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In Vitro Activity of Ceftibuten-Avibactam Against Enterobacterales Collected in the 2022 ATLAS Surveillance Program Stratified by Site of Infection

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Introduction

Ceftibuten is an oral, third-generation cephalosporin in development in combination with an oral prodrug of avibactam. