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REVIEW

Pharmacological aspects and spectrum of action of ceftazidime–avibactam: a systematic review

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Abstract
Purpose Ceftazidime–avibactam is an antimicrobial association active against several *Enterobacteriaceae* species, including those resistant to carbapenem. Considering the importance of this drug in the current panorama of multidrug-resistant bacteria, we performed a systematic review about ceftazidime–avibactam with emphasis on clinical and pharmacological published data.
Methods A systematic search of the medical literature was performed. The databases searched included MEDLINE, EMBASE and Web of Science (until September 2017). The search terms used were 'avibactam', 'NXL104' and 'AVE1330A'. Bibliographies from those studies were also reviewed. Ceftazidime was not included as a search term, once relevant studies about avibactam in association with other drugs could be excluded. Only articles in English were selected. No statistical analysis or quality validation was included in this review.
Results A total of 151 manuscripts were included. Ceftazidime–avibactam has limited action against anaerobic bacteria. Avibactam is a potent inhibitor of class A, class C, and some class D enzymes, which includes KPC-2. The best pharmacodynamic profile of ceftazidime–avibactam is $fT > MIC$, validated in an animal model of soft tissue infection. Three clinical trials showed the efficacy of ceftazidime–avibactam in patients with intra-abdominal and urinary infections. Ceftazidime–avibactam has been evaluated versus meropenem/doripenem in hospitalized adults with nosocomial pneumonia, neutropenic patients and pediatric patients.
Conclusion Ceftazidime–avibactam has a favorable pharmacokinetic profile for severe infections and highly active against carbapenemases of KPC-2 type.

Keywords Cephalosporin · Pharmacology · Avibactam · Ceftazidime

Introduction

In recent decades, there has been few options of antibiotics against multidrug-resistant bacteria, especially those producing carbapenemases. Until a few years ago, there was a great concern regarding carbapenem resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Since 2001, a new carbapenemase class was described, *Klebsiella pneumoniae* carbapenemase (KPC), found mainly in *Klebsiella pneumoniae* and other Enterobacteriaceae [1]. This type of antibiotic resistance can spread quickly among different bacterial genera [2]. Klebsiella pneumoniae carbapenemase (KPC) is a beta-lactamase that confers resistance to all beta-lactam antibiotics, including carbapenems [3]. The mortality of infections caused by KPC-producing bacteria is around 50%. Although some of the isolates show sensitivity to carbapenems, the clinical significance of this phenomenon is still under study. Current therapeutic recommendations are the association of anti-infectives, such as tigecycline and polymyxin, a fact that increases hospital costs [4].

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The KPC gene is called bla_{KPC}, which is present in a mobile element associated with the easy transmission (*transposon*). This feature has an epidemiological importance [5]. Another concern about transposons is the fact that transmission can occur between different genera, not only *Klebsiella,* but also *Escherichia coli*, *Salmonella*, *Citrobacter* and several Gram-negative bacilli [6]. KPC-producing bacteria have been identified in several countries [7–10]. The presence of bla_{KPC} in Brazil was described in 2005, although the article has been published only in 2009 [11]. Since then, several cases have been reported in different states of Brazil [12–14].

The SENTRY Antimicrobial Surveillance Program evaluated 5704 Gram-negative bacilli between January 2008 and December 2010 from Argentina, Brazil, Chile, and Mexico. Meropenem-nonsusceptible *Klebsiella* spp. rate was highest in Brazil (11.1%), followed by Argentina (8.2%). KPC-producing *K. pneumoniae* was not detected in 2008, but emerged in 2009 (10 strains) and increased significantly in 2010 (44; $p < 0.0001$) [15].

In the last years, there was a significant increase in infections caused by KPC-producing bacteria [16, 17]. Few drugs have been developed, some of them with activity against carbapenemase-producing bacteria. The ceftazidime and avibactam combination is one of these options.

Ceftazidime is a third-generation cephalosporin with broad-spectrum activity against Gram-negative bacilli, including *Pseudomonas aeruginosa* [18, 19]. It was introduced into clinical use in the 1980s, but nowadays, the usefulness of all cephalosporins has become compromised after the appearance of extended-spectrum β-lactamases (ESBLs) [20, 21], *Klebsiella pneumoniae* carbapenemases (KPCs) [22] and metallo-β-lactamases [23].

One alternative for restoring ceftazidime activity in the presence of β-lactamases is to use β-lactamase inhibitors. Avibactam is a β-lactamase inhibitor that has as substrate the β-lactamase enzymes of Ambler molecular classification A, C and some of class D. Accordingly, in association with a β-lactam, the antibiotic shows activity again. Thus, avibactam can be associated with broad-spectrum cephalosporins such as ceftazidime and ceftaroline [24–26].

In phase 2 studies, ceftazidime–avibactam showed efficacy in the treatment of intra-abdominal infections (associated with metronidazole) and complicated urinary tract infections [27, 28].

In view of the growing number of multidrug-resistant bacteria and the lack of treatment options available, in 2015 the FDA (US Food and Drug Administration) approved the use of ceftazidime–avibactam to treat those infections when there is no other option available until phase 3 studies are completed. In the same year the phase 3 study for intra-abdominal infections, showing non-inferiority compared to meropenem, was submitted for publication [29].

Although approved for those infections, the most important feature of this medication is its broad spectrum of activity, including activity against carbapenemase-producing bacteria, such as *Enterobacteriaceae* and *Pseudomonas aeruginosa* [30, 31]. After FDA approval and phase 3 study publication, ceftazidime–avibactam will be available in several countries. Considering all these facts, we performed a systematic review about ceftazidime–avibactam with emphasis on clinical and pharmacological published data.

Methods

A systematic search of the medical literature was performed. The databases searched included MEDLINE, EMBASE and Web of Science (until September 2017). The search terms used were 'avibactam', 'NXL104' and 'AVE1330A'. Bibliographies from those studies were also reviewed. Ceftazidime was not included as a search term, once relevant studies about avibactam in association with other drugs could be excluded. Only articles in English were selected. No statistical analysis or quality validation was included in this review.

A total of 323 manuscripts were found, of which 172 were excluded: only aztreonam–avibactam was evaluated (16), repeated study (17), not related to avibactam, other drugs (18), ceftaroline–avibactam (15), review (79) and others (27).

Articles will not be described individually, but are included as reference in the text in each "Results" subsection.

Results

Molecule features

Ceftazidime consists of a β-lactam ring (cephem nucleus) as in other cephalosporins [32]. The methylpyridinium group in position 3 provides its anti-pseudomonal activity, the aminothiadiazole ring in position 7 is responsible for the activity against Gram-negative rods, and the carboxypropyl-oxyimino group provides the anti-pseudomonal activity. However, ceftazidime presents reduced activity against Enterobacteriaceae when compared to ceftriaxone, which has the methoxyimino group [19]. The ceftazidime activity may also be lower than other cephalosporins against Gram-positive cocci, so its use has been restricted to infections with *P. aeruginosa* as possible etiology (Tables 1, 2).

Avibactam is a non-β-lactam β-lactamase inhibitor. Avibactam is a representative of a bridged bicyclic ((2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3,2,1] octane-2-carboxamide) (DBO) scaffold that was rationally designed by incorporating the existing knowledge about beta-lactams into the properties of a novel scaffold [33] (Fig. 1). Some

Table 1 Some studies about spectrum of ceftazidime–avibactam against β-lactamases

Author	Year	Country	Species	Enzymes
Bonnefoy	2004	France, US, Europe	*E. coli, Klebsiella* spp., *Proteus vulgaris, Citrobacter*	PSE-1, PSE-4, TEM-1, TEM-2, SHV-1, TEM-4, TEM-5, TEM-7, TEM-8, TEM-12, TEM-16, TEM-20, TEM-24, TEM-43, SHV-2, SHV-4, SHV-5, SHV-6, SHV-38, CTX-M -15, TRI-2, GES-2, VEB-1, PER-1, ACC-1, FOX-1, DHA-2, LAT-1, ACT-1
Livermore	2008	Worldwide	*Klebsiella pneumoniae, S. marcescens*	SME-1, KPC, OXA-48, IMP, VIM
Stachyra	2009	France, US	*E. coli, Klebsiella pneumoniae, Enterobacter cloacae*	KPC-2
Endimiani	2009	US	*Klebsiella pneumoniae*	KPC
Mushtaq	2010	Turkey	*E. coli, Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Hafnia* spp., *Morganella* spp.	ESBL, AmpC, OXA48, MBL (IMP, VIM), KPC
Mushtaq	2010	Turkey	*P. aeruginosa, A. baumannii, B. cepacia* complex	PER, VEB, AmpC
Lagace-Wiens	2011	Canada	*Klebsiella pneumoniae, E. coli*	CTX-M-1, CTX-M-2, CTX-M-9, CTX-M-14, CTX-M-15, CTX-M-24, CTX-M-27, CTX-M-65, SHV-2a, SHV-12, TEM-1c, SHV-5, SHV-28, SHV-31, SHV-1c, CMY-2, FOX-5, CTX-M-3, TEM-12
Walkty	2011	Canada	*P. aeruginosa*	Not defined
Citron	2011	Not defined	*B. fragilis, Prevotella* spp., *Porphyromonas* spp., *Bilophila wadsworthia, Desulfovibrio* spp., *Campylobacter* spp., *Fusobacterium* spp., *Clostridium clostridioforme* group, and *Eggerthella lenta*	Not defined
Aktas	2012	Turkey	*P. aeruginosa, A. baumannii, K. pneumoniae*	PER-1, OXA-51, OXA-58, OXA-48, CTX-M-15
Papp-Wallace	2015	US	*E. coli*	SHV-2; SHV-7; SHV-8; SHV-14; SHV-26; SHV-30; SHV-84; SHV-102; SHV-106; SHV-120; SHV-1-G238S, -E240 K, -R275L, and -N276D; SHV-154; SHV-161; TEM-10; TEM-15; TEM-17; TEM-19; TEM-26; KPC-5; KPC-6; KPC-7; KPC-8; ADC-7; CMY-32; CMY-33; P99; FOX-4; OXA-24/40; and OXA-1
Testa	2015	France, Italy, Germany, Spain	*E. coli, Klebsiella* spp., *Enterobacter* spp.; *Citrobacter* spp., *Morganella morganii, Proteus* spp., *Providencia* spp., *Serratia marcescens, Pseudomonas aeruginosa*	Not defined
Vasoo	2015	USA	Enterobacteriaceae	KPC, NDM, IMP, OXA-48, OXA-181, OXA-232, IMI, VIM, and SME
Dupont	2015	France	Enterobacteriaceae	Carpanemase (KPC, NDM, IMP, VIM, SIM, SPM, GIM, IMI OXA-48-like, OXA-23-like, OXA-24-like, OXA-58-like, and OXA-50-like), ESBL (CTX-M, TEM-like, SHV-like, PER, VEB, GES), and plasmid-mediated AmpC-(CMY-2, DHA, ACC, ECT, MOX, and FOX)

Table 2 Pharmacokinetic parameters of ceftazidime–avibactam

Pharmacokinetic parameter	Young male
Cmax (mg/L)	33.8
Half-life (h)	2.0
Plasma clearance (L/h)	10.1
Distribution volume (L)	16.8
Area under the curve (mg h/L)	49.8
Urinary excretion (%)	91.4

characteristics resemble the β-lactam ring of cephalosporins, including ceftazidime. The sulfate in position 6 is similar to the carboxyl group in ceftazidime in position 4, and the carboxamide in position 2 is similar to the aminoacyl side chain in ceftazidime in position 7. It is important to remember that all β-lactamase inhibitors have similar structure to β lactam antibiotics, which does not happen with avibactam. Sulbactam, for example, is the active agent for the treatment of infections caused by *Acinetobacter* spp. [34].

Ceftazidime (2000 mg) is combined with a fixed dosage of avibactam (500 mg) (AVYCAZ®). They do not have interactions that may disrupt activity and kinetic characteristics [35]. There is already an automated sensitivity test validated with the usual bacteria for ceftazidime–avibactam [36]. Disk diffusion with ceftazidime–avibactam 30/20 µg is standardized for susceptibility tests in *E. coli*, *S. aureus*, *P. aeruginosa, K. pneumoniae* as well as MIC in broth dilution with unsupplemented Mueller–Hinton medium [37].

A brief review of β-lactamases

The main mechanism of resistance of Gram-negative bacilli to β-lactam is the production of beta-lactamases. These enzymes hydrolyze the β-lactam ring, with different affinity for each cephalosporin. There are hundreds of β-lactamases and different classifications. One of the most used is the Ambler molecular classification. In this classification, there are 4 β-lactamase groups (A–D). Class A includes, for example, enzymes present in Esnterobacteriaceae, such as TEM and SHV, and β-lactamase inhibitors (clavulanate, tazobactam, sulbactam) that can inactivate those enzymes. On the other hand, enzymes as ESBL and KPC are also part of this group [38].

Class B includes the so-called β-lactamases, and its activity is zinc cofactor-dependent. There are no β-lactamase inhibitors against this type of enzyme.

Beta-lactamases class C are also known as the AmpC group, usually encoded by chromosomal genes. However, the emergence of this type of enzyme genes in plasmids has become increasingly common, causing AmpC no longer being a chromosomal gene but becoming a transferable gene from bacterium to bacterium [39]. These β-lactamases can be inducible by the use of antimicrobials, especially those present in *Serratia*, *P. aeruginosa*, indole-positive *Proteus*, *Citrobacter* and *Enterobacter*. In general, β-lactamase inhibitors have no activity against these enzymes.

Finally, we have the β-lactamases D group, also called oxacilinases, presenting broad spectrum of inhibition, including carbapenems. Classic β-lactamase inhibitors (e.g., clavulanate, tazobactam, sulbactam) do not have good activity against this class of enzymes [40].

Mechanism of action

Ceftazidime

Ceftazidime is a cephalosporin that promotes bactericidal effect through cell lysis by inhibiting cell wall synthesis. More specifically, ceftazidime binds to enzymes termed PBP (penicillin-binding protein). These enzymes are responsible for the polymerization of peptidoglycan, the main component of the bacterial cell wall.

There are several PBPs, being characteristic for each bacterial species. In addition, antibiotics may have different affinity for each of those PBPs, which explains the different spectrum of action and potency of beta-lactams [41]. The main resistance mechanism against ceftazidime is the production of β-lactamases, as described earlier. In addition,

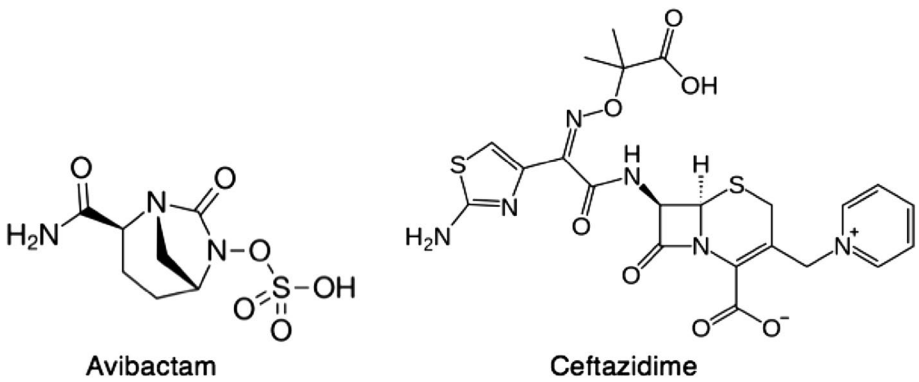

Fig. 1 Avibactam and ceftazidime molecules

other less common mechanisms for this group of antibiotics are porins and efflux pumps, as well as changes in permeability, which can be associated with overexpression of carbapenemase [42].

Avibactam

Avibactam is a β-lactamase inhibitor that forms a covalent bond with β-lactamase [43]. This covalent bond occurs through reversible acylation [44, 45]. In case of other β-lactamase inhibitors, the reaction is irreversible and there is production of intermediates, which are hydrolyzed (Fig. 2).

Avibactam is able to covalently bind not only to β-lactamase, but also to some bacterial PBPs [46], notably *E. coli* and *H. influenzae* PBP2, to PBPs 2 and 3 of *P. aeruginosa* and *S. aureus*, and to PBP3 of *S. pneumoniae*. This may explain the antibacterial activity against some bacterial strains and species [47].

The analysis of avibactam reaction with CMY-2 (a plasmid-encoded Ambler class C cephalosporinase) revealed that the CMY-2–avibactam acyl-enzyme complex was stable for as long as 24 h. A hypothesis is that successive hydrogen-bonding interactions can occur between avibactam and CMY-2 [48].

Avibactam exhibits activity against Ambler class A β-lactamases (ESBLs and KPCs), class C β-lactamases, and some class D β-lactamases. Other β-lactamase inhibitors do not exhibit activity against class B β-lactamases. More than 650 class A enzymes were evaluated to determine the potential subtypes that could impact in avibactam inhibition [49]. Only the differences in the Ω-loop of type PER enzymes were found to impact the ability of avibactam. Nevertheless, a similar study evaluated several types of class B (serine and metallo-β-lactamases) against whom avibactam showed limited activity [50].

The advantage of avibactam is its long half-life, complex reversibility through deacylation, small molecular size, low molecular weight, polarity and interaction with important catalytic residues near the active sites of β-lactamases. Another advantage of avibactam over other β-lactamase inhibitors is related to the low potential for inducing resistance [51]. As the former β-lactamase inhibitors have structures similar to β-lactams, they can induce β-lactamase expression of chromosomal genes, such as the AmpC gene. A study compared avibactam to clavulanate, and it was shown that avibactam has no such potential [52].

Against TEM-1, avibactam was 5- and 16-fold more active than tazobactam and clavulanic acid, respectively [53]. This is probably due to the better avibactam bond to TEM-1 enzyme [54]. Interestingly, in a study evaluating avibactam with ceftriaxone, this association showed lower minimum inhibitory concentrations than in ceftazidime combination with avibactam against KPC-producing *Klebsiella pneumoniae*, probably due to ceftriaxone's better spectrum for this enterobacterium [55].

