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In vitro activity of ceftazidime, ceftaroline and aztreonam alone and in combination with avibactam against European Gram-negative and Gram-positive clinical isolates

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Recent clinical isolates of key Gram-negative and Gram-positive bacteria were collected in 2012 from hospitalised patients in medical centres in four European countries (France, Germany, Italy and Spain) and were tested using standard broth microdilution methodology to assess the impact of 4 mg/L avibactam on the in vitro activities of ceftazidime, ceftaroline and aztreonam. Against Enterobacteriaceae, addition of avibactam significantly enhanced the level of activity of these antimicrobials. MIC_{90} values (minimum inhibitory concentration that inhibits 90% of the isolates) of ceftazidime, ceftaroline and aztreonam for *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Citrobacter freundii* and *Morganella morganii* were reduced up to 128-fold or greater when combined with avibactam. A two-fold reduction in the MIC_{90} of ceftazidime to 8 mg/L was noted in *Pseudomonas aeruginosa* isolates when combined with avibactam, whereas little effect of avibactam was noted on the MIC values of the test compounds when tested against *Acinetobacter baumannii* isolates. Avibactam had little effect on the excellent activity of ceftazidime, ceftaroline and aztreonam against *Haemophilus influenzae.* It had no impact on the in vitro activity of ceftazidime and ceftaroline against staphylococci and streptococci. This study demonstrates that addition of avibactam enhances the activities of ceftazidime, ceftaroline and aztreonam against Enterobacteriaceae and *P. aeruginosa* but not against *A. baumannii.*

1. Introduction

Avibactam, a novel, potent, non-β-lactam β-lactamase inhibitor of class A, class C and several class D β-lactamases (OXA-48 like enzymes), but not of metallo-β-lactamases (MBLs), is currently under clinical development in combination with ceftazidime, ceftaroline fosamil and aztreonam [1–7]. As part of this development, it is important to understand the activity profile of these antibacterial agents alone and in combination with avibactam against routine clinical isolates. In this study, recent Gram-negative and Gram-positive clinical isolates recovered from hospitalised patients with respiratory, urinary, intra-abdominal, skin and skin-structure, and bloodstream infections were prospectively collected from four European medical centres in France, Germany, Italy and Spain.

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2. Materials and methods

2.1. Bacterial isolates

In total, 606 recent bacterial isolates covering a wide spectrum of relevant clinical pathogens were collected from patients in Hospital Bicêtre (Paris, France), University of Cologne Medical Center (Cologne, Germany), Siena University Hospital (Siena, Italy) and Hospital Universitario Ramón y Cajal (Madrid, Spain). Isolates were obtained prospectively in a 3-month period in 2012 from specimen sources associated with bloodstream, respiratory, urinary, intra-abdominal or skin and skin-structure infections. Only a single isolate per patient was included in the study. Each centre collected and tested ca. 7 isolates each of different organisms for a total of 433 Gram-negative and 173 Gram-positive isolates. Detailed numbers of included Gram-negative isolates of each species are listed in Tables 1 and 2.

2.2. In vitro susceptibility test methods

Minimum inhibitory concentrations (MICs) were determined following reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution guidelines [8] using frozen pre-loaded antibiotic-growth medium microtitre plates prepared by Thermo Fisher Scientific (Oakwood Village, OH) and provided to each centre.

All isolates were tested against the following antibiotics: ceftazidime, ceftaroline (the active metabolite of ceftaroline fosamil) and aztreonam (each compound was tested alone and combined with avibactam at a fixed concentration of 4 mg/L); cefepime, piperacillin plus tazobactam (4 mg/L); doripenem; meropenem; colistin; amikacin; levofloxacin; and ampicillin. The range of concentrations tested was 0.06–128 mg/L for ceftazidime, ceftazidime-avibactam, aztreonam, aztreonam-avibactam, piperacillin/tazobactam, cefepime and amikacin, 0.015–32 mg/L for ceftaroline, ceftaroline-avibactam, doripenem, meropenem, levofloxacin and ampicillin and 0.03–32 mg/L for colistin. Avibactam powder was provided to Thermo Fisher Scientific by AstraZeneca Pharmaceuticals (Waltham, MA). *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, *Streptococcus pneumoniae* ATCC 49619, *Haemophilus influenzae* ATCC 49247 and *H. influenzae* ATCC 49766 were used for quality control according to CLSI guidelines [8].

3. Results

Susceptibility test results for the Gram-negative isolates are listed in Tables 1–3. Results with doripenem were very similar to those of meropenem and were omitted from Tables 1 and 2. Results for the Gram-positive isolates, except for oxacillin-sensitive *S. aureus* (Table 3), are not included in the tables but are described in the text. Addition of 4 mg/L avibactam restored the activities of ceftazidime, ceftaroline and aztreonam against the majority of the Enterobacteriaceae tested (Tables 1–3).

MIC_{90} values (MIC that inhibits 90% of the isolates) for ceftazidime, ceftaroline and aztreonam against *E. coli* when combined with avibactam were reduced from 4, >32 and 16 mg/L, respectively, to 0.25 mg/L (Table 1). MIC_{90} values of >32 mg/L were obtained for all β-lactam antibiotics and levofloxacin against *K. pneumoniae*. When combined with avibactam, the MIC_{90} values for ceftazidime and aztreonam were reduced from >128 mg/L to 2 mg/L and 0.5 mg/L, respectively. MIC_{90} values of ceftaroline (>32 mg/L) and aztreonam (32 mg/L) in the *Klebsiella oxytoca* isolates were reduced to 0.5 mg/L and 0.25 mg/L, respectively, when combined with avibactam. There was greater susceptibility to ceftazidime

Table 1
In vitro activities of ceftazidime, ceftaroline, aztreonam (with and without avibactam) and comparator antibiotics against Gram-negative bacteria.

Organism (no. of isolates)/antibiotic	MIC (mg/L)		
	Range	MIC_{50}	MIC_{90}
Escherichia coli (*n* = 31)			
Ceftazidime	≤0.06–128	0.12	4
Ceftazidime-avibactam	≤0.06–4	0.06	0.25
Ceftaroline	0.06 to >32	0.25	>32
Ceftaroline-avibactam	≤0.015–1	0.06	0.25
Aztreonam	≤0.06 to >128	0.12	16
Aztreonam-avibactam	≤0.06 to >128	≤0.06	0.25
Cefepime	≤0.06 to >128	≤0.06	16
Piperacillin/tazobactam	0.5 to >128	2	64
Meropenem	≤0.015–0.12	≤0.015	0.12
Colistin	0.25 to >32	0.5	0.5
Amikacin	0.5–4	1	2
Levofloxacin	≤0.015 to >32	≤0.015	16
Ampicillin	0.25 to >32	>32	>32
Klebsiella pneumoniae (*n* = 38)			
Ceftazidime	≤0.06 to >128	0.12	>128
Ceftazidime-avibactam	≤0.06 to >128	0.12	2
Ceftaroline	0.06 to >32	0.25	>32
Ceftaroline-avibactam	≤0.015 to >32	0.12	4
Aztreonam	≤0.06 to >128	≤0.06	>128
Aztreonam-avibactam	≤0.06–2	≤0.06	0.5
Cefepime	≤0.06 to >128	≤0.06	128
Piperacillin/tazobactam	0.5 to >128	4	>128
Meropenem	≤0.015 to >32	0.03	>32
Colistin	≤0.06 to >32	0.5	1
Amikacin	0.5–8	1	4
Levofloxacin	≤0.015–32	0.06	>32
Klebsiella oxytoca (*n* = 28)			
Ceftazidime	≤0.06–128	≤0.06	2
Ceftazidime-avibactam	≤0.06–128	≤0.06	1
Ceftaroline	0.03 to >32	0.25	>32
Ceftaroline-avibactam	0.03–32	0.06	0.5
Aztreonam	≤0.06–128	0.12	32
Aztreonam-avibactam	≤0.06–0.5	≤0.06	0.25
Cefepime	≤0.06–8	≤0.06	2
Piperacillin/tazobactam	0.5 to >128	2	>128
Meropenem	≤0.015–1	0.03	0.12
Colistin	0.03–2	0.5	0.5
Amikacin	0.25–8	1	1
Levofloxacin	≤0.015–16	0.03	0.5
Enterobacter cloacae (*n* = 32)			
Ceftazidime	≤0.06 to >128	0.25	>128
Ceftazidime-avibactam	≤0.06–128	0.12	1
Ceftaroline	0.06 to >32	1	>32
Ceftaroline-avibactam	0.06 to >32	0.12	1
Aztreonam	≤0.06 to >128	0.25	128
Aztreonam-avibactam	≤0.06–4	≤0.06	2
Cefepime	≤0.06–128	≤0.06	32
Piperacillin/tazobactam	0.5 to >128	2	>128
Meropenem	≤0.015–8	0.06	1
Colistin	0.25 to >32	0.25	>32
Amikacin	0.5–8	1	2
Levofloxacin	≤0.015–16	0.06	8
Enterobacter aerogenes (*n* = 29)			
Ceftazidime	≤0.06 to >128	0.25	128
Ceftazidime-avibactam	≤0.06–1	0.25	0.5
Ceftaroline	≤0.06–32	1	>32
Ceftaroline-avibactam	0.06–1	0.12	0.5
Aztreonam	≤0.06 to >128	0.25	32
Aztreonam-avibactam	≤0.06–1	0.12	0.5
Cefepime	≤0.06–1	≤0.06	0.25
Piperacillin/tazobactam	2 to >128	4	128
Meropenem	0.03–1	0.06	0.12
Colistin	0.12–32	0.25	0.5
Amikacin	0.5–2	1	2
Levofloxacin	≤0.015–16	0.03	8
Citrobacter freundii (*n* = 25)			
Ceftazidime	0.25 to >128	0.25	128
Ceftazidime-avibactam	≤0.06–0.5	0.12	0.5
Ceftaroline	0.12 to >32	0.5	>32

Table 1 (*Continued*)

Organism (no. of isolates)/antibiotic	MIC (mg/L)		
	Range	MIC_{50}	MIC_{90}
Ceftaroline-avibactam	0.03–0.5	0.12	0.5
Aztreonam	≤0.06–128	0.12	64
Aztreonam-avibactam	≤0.06–0.5	≤0.06	0.25
Cefepime	≤0.06–32	≤0.06	1
Piperacillin/tazobactam	1 to >128	2	128
Meropenem	≤0.015–0.12	0.03	0.12
Colistin	0.25–2	0.5	1
Amikacin	0.5–4	1	2
Levofloxacin	≤0.015–16	0.03	2
Citrobacter koseri (*n* = 37)			
Ceftazidime	≤0.06–16	0.12	0.5
Ceftazidime-avibactam	≤0.06–2	≤0.06	0.25
Ceftaroline	0.06 to >32	0.12	1
Ceftaroline-avibactam	0.03–16	0.06	0.25
Aztreonam	≤0.06–128	≤0.06	0.12
Aztreonam-avibactam	≤0.06–128	≤0.06	≤0.06
Cefepime	≤0.06 to >128	≤0.06	0.12
Piperacillin/tazobactam	1–32	2	8
Meropenem	≤0.015–0.5	≤0.015	0.06
Colistin	0.25–2	0.25	0.5
Amikacin	0.25–128	0.5	1
Levofloxacin	≤0.015–16	≤0.015	0.12
Morganella morganii (*n* = 24)			
Ceftazidime	≤0.06–64	0.5	32
Ceftazidime-avibactam	≤0.06–2	≤0.06	0.12
Ceftaroline	0.06 to >32	0.25	>32
Ceftaroline-avibactam	≤0.015–0.5	0.06	0.5
Aztreonam	≤0.06–64	0.12	4
Aztreonam-avibactam	≤0.06–2	≤0.06	≤0.06
Cefepime	≤0.06 to >128	≤0.06	≤0.06
Piperacillin/tazobactam	0.12–128	0.25	4
Meropenem	≤0.015–0.5	0.12	0.25
Amikacin	0.5 to >128	1	8
Levofloxacin	≤0.015 to >32	0.03	16

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively.

alone (MIC_{90}, 2 mg/L) among these isolates compared with susceptibility to piperacillin/tazobactam (MIC_{90}, >128/4 mg/L).

Elevated MIC_{90} values (≥32 mg/L) were noted for ceftazidime, ceftaroline, aztreonam and piperacillin/tazobactam against *Enterobacter cloacae* and *Enterobacter aerogenes* isolates (Table 1). MIC_{90} values for the avibactam combinations were reduced to ≤2 mg/L for these isolates. MIC_{90} values for ceftazidime, ceftaroline and aztreonam for *Citrobacter freundii* were 128, >32 and 64 mg/L, respectively, but when combined with avibactam the MIC_{90} values were 0.5, 0.5 and 0.25 mg/L, respectively. In contrast to the MIC values for *C. freundii*, the MIC_{90} values for ceftazidime, ceftaroline and aztreonam for *Citrobacter koseri* were ≤1 mg/L.

The MIC_{90} values for ceftazidime and ceftaroline were ≥16 mg/L and >32 mg/L, respectively, when tested against the *Morganella morganii* and *Proteus mirabilis* isolates. When combined with avibactam, the ceftazidime and ceftaroline MIC_{90} values were reduced to 0.12 mg/L and 0.5 mg/L, respectively (Tables 1 and 2). Similar reductions in MIC_{90} values were noted with the avibactam combinations for the *Proteus vulgaris* isolates (Table 2).

High MIC_{90} values were observed for ceftazidime (>128 mg/L), ceftaroline (>32 mg/L), aztreonam (32 mg/L), cefepime (4 mg/L) and piperacillin/tazobactam (32 mg/L) for *Providencia stuartii* (Table 2). The activities of ceftazidime, ceftaroline and aztreonam were increased when combined with avibactam as indicated by lower MIC_{90} values of 16, 8 and 0.25 mg/L, respectively.

Except for one isolate, *Serratia marcescens* isolates had low ceftazidime (≤0.5 mg/L) and aztreonam MICs (≤0.25 mg/L) and therefore there was little discernible effect with avibactam combinations (Table 2). Ceftazidime and aztreonam MICs for that single

Table 2
In vitro activities of ceftazidime, ceftaroline, aztreonam (with and without avibactam) and comparator antibiotics against Gram-negative bacteria.

Organism (no. of isolates)/antibiotic	MIC (mg/L)		
	Range	MIC_{50}	MIC_{90}
Proteus mirabilis (*n* = 31)			
Ceftazidime	≤0.06–32	≤0.06	16
Ceftazidime-avibactam	≤0.06–4	≤0.06	0.12
Ceftaroline	0.06 to >32	0.25	>32
Ceftaroline-avibactam	≤0.06–8	0.12	0.5
Aztreonam	≤0.06–4	≤0.06	2
Aztreonam-avibactam	≤0.06	≤0.06	≤0.06
Cefepime	≤0.06 to >128	≤0.06	4
Piperacillin/tazobactam	0.25–32	0.25	4
Meropenem	≤0.015–0.5	0.06	0.25
Amikacin	1 to >128	2	8
Levofloxacin	≤0.015 to >32	0.5	>32
Proteus vulgaris (*n* = 15)			
Ceftazidime	≤0.06–8	≤0.06	4
Ceftazidime-avibactam	≤0.06–0.12	≤0.06	≤0.06
Ceftaroline	0.12 to >32	8	>32
Ceftaroline-avibactam	0.06–0.25	0.12	0.25
Aztreonam	≤0.06–2	≤0.06	0.12
Aztreonam-avibactam	≤0.06	≤0.06	≤0.06
Cefepime	≤0.06–1	≤0.06	1
Piperacillin/tazobactam	0.12–0.5	0.25	0.5
Meropenem	0.06–0.12	0.06	0.12
Amikacin	0.25–4	1	2
Levofloxacin	≤0.015–0.25	≤0.015	0.25
Providencia rettgeri (*n* = 8)			
Ceftazidime	0.03–0.25	0.12	
Ceftazidime-avibactam	≤0.06–0.25	0.06	
Ceftaroline	0.03–0.25	0.12	
Ceftaroline-avibactam	≤0.015–0.25	0.06	
Aztreonam	≤0.06	≤0.06	
Aztreonam-avibactam	≤0.06	≤0.06	
Cefepime	≤0.06	≤0.06	
Piperacillin/tazobactam	0.25–1	0.25	
Meropenem	0.03–0.12	0.06	
Amikacin	1–8	2	
Levofloxacin	≤0.015–2	0.12	
Providencia stuartii (*n* = 13)			
Ceftazidime	0.03 to >128	0.5	>128
Ceftazidime-avibactam	0.03–16	0.25	16
Ceftaroline	0.06 to >32	8	>32
Ceftaroline-avibactam	0.06–8	1	8
Aztreonam	≤0.06–64	≤0.06	32
Aztreonam-avibactam	≤0.06–64	≤0.06	0.25
Cefepime	≤0.06–16	≤0.06	4
Piperacillin/tazobactam	0.25–128	2	32
Meropenem	0.06–0.5	0.06	0.25
Amikacin	0.5 to >128	2	8
Levofloxacin	0.12 to >32	2	>32
Serratia marcescens (*n* = 28)			
Ceftazidime	≤0.06–4	0.25	0.5
Ceftazidime-avibactam	≤0.06–0.5	0.12	0.5
Ceftaroline	0.5 to >32	1	8
Ceftaroline-avibactam	0.25–4	0.5	1
Aztreonam	≤0.06–16	0.12	0.5
Aztreonam-avibactam	≤0.06–0.5	≤0.06	0.25
Cefepime	≤0.06–8	≤0.06	0.25
Piperacillin/tazobactam	0.5–128	2	4
Meropenem	0.03–0.25	0.06	0.12
Levofloxacin	≤0.015–0.25	0.12	0.25
Pseudomonas aeruginosa (*n* = 33)			
Ceftazidime	0.5–128	4	16
Ceftazidime-avibactam	0.5–16	2	8
Ceftaroline	0.12 to >32	8	>32
Ceftaroline-avibactam	1 to >32	8	16
Aztreonam	0.25 to >128	8	32
Aztreonam-avibactam	≤0.06–64	8	32
Cefepime	1–64	2	16
Piperacillin/tazobactam	0.5 to >128	8	64
Meropenem	≤0.015 to >32	1	32
Colistin	0.25–4	0.5	1

