg), 2:1 ceftazidime/clavulanic acid (150/75 mg/kg), 4:1 ceftazidime/clavulanic acid (150/37.5 mg/kg) or 1:1 imipenem/cilastatin (150 mg/kg each) beginning 16–18 hours after infection. Thirty mice were tested per treatment group, 20 mice were tested per control group, and lung bacterial burden was assessed at 24 and 48 h after initiation of treatment. Untreated mice died within 48 h of infection. Compared with treatment with ceftazidime alone, lung bacterial burden was significantly reduced at 48 h by the 2:1 and 4:1 ceftazidime-avibactam regimens and the imipenem/cilastatin regimen ($p < 0.05$ in all cases). A CFU reduction of 6.6 ± 1.0 $\log_{10}$ was found for the 2:1 ceftazidime-avibactam regimen and 7.9 ± 0.1 $\log_{10}$ for the 4:1 ceftazidime-avibactam regimen compared with a 0.7 ± 1 $\log_{10}$ reduction for ceftazidime alone.

In a rabbit meningitis model study, pathogen-free New Zealand rabbits were infected via direct injection to the subarachnoid space of approximately 10^5 CFU of an AmpC-producing *K. pneumoniae* strain (ceftazidime MIC >128 mg/L) [69]. Rabbits were treated starting 8 h post-infection with an intravenous regimen of 150 mg/kg ceftazidime at h 0 and 4, 150/37.5 mg/kg ceftazidime-avibactam at h 0 followed by 150 mg/kg ceftazidime at h 4, or 125 mg/kg meropenem at h 0 and 4. Five rabbits were used per treatment and control group and cerebrospinal fluid (CSF) was sampled at 0, 1, 2, 4, 6 and 8 h following start of treatment. Both the ceftazidime-avibactam regimen and the meropenem regimen were found to be bactericidal (>3 $\log_{10}$ CFU reduction in CSF from initial values) 5 h after start of treatment. Eight h after start of treatment, CSF CFU levels were reduced by 0.10 ± 0.45 for ceftazidime, 4.23 ± 0.60 for meropenem, and 5.66 ± 0.83 for the ceftazidime-avibactam regimen. By two-tailed Fisher exact test, the meropenem and ceftazidime-avibactam regimens were reported as significantly different from the ceftazidime regimen ($p < 0.05$) and the ceftazidime-avibactam regimen was reported as significantly different from the meropenem regimen ($p < 0.05$).

In summary, these animal studies show that ceftazidime-avibactam is effective in a variety of animal infection models including murine septicaemia, murine kidney infection, neutropenic murine thigh infection, neutropenic murine pneumonia and rabbit meningitis, infected with a variety of β-lactamase-producing organisms including ESBL, KPC and AmpC. More studies are required to assess the optimal way to administer ceftazidime-avibactam and the optimal pharmacodynamic parameters to optimize efficacy and minimize resistance selection.

9 Clinical Trials

The results of two ceftazidime-avibactam phase II clinical trials have been published to date (Table 7) and are