The most common mechanism of resistance to ceftazidime–avibactam is the presence of β-lactamase that is not inactivated by avibactam, such as the class B β-lactamases and the majority of the class D β-lactamases. Other mechanisms would be those that act on ceftazidime not by hydrolysis, such as efflux pump and loss of porins [56]. Several mechanisms will be detailed below.

Spectrum of action

Gram-negative bacilli: *Enterobacteriaceae*

The novel β-lactamase inhibitor avibactam is a potent inhibitor of class A, class C, and some class D enzymes [57]. The addition of avibactam ceftazidime decreases its MIC when used in combination [58–60]. A study evaluating those three classes of β-lactamases in *Escherichia coli*, avibactam combined with ceftazidime, ceftaroline, or aztreonam reduced the MIC in 91.4, 80.0, and 80.0% of isolates, respectively [61].

The ceftazidime–avibactam combination has excellent activity against ESBL- and AmpC-producing *Enterobacteriaceae*, including strains producing both enzymes [62–65]. In a test with more than 700 samples of ESBL-producing *Enterobacteriaceae*, ceftazidime–avibactam proved to be

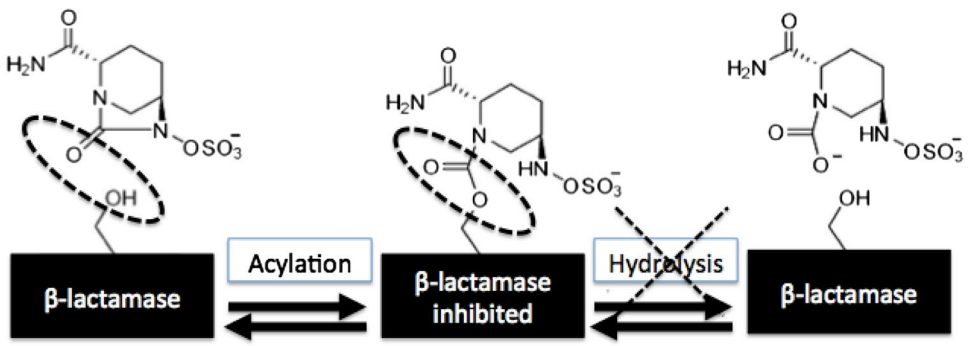

Fig. 2 Reaction between avibactam and β-lactamase, showing that there is no hydrolysis of β-lactamase inhibitor after acylation

extremely active in various regions of the United States [66]. In a Spanish collection, similar results were found in ESBLs, acquired AmpC β-lactamases and porin loss in *Klebsiella pneumoniae* [67]. The largest study included 36,380 isolates published in 2017, with 99.2% of susceptibility among *Enterobacteriaceae* tested in United States. However, only 2953 were multidrug-resistant with 513 carbapenem-resistant *Enterobacteriaceae* (97.5% susceptible) [68]. Another large sample of isolates tested for ceftazidime–avibactam was published in 2016 with 34,062 isolates of *Enterobacteriaceae* from patients with intra-abdominal, urinary tract, skin and soft tissue, lower respiratory tract, and blood infections collected in the INFORM (International Network For Optimal Resistance Monitoring) global surveillance study (176 medical center laboratories in 39 countries) [69]. Overall, 99.5% of *Enterobacteriaceae* isolates were susceptible to ceftazidime–avibactam using FDA-approved breakpoints (susceptible MIC ≤ 8 μg/mL; resistant MIC ≥ 16 μg/mL). Ceftazidime–avibactam demonstrated potent activity against molecularly confirmed ESBL-producing ($n = 5354$; MIC90, 0.5 μg/mL; 99.9% susceptible), plasmid-mediated AmpC-producing ($n = 246$; MIC90, 0.5 μg/mL; 100% susceptible), and ESBL- and AmpC-producing ($n = 152$; MIC90, 1 μg/mL; 100% susceptible) isolates of *E. coli, K. pneumoniae, K. oxytoca,* and *P. mirabilis*. In other two surveys with isolates only from intra-abdominal and urinary infections showed that ceftazidime–avibactam had high susceptibility [70]. A subpopulation of isolates from patients hospitalized by pneumonia in US from 2011 and 2015 showed high susceptibility to ceftazidime–avibactam, achieving 99.9% against *Enterobacteriaceae* [71].

For Gram-negative bacilli it has activity against strains producing class D carbapenemases as OXA-24 and OXA-48 [72], as well as OXA-40 and OXA-69 [73]. In some SHV enzymes such as SHV-1, resistance has been reported related to some mutations [74]. A high percentage of susceptibility (> 95%) to ceftazidime–avibactam was also demonstrated in isolates from airways of patients with mechanical ventilation-associated pneumonia in the intensive care unit [75, 76].