Table 2 (*Continued*)

Organism (no. of isolates)/antibiotic	MIC (mg/L)		
	Range	MIC_{50}	MIC_{90}
Amikacin	0.25–128	2	32
Levofloxacin	0.12 to >32	0.5	32
Acinetobacter baumannii ($n = 30$)			
Ceftazidime	0.5 to >128	32	>128
Ceftazidime-avibactam	2 to >128	16	64
Ceftaroline	0.5 to >32	16	>32
Ceftaroline-avibactam	0.5 to >32	8	>32
Aztreonam	4 to >128	64	>128
Aztreonam-avibactam	4 to >128	64	>128
Cefepime	0.5 to >128	16	64
Piperacillin/tazobactam	≤0.06 to >128	8	>128
Meropenem	0.12 to >32	1	>32
Colistin	0.25–2	0.5	1
Amikacin	0.25 to >128	2	>128
Levofloxacin	0.03 to >32	1	32
Haemophilus influenzae ($n = 31$)			
Ceftazidime	≤0.06–1	≤0.06	0.25
Ceftazidime-avibactam	≤0.015–2	≤0.06	≤0.06
Ceftaroline	≤0.015–2	≤0.015	0.06
Ceftaroline-avibactam	≤0.015–2	≤0.015	≤0.015
Aztreonam	≤0.06–8	≤0.06	0.5
Aztreonam-avibactam	≤0.06–8	≤0.06	0.12
Cefepime	≤0.06–2	≤0.06	0.12
Piperacillin/tazobactam	≤0.06–0.12	≤0.06	≤0.06
Meropenem	≤0.015–0.5	0.06	0.12
Colistin	≤0.06–1	0.5	1
Amikacin	1–4	4	4
Levofloxacin	≤0.015–0.03	≤0.015	≤0.015
Ampicillin	0.03 to >32	0.5	>32

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively.

isolate were reduced from 4 mg/L and 16 mg/L, respectively, to 0.5 mg/L when combined with avibactam.

For *P. aeruginosa* isolates, there was a trend towards decreased MICs of ceftazidime when combined with avibactam as indicated by a two-fold reduction in the MIC_{90} (from 16 mg/L to 8 mg/L) (Table 2). The MIC_{90} values of the other β-lactams, amikacin and levofloxacin in this study were all ≥16 mg/L.

High MICs (MIC_{90}, ≥32 mg/L) were observed for all antibiotics, except colistin, for the 30 *Acinetobacter baumannii* isolates (Table 2). Except for a few isolates with a two- to three-fold reduction in the MIC with the ceftazidime-avibactam combination, addition of avibactam had little impact on the activity profile of the antibiotics alone.

All but one of the *H. influenzae* isolates, including those with ampicillin MICs of ≥8 mg/L, had ceftazidime, ceftaroline and aztreonam MICs ≤0.5 mg/L. There was little reduction in the MICs of the antibiotics when combined with avibactam (Table 2).