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reviewed. A prospective, international, multicentre, double-blinded, randomized (1:1) trial compared safety and efficacy of ceftazidime-avibactam (2,000/500 mg) plus metronidazole (500 mg) with meropenem (1,000 mg), each administered intravenously three times daily for the treatment of complicated intra-abdominal infection in hospitalized adults (NCT00752219) [95]. Male and female patients aged 18–90 years with indications of complicated intra-abdominal infection (including infection in the appendix 47.3 %, stomach/duodenum 25.6 %, colon or small bowel 17.2 %, gall bladder, liver or spleen 9.4 %) caused by organisms determined to be susceptible to either treatment arm and requiring surgery and antibacterial therapy, were recruited if they were free of sepsis, did not have abnormal liver function tests (ALT, AST alkaline phosphatase [AP] or bilirubin >3 times the upper limit of normal) or impaired renal function (CL_{CR} <50 mL/min), were not immunocompromised, had Acute Physiology and Chronic Health Evaluation (APACHE)-II scores ≤25, were expected to survive for the entire study period, and had not had systemic antibacterials within 72 h pre-study (with the exception of previous failed therapy or surgical prophylaxis for less than 24 h). Both ceftazidime-avibactam plus metronidazole and meropenem regimens (Table 7) were administered for 5–14 days. A total of 203 patients were initially enrolled in the study, with 68 patients clinically evaluable for ceftazidime-avibactam plus metronidazole and 76 for meropenem at the end of the study. Patients did not finish the study for a variety of reasons, including patient withdrawal, protocol violation, lost to follow-up and adverse effects (no differences between treatment arms). Favourable clinical response rates (complete resolution or significant improvement of the signs and symptoms of infection 2 weeks after the last treatment dose) were 91.2 % (62/68) for patients receiving ceftazidime-avibactam plus metronidazole and 93.4 % (71/76) for patients receiving meropenem. Response rates were not significantly different ($p = 0.60$). Microbiological eradication was considered equivalent to favourable clinical response. The most common pathogens isolated included Enterobacteriaceae (89.7 % in the ceftazidime-avibactam plus metronidazole arm) and 92.1 % in the meropenem arm. For patients found to have one or more ceftazidime-resistant (MIC >8 mg/L) Gram-negative bacilli, a favourable microbiological response was achieved in 96.2 % (25 of 26) of patients in the ceftazidime-avibactam plus metronidazole arm and 94.1 % (16 of 17) of patients in the meropenem arm. Adverse effects occurred in 15 % of patients in the ceftazidime-avibactam plus metronidazole arm and 17 % of patients in the meropenem arm.

A prospective, international, multicentre, investigator-blinded, randomized (1:1) study compared safety and efficacy of ceftazidime-avibactam (500/125 mg) administered three times daily (30-min infusion) to imipenem/

Table 7 Clinical trials of ceftazidime/avibactam

Trial (clinicaltrials.gov ID)	Number of patients (clinically evaluable)	Dosage regimen (number treated)	Microbiological response	Clinical response	Reference
Phase II treatment of complicated intra-abdominal infection in hospitalized adults (NCT00752219)	203 (144)	Ceftazidime-avibactam + metronidazole: 2,000/500 mg + 500 mg, IV, q8 h (101)	Ceftazidime-avibactam: 91.2 % eradication	Ceftazidime-avibactam: 91.2 % favourable outcome	[95]
		Standard therapy: meropenem 1,000 mg + placebo, IV, q8 h (102)	Meropenem: 93.4 % eradication	Meropenem: 93.4 % favourable outcome	[95]
Phase II treatment of complicated urinary tract infection in hospitalized adults (NCT00690378)	137 (64)	Ceftazidime-avibactam: 500/125 mg, IV, q8 h (68)	Ceftazidime-avibactam: 70.4 % eradication	Ceftazidime-avibactam: 85.7 % favourable outcome	[96]
		Standard therapy: imipenem/cilastatin 500 mg, IV, q6 h (67)	Imipenem: 71.4 % eradication	Imipenem: 80.6 % favourable outcome	[96]

IV intravenous, *qxh* every x hours

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cilastatin (500 mg) administered four times daily (30-min infusion), for the treatment of complicated urinary tract infections, including acute pyelonephritis in hospitalized adults (NCT00690378) [96]. Recruited patients were males and females aged 18–90 years with documented acute pyelonephritis (59.7 %) or other complicated urinary tract infection (40.3 %) caused by Gram-negative organisms not resistant to one or both study drugs. Patients were excluded if they had received more than one dose of a potentially effective antibacterial within 48 h prior to admission urine culture (or any doses after culture), had an ileal loop, vesicoureteral reflux, complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, a permanent indwelling catheter or nephrostomy, or a history of hypersensitivity to either study medication. Both ceftazidime-avibactam and imipenem/cilastatin (Table 7) were administered for 7–14 days. Patients meeting pre-defined clinical criteria for improvement (afebrile $\geq$24 h, resolution of nausea and vomiting, improved signs and symptoms) after a minimum of 4 days of either therapy were switched to oral ciprofloxacin 500 mg every 12 h, or an appropriate oral alternative if necessary (maximum 14 days). A total of 135 patients received study therapy, of whom 62 were microbiologically evaluable (27 in the ceftazidime-avibactam arm and 356 in the imipenem arm). Clinically evaluable patients included 28 in the ceftazidime-avibactam arm and 36 in the imipenem arm. Patients were excluded from the clinical and microbiologically evaluable populations mainly due to lack of an isolated pathogen (23 in the ceftazidime-avibactam group, 19 in the imipenem/cilastatin group). Favourable microbiological response was the primary outcome, defined as both eradication of pathogens in the urinary tract (reduction of levels in the urine from $\geq 10^5$ CFU/mL to $<10^4$ CFU/mL) and no pathogens in the blood at a follow-up 5–9 days after completion of therapy. Favourable clinical response was a secondary outcome, defined as resolution of all or most pre-therapy signs and symptoms, with no further (non-study) antibacterial required. Favourable microbiological response rates were 70.4 % for the ceftazidime-avibactam arm and 71.4 % for the imipenem/cilastatin arm. Favourable clinical response rates were 85.7 % for the ceftazidime-avibactam arm and 80.6 % for the imipenem/cilastatin arm. Microbiological response rates were not significantly different (95 % CI difference of −27.2 % to 25.0 %), but the significance of clinical response rate was not tested. Six of seven patients in the ceftazidime-avibactam arm and 9 of 11 patients in the imipenem/cilastatin arm had favourable microbiological outcomes against ceftazidime-resistant pathogens (MIC >8 mg/L). Adverse effects in this study were reported in 67.7 % of patients in the ceftazidime-avibactam arm and 76.1 % of patients in the imipenem/cilastatin arm.

Clinical trials to date suggest that ceftazidime-avibactam is as effective as standard carbapenem therapy in complicated intra-abdominal infection and complicated urinary tract infection, including infection caused by ceftazidime-resistant Gram-negative bacilli. At the time of writing, phase III trials are still in progress.

10 Adverse Effects

The safety and tolerability of ceftazidime-avibactam has been reported in three phase I pharmacokinetic studies and two phase II clinical studies. In these studies, assessment was conducted by physical examination, laboratory tests, vital sign monitoring, ECG recording and recording of treatment-emergent adverse events [88, 91, 95, 96], except in one phase I study where adverse events were assessed by subject interview [97].

In three phase I pharmacokinetic studies encompassing 119 subjects, treatment-emergent events were observed in 14 healthy subjects (one or more per subject). One event, orthostatic hypotension, was reported as moderate, while the remainder, including abdominal pain, anxiety, application site bruising, dry mouth, dysgeusia, feeling hot, feeling jittery, headache, hyperhidrosis, postural dizziness, sense of oppression, and somnolence, were reported as minor. Four treatment-related events were reported in three anuric subjects: general discomfort, stomach pain, ructus and symptoms of hypoglycaemia (in a diabetic patient) [91]. No subject withdrew from these studies as a result of an adverse event.

In a phase II study comparing the treatment of complicated intra-abdominal infection by ceftazidime-avibactam plus metronidazole (safety population 101) and meropenem (safety population 102), treatment-emergent events (drug related or not) reported by 5 % or more patients were nausea, vomiting, abdominal pain, pyrexia, wound secretion, cough, haematuria and increases in liver enzymes (ALT, AST, AP), platelet count and white blood cell count tests [95]. Drug-related adverse effects were reported in 15 % of the ceftazidime-avibactam plus metronidazole arm and 17 % of the meropenem arm. The types and frequency of all treatment-emergent adverse effects were similar for both arms, though it was noted that the ceftazidime-avibactam plus metronidazole arm had a higher number of gastrointestinal (GI)-tract events (nausea, vomiting, abdominal pain) and the meropenem arm had a higher number of liver enzyme elevation events (ALT, AST, AP). Serious adverse events were observed in nine patients in the ceftazidime-avibactam and 11 patients in the meropenem arm, though only one of these events (elevated liver enzymes in a ceftazidime-avibactam plus metronidazole patient) was considered drug related.