FLAMM et al. studied ceftazidime–avibactam in over 1500 isolates from urine samples from Europe, United States and Latin America [77]. This study also verified the high sensitivity of pathogens to ceftazidime associated with avibactam. Similar results were observed in Brazilian isolates [78] and two studies with isolates from patients with cancer in USA [79, 80]. In a European study including samples from France, Germany, Spain and Italy, the combination of 4 mg/L avibactam with ceftazidime broadens their spectrum of activity to include the majority of β-lactam-resistant *Enterobacteriaceae* against which this antibiotic alone has poor activity [81]. Despite the unfavorable current sensitivity profile of *Enterobacteriaceae* to quinolones and resistance profile associated with other genes, including β-lactamase, testing of *Enterobacteriaceae* strains resistant to fluoroquinolones did not change the activity spectrum of ceftazidime–avibactam against sensitive strains [82]. With the increase in use of aminoglycosides due to the emergence of carbapenemases and polymyxins resistance, 338 isolates of *Enterobacteriaceae* and *P. aeruginosa* resistant to aminoglycosides were tested in Canada, yielding 100 and 87.8% of MIC ≤ 8 μg/mL, respectively [83]. The resistance to aminoglycoside in these samples was from methylases (ArmA, RmtA, RmtB, RmtC and RmtD) and modifying enzymes and aminoglycosides (AAC(3)-Ia, AAC(3)-IIa, AAC(3)-IVa, AAC(6′)-Ib/II, ANT(2″)-Ia, APH(3′)-Via). Avibactam also showed to be active against KPC-2-producing bacteria when associated with different β-lactams, such as aztreonam, piperacillin, cefotaxime, ceftazidime and cefepime [84]. The association with ceftaroline was also effective at ≤ 4 mg/L, except for metallo-β-lactamases (VIM and IMP) [85, 86]. In several carbapenemases, not in group B, ceftazidime–avibactam showed sensitivity close to 100% [87, 88]. In one case it has been reported that S130 residues, as well as K234 and R220, contribute significantly to the avibactam inactivation mechanism of KPC-2 [89]. Ceftazidime–avibactam was very active against isolates producing the most common β-lactamases detected in US hospitals, including CTX-M and KPC variants [90, 91]. The resistance of KPC-producing *Enterobacteriaceae* to ceftazidime–avibactam can occur due to mutations that increase ceftazidimase specificity rather than conferring avibactam resistance; however, the clinical relevance remains uncertain [24]. In 2015 the first case of ceftazidime–avibactam resistance in a KPC-3-producing *K. pneumoniae* was published [92] and more cases have been described ever since. [93]. For this reason, despite being a promising drug, its use should be cautious [25]. This is because, unlike other β-lactamases, the bond between avibactam and KPC-2 and KPC-3 is different in relation to the others, which theoretically could reduce potency or induce resistance [94].

In the case of NDM enzyme, which is a metallo-β-lactamase, the resistance to ceftazidime–avibactam is well established [95]. Avibactam associated with aztreonam would be an option [96, 97], but there are studies already showing that mutation in PBP3 can confer resistance to the scheme [98]. Furthermore, no synergic activity was found with ceftazidime–avibactam and carbapenem [99]. In other study including KPC-carrying isolates of *Klebsiella pneumoniae*, synergism was found with amikacin and polymyxin [100].

Ceftazidime hydrolytic activity may limit the usefulness of ceftazidime/avibactam monotherapies in infections caused by isolates carrying blaCTX-M-14 and blaOXA-48 [101]. Recently, it was described a resistance mechanism based on a mutation of an AmpC variant by deletion of one amino acid in the omega loop [102]. Another author also

described a lower affinity for extended-spectrum AmpC (ESAC) β-lactamase enzymes in *Enterobacter cloacae* [103, 104].

Mutations within the KPC Ω-loop (positions 165–179), including a report in KPC-3, can enhance ceftazidime affinity and restrict avibactam binding [25]. Although rare, mutations in specific PBP can be associated with resistance to beta-lactams. Carbapenems have high affinity to PBP2 and PBP3 from *E. coli*, in contrast to ceftazidime. Single point mutations in PBPs are associated with resistance do ceftazidime, a mechanism which is not reversible with avibactam [105]. A specific mutation of carbapenemase type 2 (KPC-2) harboring the D179Y substitution impaired inhibition by avibactam combined with significant residual activity for ceftazidime hydrolysis, which accounts for resistance. However, such mutations are more common with KPC-3 [106, 107].

Until 2016, resistance to ceftazidime–avibactam was restricted to case reports [108]. Unfortunately, considering recent data, it is important to know that resistance is increasing. As for the KPC-2 enzyme, one of carbapenemases that has brought greater concern nowadays, there is evidence of avibactam hydrolysis by this carbapenemase, and slow deacylation properties [109]. In this slow deacylation, there is no evidence that this could have clinical significance so far. When tested in colistin-resistant *Enterobacteriaceae*, all the avibactam/ceftazidime activity was independent of the presence of efflux pumps or loss of porins [110]. Nevertheless, in China decreased ceftazidime/avibactam susceptibility in KPC-producing *Klebsiella pneumoniae* clinical isolates was caused by high ceftazidime hydrolysis activity and OmpK35 porin deficiency in the majority of isolates [111]. On the other hand, in *E. coli*, none of the porin experimental mutations caused a decrease in susceptibility to ceftazidime–avibactam [112].

Gram-negative bacilli: non-fermenter

In another USA study, over 95% of *Pseudomonas aeruginosa* isolates from BSI, from pneumonia patients, from intra-abdominal infection and urine exhibited a ceftazidime–avibactam MIC ≤ 8 mg/L (CLSI susceptible breakpoint for ceftazidime when tested alone against *P. aeruginosa*) [113].

Similarly, ceftazidime–avibactam is effective against *P. aeruginosa* [114, 115]. Another study evaluating *P. aeruginosa* showed 18% resistance, but the resistance mechanism was related to loss of porin and efflux pump [116]. The sensitivity profile for *P. aeruginosa* was good even in strains with high resistance, such as those isolated from patients with cystic fibrosis [117]. A survey of 3902 isolates of *P. aeruginosa* from 75 US medical centers identified that 96.9% of the strains were susceptible (MIC ≤ 8 µg/mL) [118]. In the same study, susceptibility to ceftazidime–avibactam for multidrug-resistant and extensively drug-resistant phenotypes was 81.0 and 73.7%, respectively. In 2017, the same authors evaluated 7686 isolates from same hospitals, showing similar results [68]. The enzymatically driven β-lactam resistance is the most searched mechanism. One study revealed the exclusive presence of VIM among only 4% of the subset of *P. aeruginosa* isolates nonsusceptible to ceftazidime–avibactam [119]. Ceftazidime–avibactam has been compared with ceftolozane–tazobactam against *P. aeruginosa* with similar susceptibility percentages, but lower MIC for ceftolozane–tazobactam [120].

Emergence of resistance during therapy with ceftazidime–avibactam has also been reported. In one case of *P. aeruginosa* surgical site infection, both initial and final isolates were resistant to carbapenems and evolved with resistance to ceftazidime–avibactam. Sequencing identified *bla*OXA-2 in initial isolate, but the final isolate contained a 3-bp insertion leading to the duplication of a key residue, designated as OXA-539 [121].