Ceftaroline was the most potent cephalosporin evaluated against oxacillin-sensitive *S. aureus* ($n = 34$), with all isolates inhibited at 1 mg/L (Table 3). In contrast, the MIC_{50} (MIC that inhibits 50% of the isolates)/MIC_{90} values of ceftazidime and cefepime were 8/8 and 2/4 mg/L, respectively. Addition of avibactam did not alter the activity of ceftazidime or ceftaroline

Potent activity was also observed with ceftaroline against oxacillin-resistant *S. aureus* ($n = 28$) and against *Staphylococcus saprophyticus* ($n = 15$), *S. pneumoniae* ($n = 30$), *Streptococcus agalactiae* ($n = 34$) and *Streptococcus pyogenes* ($n = 24$), with MIC_{90} values of 2, 1, 0.12, 0.03 and ≤0.015 mg/L, respectively (data not shown). As noted in the study by Karlowsky et al. [9], addition of avibactam did not have any relevant impact on the MICs of ceftaroline or ceftazidime against staphylococci or streptococci.

4. Discussion

Avibactam is a β-lactamase inhibitor that targets important β-lactamases produced by clinically relevant Gram-negative bacilli, including class A, C and some class D enzymes [7]. This study was conducted to investigate the spectrum and level of activity of ceftazidime, ceftaroline and aztreonam in the presence and absence of avibactam against a recent collection of geographically distributed clinical isolates representing commonly encountered relevant bacterial species from medical centres in four European countries (France, Germany, Italy and Spain). Although this study has the limitation that the potential resistance mechanisms of the isolates were not characterised, it clearly provides useful information on the activity of avibactam in combination with β-lactam antibiotics for which clinical trials are currently being performed.

Against a wide variety of Enterobacteriaceae, the combination of avibactam at a fixed concentration of 4 mg/L substantially reduced the MIC_{90} values of ceftazidime, ceftaroline and aztreonam in the majority of isolates to levels similar to those observed for meropenem and doripenem. These results are similar to those obtained in studies carried out in Canada, Latin America, China and the USA [9–12]. Among *K. pneumoniae*, several isolates from one centre had high MICs (≥128 mg/L) for ceftazidime, aztreonam, cefepime and piperacillin/tazobactam and >32 mg/L for ceftaroline, meropenem, doripenem and levofloxacin. The MICs for ceftazidime-avibactam against all but one of these isolates were reduced to ≤8 mg/L and for aztreonam-avibactam all MICs were reduced to ≤2 mg/L. Given the reduced MIC of aztreonam-avibactam but not that of the corresponding cephalosporin/avibactam combinations, that isolate likely produced a MBL because aztreonam is not susceptible to hydrolysis by these enzymes [13]. Among *E. cloacae*, the MICs of ceftazidime and ceftaroline against two isolates were not reduced when combined with avibactam although MICs were reduced for aztreonam-avibactam, also consistent with the production of a MBL as reasoned above. The MICs against these two isolates were elevated for cefepime (64 mg/L and 128 mg/L), piperacillin/tazobactam (>128 mg/L) and meropenem (4 mg/L and 8 mg/L).

Likely due to the multifactorial nature of resistance in this species, high MICs were observed for all *P. aeruginosa* isolates against all antibiotics in the study, except for colistin. Among the collected *P. aeruginosa* isolates, a two-fold reduction in the MIC_{90} was noted for ceftazidime when combined with avibactam, consistent with other studies of *P. aeruginosa* clinical isolates conducted in Europe and Canada [14,15]. Except for colistin, high MICs were shown for all antibiotics for the majority of *A. baumannii* isolates. Since avibactam, unlike sulbactam, has no intrinsic activity against *A. baumannii*, and resistance to cephalosporins and aztreonam in these organisms is usually mediated not only by class A and class C β-lactamases but also by other resistance mechanisms, the lack of any effect of the avibactam combinations is not surprising. Avibactam did not have any additional effect over the excellent activity of ceftazidime, ceftaroline and aztreonam against *H. influenzae*. These data are consistent with the lack of β-lactamase-mediated resistance mechanisms to extended-spectrum cephalosporins in this species.