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In a phase II study comparing the treatment of complicated urinary tract infection by ceftazidime-avibactam (safety population 68) and imipenem/cilastatin (safety population 67), treatment-emergent events (drug related or not) reported by 5 % or more patients were constipation, diarrhoea, abdominal pain, upper abdominal pain, abdominal distension, headache, dizziness, chest pain, anxiety, insomnia, injection/infusion site reaction, increased ALT levels, back pain and hypertension [96]. Drug-related adverse effects were reported by 35.3 % of patients in the ceftazidime-avibactam arm and 50.7 % of patients in the imipenem/cilastatin arm, though it should be noted that adverse events continued to be recorded after conversion to oral therapy following clinical improvement (see "Clinical Trials" section). Serious drug-related adverse events were reported for three patients in the ceftazidime-avibactam arm (accidental overdose, diarrhoea, renal failure) and one in the imipenem/cilastatin arm (increased serum creatinine). The overdose caused no sequelae.

A double-blind, randomized, placebo-controlled, four-way crossover, phase I study conducted in a single centre investigated the effect of a supra-therapeutic dose of ceftazidime-avibactam on cardiac depolarization [98]. Non-smoking male subjects ($n = 51$) with median age 26 years (range 18–45) and median body mass index (BMI) 26.5 kg/m^2 (range 19.4–30.0) were enrolled in the study; 43 were evaluable. Subjects received four treatments in random order (with minimum 3-day washout between treatments): a 30-min infusion of 3,000/2,000 mg ceftazidime-avibactam following a 30-min infusion of saline placebo; a 60-min infusion of 1,500/2,000 mg ceftaroline fosamil-avibactam administered as two 30-min infusions; saline placebo administered as two 30-min infusions; a single, open-label, oral dose of 400 mg moxifloxacin as active control. Primary outcome was Fridericia-corrected QT interval; ECG values (heart rate and RR, PR, QRS and QT intervals) were also assessed at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h. Ceftazidime-avibactam was found not to significantly elevate the Fridericia-corrected QT interval, and observed ECG values were similar for ceftazidime-avibactam and placebo. Compared with moxifloxacin, ceftazidime-avibactam was found to result in significantly lower elevations in the Fridericia-corrected QT interval. Urticaria (in one patient) was the only reported non-mild adverse event related to ceftazidime-avibactam. Eleven mild adverse events experienced by patients in the ceftazidime-avibactam group were reported by system-organ-class: four skin/soft tissue disorders, three GI tract disorders, three administration-site conditions and one cardiac palpitation. No abnormalities were observed in vital signs, laboratory tests or physical examinations.

To date, ceftazidime-avibactam appears to be well tolerated in healthy subjects as well as patients with infectious diseases, with few serious drug-related treatment-emergent adverse events reported.

11 Place of Ceftazidime/Avibactam in Therapy

The addition of avibactam restores the activity of ceftazidime against Gram-negative bacilli that achieve β-lactam resistance through expression of the Ambler class A ESBLs, chromosomal or mobile class C β-lactamases, serine carbapenemases, or some class D β-lactamases. Safety and pharmacokinetic results published to date suggest that no additional considerations need to be taken when dosing ceftazidime-avibactam compared with ceftazidime alone. Ceftazidime-avibactam has demonstrated clinical efficacy similar to that of carbapenem therapy in phase II studies of complicated intra-abdominal infection and complicated urinary tract infection (including acute pyelonephritis). The extensive clinical experience with ceftazidime and the knowledge that avibactam broadens the spectrum of ceftazidime versus ß-lactamase-producing Gram-negative bacilli, will provide clinicians with confidence in using this agent. To date, no data are available on the efficacy of ceftazidime-avibactam for the treatment of difficult-to-treat infections such as hospital-acquired and ventilator-acquired pneumonia. The exact roles for ceftazidime-avibactam in the treatment of infectious diseases will, in part, depend on the development of other β-lactam/β-lactamase inhibitor combinations including ceftaroline-avibactam, imipenem-MK7655 and ceftolozane-tazobactam. An important advantage of ceftazidime-avibactam is that its development is furthest along and it may be first to market.

Potential future roles for ceftazidime-avibactam include the treatment of suspected or documented infections caused by resistant Gram-negative bacilli-producing ESBL, KPC and/or AmpC β-lactamases. In addition, ceftazidime-avibactam may be used in combination (with metronidazole) for suspected polymicrobial infections. Finally, the increased activity of ceftazidime-avibactam versus *P. aeruginosa* may be of clinical benefit in patients with suspected or documented *P. aeruginosa* infections.

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