Avibactam increased the potency of ceftazidime against many β-lactamase-producing *P. aeruginosa* and *B. cepacia* strains complex but not for efflux-mediated resistance, including a high affinity by PenaA carbapenemase found in some strains of *B. cepacia* complex [122]. Unfortunately, there are few epidemiological studies evaluating B. cepacia complex, one of them with seven isolates [123].

In a previous study, there was a lack of potentiation of ceftazidime with avibactam against *A. baumannii*, which was (supposed) to be a failure of avibactam to penetrate and inhibit relevant (OXA-23, -40, -51 and -58) carbapenemases [85, 86, 124]. For *P. aeruginosa*, the ceftazidime–avibactam activity was superior to imipenem in a study [125]. Part of the resistance in these cases is due to metallo-β-lactamases, or other common mechanisms in *P. aeruginosa* as efflux pump and loss of porins [126]. On the other hand, there are rare cases of AmpC resistant to avibactam in *P. aeruginosa* [127]. In *P. aeruginosa* isolates resistant to carbapenems but without carbapenemases (loss of porin), ceftazidime–avibactam proved to be active in 92% [128]. Avibactam cannot inhibit metallo-carbapenemases, and nor can any other inhibitor in advanced development. The use of a monobactam as the partner drug can be a choice since these are stable to metallo-carbapenemases [87]. Livermore et al. presented a study illustrating the potential of this approach, with MICs of aztreonam–avibactam found to be ≤ 4 µg/mL against all carbapenemase producers, including those with metallo-enzymes [129]. However, in vitro resistance data found were discordant to ceftazidime–avibactam compared to the in vivo response [63].

Anaerobics

Ceftazidime–avibactam has limited action against anaerobic bacteria. Production of beta-lactamases by anaerobes is common in *Bacteroides* isolates (80–100%) [130]. Most enzymes are chromosomally mediated including serine at the active site as well as metallo-beta-lactamases (class B) [131].

A study with 396 samples demonstrated the inefficiency of this combination against anaerobics, mainly in the most relevant such as *Bacteroides fragilis*, as well as in other less important bacteria, such as *Prevotella* spp., *Porphyromonas* spp., *Bilophila wadsworthia*, *Desulfovibrio* spp., *Campylobacter* spp., *Fusobacterium* spp., *Clostridium* clostridioforme group spp., and *Eggerthella lenta* [132]. In another study, ceftazidime–avibactam was tested in combination with metronidazole then demonstrating superior activity to monotherapy [133]. However, in the study of Goldstein et al., avibactam improved anaerobicide activity of ceftaroline in strains from diabetic foot infection [134].

Other

Some mycobacteria can produce β-lactamases. *Mycobacterium abscessus* has recently been shown to produce a broad-spectrum β-lactamase (BlaMab). Ceftazidime–avibactam activity was evaluated in an animal model of *M. abscessus* infection, showing an efficient activity against BlaMab [135].

A macrolide, an aminoglycoside and a β-lactam are used in the treatment of pulmonary infection caused by *M. abscessus*. Another study evaluated the bactericidal activity of drug combinations assayed in broth and in human macrophages [136]. Inhibition of BlaMab by avibactam improved the efficacy of imipenem. The substitution N132G in the SDN motif of class A β-lactamases from rapidly growing mycobacteria impair the activity of avibactam [137]. This substitution was included in *Enterobacteriaceae,* but no interference in the activity was detected [138].

Pharmacokinetics

In the mass balance study, the measurement of plasma avibactam and total radioactivity in plasma, whole blood, urine, and feces indicated that most of the avibactam was excreted unchanged in urine with a renal clearance of 158 mL/min, suggesting active tubular secretion. There was no evidence of metabolism in plasma and urine. Avibactam did not interact with various membrane transport proteins or cytochrome P450 enzymes in vitro, decreasing interactions involving cytochrome P450 enzymes [139]. Avibactam is excreted largely unchanged in urine. Ceftazidime–avibactam in patients under continuous venovenous hemofiltration (CVVH) was reported in one case. The authors described the pharmacokinetic; however, it was not possible to predict any drug adjustment [140].

Avibactam was generally well tolerated in healthy young and elderly male and female cohorts in the present study. There were no notable differences in pharmacokinetic parameters between male and female cohorts. The small differences in pharmacokinetic parameters between the young and elderly cohorts are not sufficient to warrant dose adjustments based on age beyond that necessary due to reduced renal function [141, 142]. The pharmacokinetic of avibactam follows a similar tendency of ceftazidime in patients with renal failure, including anuric patients. Thus, the adjustment of dose must maintain the relation with ceftazidime adjustment [143].

A pharmacokinetic evaluation in two patients with acute kidney injury showed that, despite reduced renal clearance, the obesity and large distribution volume can interfere with serum levels of ceftazidime–avibactam, suggesting that dosage for obese patient or increased distribution volume should be reevaluated [144].

Pharmacokinetic parameters of ceftazidime–avibactam are similar to those found in other β-lactams. As a hydrophilic drug, it has distribution volume compatible with its characteristic, being restricted to the extracellular volume.

The penetration of ceftazidime–avibactam in lung tissue is around 30%, based on the drug concentration in lung epithelial fluid [145]. Studies in critically ill patients are needed for future optimized doses for this group of patients.

Ceftazidime–avibactam was described by 1-compartment models in acute pulmonary exacerbation in cystic fibrosis [146]. Total body clearances (CAZ CLt: 7.53 ± 1.28 L/h, AVI CLt: 12.30 ± 1.96 L/h) and volumes of distribution (CAZ Vd: 18.80 ± 6.54 L, AVI Vd: 25.30 ± 4.43 L) were broadly similar to published in healthy adults.

It is important to report that ceftazidime–avibactam was incompatible with vancomycin [147].

Pharmacodynamics

The best pharmacodynamic profile of ceftazidime–avibactam is $fT > MIC$, validated in an animal model of soft tissue infection [59, 60].