As expected, ceftaroline was more active than ceftazidime and cefepime against *S. aureus* and *S. saprophyticus* and was more active than the other tested antibiotics against oxacillin-resistant isolates of *S. aureus* (data not shown). Avibactam had no impact on the activity of ceftaroline or ceftazidime against staphylococci, which is not surprising since ceftaroline and ceftazidime resistance is not β-lactamase-mediated in these species. As in the case of staphylococci, ceftaroline was more active than ceftazidime against *S. pneumoniae*, *S. pyogenes*, *Streptococcus milleri* group and

Table 3
Activity of ceftazidime, ceftaroline and aztreonam with and without avibactam (4 mg/L) against selected clinical isolates.

Organism (no. of isolates)	Antibiotic	No. of isolates inhibited at an MIC (mg/L) of											
		≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥128
Escherichia coli (*n* = 31)	Ceftazidime	3	16	5		1	1	2	2				1
	Ceftazidime-avibactam	17	10	2	1			1					
	Ceftaroline	6	6	10	1	2					6		
	Ceftaroline-avibactam	22	3	4	1	1							
	Aztreonam	15	8	1					2	2	1		2
	Aztreonam-avibactam	22	5	3									1
Klebsiella spp. (*n* = 66)[a]	Ceftazidime	24	15	7	2	3	2	1		1	2		9
	Ceftazidime-avibactam	32	16	5	4	3	1	2	1				2
	Ceftaroline	13	16	11	5	1	4				16		
	Ceftaroline-avibactam	33	12	8	5	1		4		1	2		
	Aztreonam	40	7	3	1		2	1	1		1	1	9
	Aztreonam-avibactam	45	11	5	3	1	1						
Enterobacter spp. (*n* = 61)[b]	Ceftazidime	5	10	16	3	2			1	1	8	5	10
	Ceftazidime-avibactam	11	20	14	9	4	1					2	
	Ceftaroline	7	8	8	5	7	1			4	21		
	Ceftaroline-avibactam	22	17	5	9	5	1				2		
	Aztreonam	26	3	4	1	1		3	1	2	9	5	6
	Aztreonam-avibactam	33	8	7	6	3	2	2					
Citrobacter freundii (*n* = 25)	Ceftazidime			13	5	1					1	2	3
	Ceftazidime-avibactam	7	12	2	4								
	Ceftaroline		2	9	5	2			1		6		
	Ceftaroline-avibactam	9	8	4	4								
	Aztreonam	7	8	2	1	1					2	3	1
	Aztreonam-avibactam	16	5	3	1								
Pseudomonas aeruginosa (*n* = 33)	Ceftazidime				3	2	11	6	6	2	2		1
	Ceftazidime-avibactam		1		2	6	13	7	3	1			
	Ceftaroline					1	1	5	10	4	12		
	Ceftaroline-avibactam				1	1	5	8	11	6	1		
	Aztreonam			2			1	9	9	4	6	1	1
	Aztreonam-avibactam		1	2				10	10	3	6	1	
Staphylococcus aureus (oxacillin-sensitive) (*n* = 34)	Ceftazidime						1	9	21	3			
	Ceftazidime-avibactam						1	7	24	2			
	Ceftaroline	1	1	18	11	3							
	Ceftaroline-avibactam	1	1	20	10	2							

MIC, minimum inhibitory concentration.
[a] *Klebsiella pneumoniae* (*n* = 38); Klebsiella oxytoca (*n* = 28).
[b] *Enterobacter cloacae* (*n* = 32); *Enterobacter aerogenes* (*n* = 29).

S. agalactiae isolates. The activity of both antibiotics was essentially the same with or without the presence of avibactam.

In conclusion, the results of this study demonstrated that the combination of 4 mg/L avibactam with ceftazidime, ceftaroline or aztreonam broadens their spectrum of activity to include the majority of β-lactam-resistant Enterobacteriaceae against which these antibiotics alone have poor activity. The activity was enhanced against many isolates to the extent that their activities were frequently comparable with, or in some cases greater than, those of the carbapenems. An isolate-dependent enhancement of activity was observed with the avibactam combinations against *P. aeruginosa* isolates, resulting in a ceftazidime-avibactam MIC_{90} of 8 mg/L. Avibactam combinations were not active against *A. baumannii*. Furthermore, avibactam had no impact on the in vitro activity of ceftaroline or ceftazidime against staphylococci and streptococci. This is consistent with the absence of β-lactamase-mediated resistance mechanisms to extended-spectrum cephalosporins among these genera.

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Ethical approval

Not required.

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