P1400

In Vitro Activity of Ceftibuten-Avibactam and Comparator Agents Against Enterobacterales Collected Globally as Part of the ATLAS Surveillance Program, 2022 by Length of Stay

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Introduction

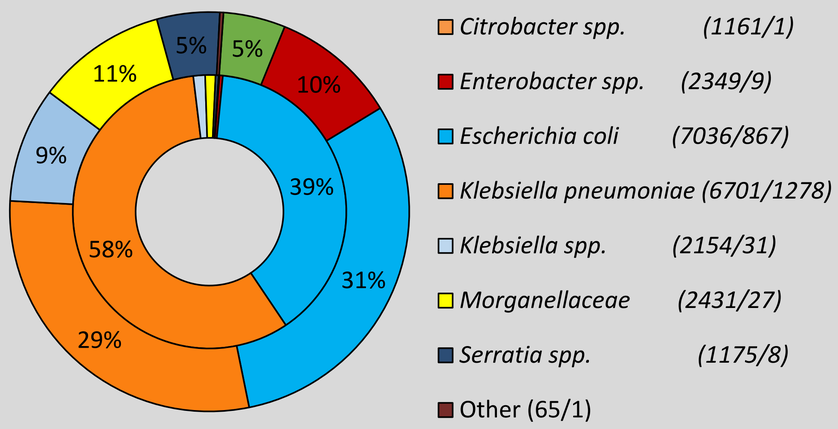
Ceftibuten is an orally administered third-generation cephalosporin in early clinical development in combination with an oral prodrug of avibactam, a non-β-lactam inhibitor of Ambler class A β-lactamases, including ESBLs and KPCs, class C (AmpC) β-lactamases, and some class D (OXA-48) β-lactamases. This study evaluated the *in vitro* activity of ceftibuten-avibactam and comparators against Enterobacterales isolates collected ≥48 hours and <48 hours of hospitalization as part of the 2022 Antimicrobial Testing Leadership and Surveillance (ATLAS) program.

Methods

The 23,072 non-duplicate, clinically isolated Enterobacterales analyzed in this study were collected through the ATLAS program during 2022 by 217 medical centers in 56 countries (Figure 1, Figure 2). Identification was confirmed by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Daltronics, Bremen, Germany) library version MBT Compass 4.1.100. A total of 10,965 (47.5%) were from patients hospitalized <48 hours and 12,107 (52.5%) were from patients hospitalized ≥48 hours. Susceptibility testing was done by broth microdilution according to CLSI guidelines [1] and interpreted using EUCAST 2023 breakpoints [2]. Ceftibuten-avibactam was tested with a fixed concentration of 4 mg/L avibactam. As there are no ceftibuten-avibactam breakpoints, the EUCAST ceftibuten breakpoint of ≤1 mg/L was applied for comparison purposes only. Isolates testing with meropenem MIC >1 mg/L or *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, or *Proteus mirabilis* testing with ceftazidime and/or aztreonam MIC >2 mg/L were screened for β-lactamases by PCR as described previously [3].

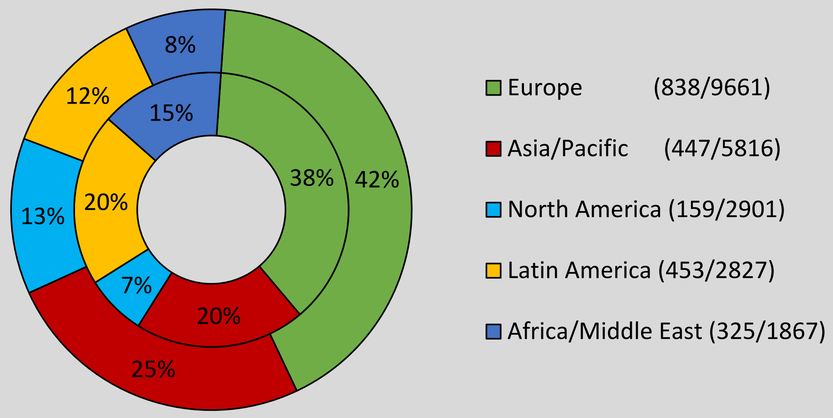
Results

Figure 1. Distribution of species included in the study (n all Enterobacterales/n ESBL+, MBL-)



Outer ring includes all Enterobacterales; inner ring includes ESBL+, MBL- Enterobacterales
Klebsiella spp. and *Morganellaceae*, 1% ESBL+, MBL-; *Citrobacter* spp., *Enterobacter* spp., *Serratia* spp., and Other <1% ESBL+, MBL-

Figure 2. Distribution of regions contributing isolates to the study (n all Enterobacterales/n ESBL+, MBL-)



Outer ring includes all Enterobacterales; inner ring includes ESBL+, MBL- Enterobacterales

Table 1. Activity of ceftibuten-avibactam and comparators against Enterobacterales isolates collected ≥48 hours and <48 hours of hospitalization

Organism group (n)	Antimicrobial	mg/L			%S	%I	%R
		MIC_{50}	MIC_{90}	Range			
All Enterobacterales (23,072)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.5	≤0.06 – >64	93.5	na	na
	Ceftibuten	0.25	64	≤0.06 – >64	69.3	--	30.7
	Cefepime	≤0.12	>32	≤0.12 – >32	72.9	4.9	22.2
	Cefixime	0.5	>64	≤0.12 – >64	60.5	--	39.5
	Cefpodoxime	1	>16	≤0.12 – >16	54.7	--	45.3
	Ceftazidime	0.25	>64	≤0.03 – >64	68.5	4.2	27.4
	Ceftazidime-avibactam	0.12	0.5	≤0.03 – >64	96.0	--	4.0
	Levofloxacin	≤0.25	>8	≤0.25 – >8	69.3	5.4	25.2
	Trimethoprim sulfa	≤1	>32	≤1 – >32	68.0	1.1	30.9
All, <48 hours (10,965)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.12	≤0.06 – >64	95.4	na	na
	Ceftibuten	0.25	32	≤0.06 – >64	74.7	--	25.3
	Cefepime	≤0.12	32	≤0.12 – >32	77.8	4.4	17.8
	Cefixime	0.5	>64	≤0.12 – >64	66.1	--	33.9
	Cefpodoxime	0.5	>16	≤0.12 – >16	60.7	--	39.3
	Ceftazidime	0.25	64	≤0.03 – >64	74.1	4.0	21.9
	Ceftazidime-avibactam	0.12	0.5	≤0.03 – >64	97.4	--	2.6
	Levofloxacin	≤0.25	>8	≤0.25 – >8	73.4	4.9	21.7
	Trimethoprim sulfa	≤1	>32	≤1 – >32	70.9	0.9	28.2
All, ≥48 hours (12,107)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.5	≤0.06 – >64	91.7	na	na
	Ceftibuten	0.25	>64	≤0.06 – >64	64.4	--	35.6
	Cefepime	≤0.12	>32	≤0.12 – >32	68.5	5.4	26.1
	Cefixime	1	>64	≤0.12 – >64	55.5	--	44.5
	Cefpodoxime	2	>16	≤0.12 – >16	49.4	--	50.6
	Ceftazidime	0.25	>64	≤0.03 – >64	63.3	4.3	32.3
	Ceftazidime-avibactam	0.12	1	≤0.03 – >64	94.8	--	5.2
	Levofloxacin	≤0.25	>8	≤0.25 – >8	65.6	5.9	28.4
	Trimethoprim sulfa	≤1	>32	≤1 – >32	65.4	1.2	33.4
ESBL+, MBL-, all (2,222)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.25	≤0.06 – >64	98.2	na	na
	Ceftibuten	8	>64	≤0.06 – >64	9.8	--	90.2
	Cefepime	32	>32	≤0.12 – >32	2.6	10.3	87.1
	Cefixime	>64	>64	≤0.12 – >64	0.8	--	99.2
	Cefpodoxime	>16	>16	≤0.12 – >16	0.5	--	99.5
	Ceftazidime	32	>64	1 – >64	0	10.7	89.2
	Ceftazidime-avibactam	0.25	1	≤0.03 – >64	98.9	--	1.1
	Levofloxacin	>8	>8	≤0.25 – >8	24.3	9.5	66.2
	Trimethoprim sulfa	>32	>32	≤1 – >32	23	2.4	74.6
ESBL+, MBL-, <48 hours (912)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.25	≤0.06 – >64	98.6	na	na
	Ceftibuten	8	64	≤0.06 – >64	10.4	--	89.6
	Cefepime	32	>32	≤0.12 – >32	3.0	12.1	85.0
	Cefixime	64	>64	≤0.12 – >64	0.4	--	99.6
	Cefpodoxime	>16	>16	≤0.12 – >16	0.3	--	99.7
	Ceftazidime	32	>64	2 – >64	0.0	14.0	86.0
	Ceftazidime-avibactam	0.25	1	≤0.03 – >64	99.0	--	1.0
	Levofloxacin	8	>8	≤0.25 – >8	25.5	10.1	64.4
	Trimethoprim sulfa	>32	>32	≤1 – >32	28.2	1.4	70.4
ESBL+, MBL-, ≥48 hours (1,310)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.5	≤0.06 – >64	98.0	na	na
	Ceftibuten	8	>64	≤0.06 – >64	9.4	--	90.6
	Cefepime	32	>32	≤0.12 – >32	2.3	9.1	88.6
	Cefixime	>64	>64	≤0.12 – >64	1.1	--	98.9
	Cefpodoxime	>16	>16	≤0.12 – >16	0.5	--	99.5
	Ceftazidime	32	>64	1 – >64	0.1	8.4	91.5
	Ceftazidime-avibactam	0.25	2	≤0.03 – >64	98.8	--	1.2
	Levofloxacin	>8	>8	≤0.25 – >8	23.4	9.2	67.5
	Trimethoprim sulfa	>32	>32	≤1 – >32	19.5	3.1	77.5

%S/I/R, percent susceptible/intermediate/resistant based on EUCAST 2022 v13.0 (ceftibuten-avibactam susceptible breakpoint of ≤1 mg/L was applied for comparison purposes only); LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSTI, skin/soft tissue infection; IAI, intra-abdominal infection.

Figure 3. Distribution of ceftibuten-avibactam MIC values for all Enterobacterales and ESBL-positive, MBL-negative Enterobacterales

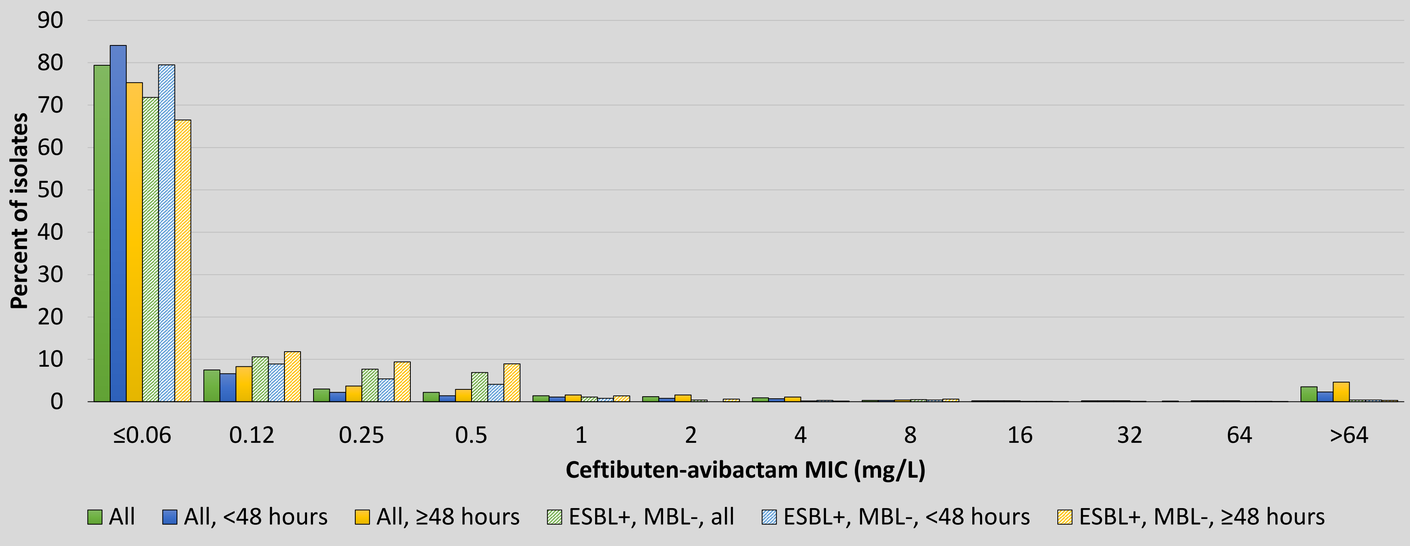
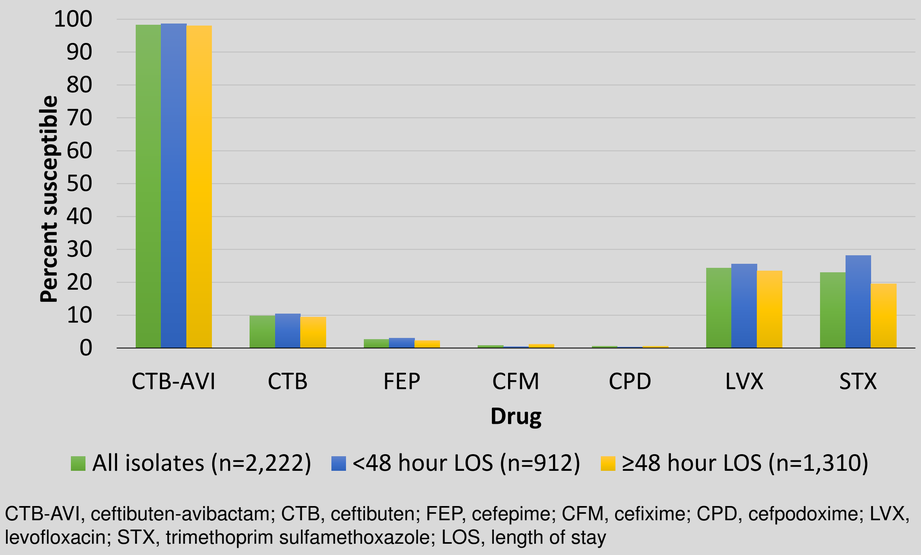


Figure 4. Susceptibility of ESBL-positive, MBL-negative isolates to ceftibuten-avibactam and comparator agents



CTB-AVI, ceftibuten-avibactam; CTB, ceftibuten; FEP, cefepime; CFM, cefixime; CPD, cefpodoxime; LVX, levofloxacin; STX, trimethoprim sulfamethoxazole; LOS, length of stay

Results Summary

- Ceftibuten-avibactam MIC_{90} values against isolates collected <48 hours and ≥48 hours of hospitalization were 0.12 mg/L and 0.5 mg/L, respectively, lower than the MIC_{90} values for all comparators tested (Table 1).
- The percentage of isolates collected <48 hours and ≥48 hours of hospitalization inhibited at a ceftibuten-avibactam MIC of ≤1 mg/L was 95.4% for and 91.7%, respectively. Susceptibility to comparator agents was 5-12 percentage points lower among isolates collected ≥48 hours post-admission than <48 hours.
- Ceftibuten-avibactam was the most active oral compound tested against all Enterobacterales, with 93.5% of isolates inhibited at an MIC of ≤1 mg/L. Susceptibility of oral comparator agents ranged from 54.7% (cefpodoxime) to 72.9% (cefepime).
- A total of 2,222 (61.1% of 3,638 isolates screened) isolates were ESBL+, MBL-. Of these 912 (41.0%) were from patients hospitalized <48 hours, and 1,310 (59.0%) were from patients hospitalized ≥48 hours.
- Ceftibuten-avibactam maintained activity against ESBL+, MBL- isolates, with an MIC_{90} of 0.25 mg/L and 98.6% of isolates inhibited at an MIC of ≤1 mg/L from patients with <48 hours hospitalization, and an MIC_{90} of 0.5 mg/L and 98.0% of isolates inhibited at an MIC of ≤1 mg/L from patients with ≥48 hours hospitalization (Figure 3). Activity against these isolates was comparable to that of ceftazidime-avibactam (Table 1).
- Susceptibility of ESBL+, MBL- isolates to oral comparators ranged from 0.3 to 28.2% for isolates from patients hospitalized <48 hours, 0.5 to 23.4% for isolates from patients hospitalized ≥48 hours (Figure 4).

Conclusions

Ceftibuten-avibactam appears to have potential as an oral treatment option for infections for which there are currently few oral treatment options available.

References

1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eleventh Edition*. CLSI document M07-Ed11. 2018. CLSI, Wayne, PA.
2. The European Committee on Antimicrobial Susceptibility Testing. *Breakpoint tables for interpretation of MICs and zone diameters*. Version 13.0, 2023. http://www.eucast.org.
3. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahm, DF. 2015. *Trends in susceptibility of Escherichia coli from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART program, 2009 to 2013*. Antimicrob Agents Chemother 59:3606-3610.

Disclosures

This study was sponsored by Pfizer. GS is an employee of Pfizer. MH and DS are employees of IHMA, which received fees from Pfizer for the conduct of the study and poster preparation.

Presented at ECCMID 2024 on April 27 - 30, 2024 in Barcelona, Spain