An in vitro study of continuous infusion of ceftazidime–avibactam or ceftazidime continuous with avibactam as bolus showed that in this case, both drugs should run in continuous infusion, as the time period that ceftazidime is uncovered by avibactam allows bacterial regrowth [148]. Ceftazidime–avibactam showed no antagonism when combined with tobramycin, levofloxacin, linezolid, vancomycin, tigecycline and colistin [149]. Furthermore, it was shown that ceftazidime/avibactam activity is not influenced by the surfactant, as with daptomycin. A pharmacodynamic

simulation using KPC-producing *K. pneumoniae*, CTX-M producing *E. coli* and AmpC-hyperproducing *Enterobacter cloacae* showed that higher level of avibactam (2–4 times) are necessary to achieve antibacterial effect in carbapenemase-producing isolate [150].

In chronic dialysis patients, a dose of 1 g ceftazidime after dialysis is sufficient to maintain a $fT > MIC$ profile of 70%, a value defined by the author [151]. With larger phase 3 studies, more pharmacodynamic information is available for evaluation and mathematical models of projection.

Pseudomonas aeruginosa can present intracellular and extracellular forms, which can be associated with therapeutic failure. Buyck et al. evaluated the concentration of ceftazidime–avibactam in these different compartments. The efficacy of ceftazidime–avibactam against intracellular isolates was suboptimal, probably associated with concentrations near to MIC [152]. In a time–kill curve model using *P. aeruginosa* resistant to carbapenem, ceftazidime and piperacillin–tazobactam, the activity of ceftazidime was restored [153].

The post-antibiotic effect is a well studied characteristic of aminoglycosides. However, beta-lactamics can also present a variable effect. In this aspect, avibactam was evaluated and curiously, the effect was not a constant, but strain dependent, a mechanism that needs more studies to be confirmed [154].

In vivo studies

A time–kill curve (TKC) study showed that ceftazidime–avibactam has potent bactericidal activity in 18 strains of *P. aeruginosa* [155]. Several carbapenemases were tested, and regrowth occurred in a few isolates.

A study in the mouse septicemia model demonstrated that the potent in vitro activity observed with the ceftazidime–avibactam combination against ceftazidime-resistant Enterobacteriaceae species bearing class A and class (TEM-1, TEM-2, SHV-5, SHV-4, CTX-M-2, CTX-M-15, CTXM-16) C-lactamases (AmpC).

In two murine models of infection by KPC-producing *K. pneumoniae* with MIC ≥ 256 mg/L to ceftazidime, ceftazidime–avibactam proved to be active and was effective in models of septicemia and soft tissue infection [156].

In a pharmacokinetics simulation in an infection model in mice, the standard would be the ideal conditions of $fT > MIC$ of 100%. In this model, the ceftaroline/avibactam combination demonstrated efficacy in the treatment of ESBL- and KPC-producing bacteria when MIC ≤ 1 mg/L [157]. A similar study was conducted by the same group, but testing *P. aeruginosa* with high MIC for ceftazidime and aztreonam–avibactam [158, 159]. In vitro synergy was observed with ceftazidime–avibactam and aztreonam against *Klebsiella pneumoniae* harboring blaNDM, blaOXA-48, and blaCTX-M. Despite the in vitro synergism, no in vivo synergy was observed [160].

Ceftazidime–avibactam was evaluated in a murine model of pneumonia caused by *P. aeruginosa*. This model showed that a dose equivalent to 2 g ceftazidime and 500 mg avibactam every 8 h was sufficient to inhibit the growth of strains with MIC < 32. However, when the MIC was ≥ 32, the response was not effective. It was evident that ceftazidime–avibactam is an effective drug combination in pneumonia caused by *P. aeruginosa* [161]. Another study also has measured the ceftazidime–avibactam levels in the epithelial lining fluid (ELF), which were linear with serum levels and probably effective for lower respiratory tract infection [59].

Effect on human microbiota

Ceftazidime–avibactam is a broad-spectrum antibiotic, and thus it is expected to cause modification of the intestinal microbiota. The number of *Escherichia coli* and other *Enterobacteriaceae* decreases significantly during administration, whereas the number of enterococci increases. Lactobacilli, bifidobacteria, clostridia and *Bacteroides* decrease significantly during ceftazidime–avibactam administration. Toxigenic *Clostridium difficile* strains were detected in five volunteers during the study. Feces samples were collected and ceftazidime–avibactam concentrations varied from 0 to 468.2 mg/kg and avibactam 0–146.0 mg/kg of feces, respectively [162].

Clinical trials

Intra-abdominal infection

The phase II study published in 2014 evaluated the efficacy, safety and tolerability of ceftazidime–avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in 204 hospitalized adults [27]. Patients were enrolled by the clinical investigator and randomized in a 1:1 ratio balanced according to the baseline severity of disease. The dose was a combination of 2000 mg ceftazidime and 500 mg avibactam iv every 8 h. Treatment was given for a minimum of 5 days and a maximum of 14 days, depending upon clinical response. No other concomitant systemic antibiotics were permitted except for vancomycin, linezolid or daptomycin, which were permitted for suspected or documented MRSA or enterococcal infections. The primary efficacy endpoint was the clinical response at the test-of-cure (TOC) visit in the microbiologically evaluable (ME) population, a subset of the clinically evaluable (CE) population.

Clinical response in the ME population at the TOC visit was observed in 91.2% (62/68) and 93.4% (71/76) of ceftazidime–avibactam plus metronidazole and meropenem

patients, respectively. The estimated difference in response rates was − 2.2% (95% CI − 20.4, 12.2%). At the end of iv therapy, a favorable clinical response was observed in 97.1% (66/68) and 97.4% (74/76) of ME patients in the ceftazidime–avibactam plus metronidazole and meropenem groups, respectively (observed difference: − 0.3%; 95% CI − 17.1, 15.4%).

A phase 3 study with data from 2 identical, prospective, randomized, multicenter, double-dummy, double-blind, comparative, global studies at 136 centers in 30 countries [29]. Patients were randomly allocated 1:1 to receive either ceftazidime–avibactam (2000 mg ceftazidime and 500 mg avibactam as a 2-h intravenous infusion every 8 h), followed by metronidazole (500 mg as a 60-min intravenous infusion every 8 h); or meropenem (1000 mg as a 30-min intravenous infusion every 8 h). Of 1066 patients, 529 received ≥ 1 dose of ceftazidime–avibactam plus metronidazole, and 529 ≥ 1 dose of meropenem. At the end of iv therapy, a favorable clinical response was observed in 97.1 and 92.5% of ME patients in the ceftazidime–avibactam plus metronidazole and meropenem groups, respectively (observed difference: − 0.3%; 95% CI − 17.1, 15.4%). Similar results were found in another phase 3 study in Asia. This study included 441 patients with similar clinical response between meropenem and ceftazidime–avibactam plus meropenem, 93.8% (166/177) and 94.0% (173/184) of subjects, respectively.

A post hoc analysis of clinical cure according with type of beta-lactamase was performed. Ceftazidime–avibactam had clinical cure rates of more than 90% among patients infected with ESBL- and/or carbapenemase-producing *Enterobacteriaceae*, but only 75% among patients with pathogens producing AmpC enzymes [163].

Urinary infection

Ceftazidime–avibactam was tested in a prospective phase II, randomized, investigator-blind study to compare the efficacy and safety using imipenem as comparator in hospitalized adults with serious complicated urinary tract infection (cUTI) [28]. Patients were stratified by infection type (acute pyelonephritis or other cUTI) and randomized 1:1 to receive intravenous ceftazidime 500 mg plus avibactam 125 mg every 8 h or imipenem–cilastatin 500 mg every 6 h. The primary efficacy objective was a favorable microbiological response at the test-of-cure (TOC) visit 5–9 days post-therapy in microbiologically evaluable (ME) patients. Sixty-two patients were included in the ME population (ceftazidime–avibactam, $n = 27$; imipenem–cilastatin, $n = 35$) with favorable microbiological response achieved in 70.4% of ME patients receiving ceftazidime–avibactam and 71.4% receiving imipenem–cilastatin at the TOC visit [observed difference − 1.1% (95% CI − 27.2, 25.0%)].

The phase III study, ceftazidime–avibactam was compared with doripenem for the treatment of cUTI, including pyelonephritis. From 1033 patients, the drug were equally effective, however, ceftazidime–avibactam is an option to avoid carbapenem use in ESBL isolates [164].

After 1 year, the activity of ceftazidime–avibactam against ceftazidime-nonsusceptible Gram-negative isolates from both clinical trials was evaluated. Overall, the ceftazidime–avibactam activity was comparable to previously reported against ceftazidime-susceptible isolates [165].

Other

Ceftazidime–avibactam is been evaluated versus meropenem in hospitalized adults with nosocomial pneumonia (NCT01808092) and neutropenic patients (NCT02732327). In pediatric patients, the first study (NCT01893346), a phase I study, assessed the pharmacokinetic profile and safety of a single dose of ceftazidime–avibactam. Four cohorts were evaluated, including age ≥ 12 to < 18 years and ≥ 3 months to < 2 years. The dose varied as 12.5–50 mg/kg, showing similar profile of adults' patients. The study evaluates only one dose; thus, more studies are necessary to evaluate the kinetic and safety after multiple doses [166].

Although clinical studies direct the drug for intra-abdominal and urinary infection, ceftazidime–avibactam is a drug with perspective for use in carbapenemase-producing bacteria, which usually involve critically ill patients in the ICU. The pharmacokinetic properties of ceftazidime in severely ill patients are already known; however, it lacks studies for avibactam. Anyway, there are already reports of treatment of serious infections in this population. A study comparing colistin versus ceftazidime–avibactam showed good response, including lower mortality percentage, but with a small number of patients to reach a conclusion [167]. The fact is that it is hard to believe that a drug with ceftazidime–avibactam profile will have a response lower to that of polymyxins, knowing the poor pharmacokinetic profile of polymyxins in critically ill patients, when compared with a β-lactam.

After clinical trial, some retrospective studies have been published, including comparative analysis against polymyxin and amikacin in the treatment of carbapenem-resistant *Klebsiella* spp. [168]. Ceftazidime–avibactam treatment of carbapenem-resistant *Klebsiella* pneumoniae bacteremia was associated with higher rates of clinical success and survival than aminoglycoside- or colistin-containing regimens. According to the authors from a retrospective study with only descriptive data, ceftazidime–avibactam was an appropriate option with in-hospital mortality of 32% in 60 patients [169]. Another study evaluated bacteremia by carbapenem-resistant *Enterobacteriaceae* in hematologic

patients, suggesting better results than comparator (85.7 vs. 34.8%, respectively, $p = 0.031$) [170].

Other descriptive studies have shown discrepant results, in general, with few patients [171]. One study evaluated 121 patients with carbapenem-resistant *Enterobacteriaceae* bacteremia. The mortality was high, independent of therapy choice, including ceftazidime–avibactam. However, there was a median of 47 h until patients receive active antimicrobial therapy [172].

In a compassionate-use basis, ceftazidime–avibactam was used for treatment of 36 patients with severe infection caused by carbapenem-resistant bacteria. Survival was attributed to microbiological cure (71.4% mortality in patients without microbiological cure, $p = 0.01$). Most of these patients received previous therapy and the mean duration of ceftazidime–avibactam therapy was 16 days. This report reaffirms the importance of microbiological cure to improve survival. However, with recent publications of ceftazidime–avibactam resistance, a careful stewardship program is important to avoid rapid resistance emergence [173]. In another descriptive study, microbiological cure failure was associated with low susceptibility of isolates to ceftazidime–avibactam, achieving 30% in ten isolates from 37 patients evaluated [174].

In summary, ceftazidime–avibactam is a very attractive antimicrobial combination given its broad spectrum of action, including multidrug-resistant bacteria. The pharmacokinetic profile is similar to that of injectable cephalosporins. The susceptibility profile is still high, but there are already resistant strains and the risk is higher in carbapenemases of KPC-2 type. It will be a very important drug in the treatment of nosocomial infections.

Compliance with ethical standards

Conflict of interest FFT and JLR received grants from Astra-Zeneca. Marcelo R. Formigoni-Pinto works in the medical scientific division of Astra-Zeneca.

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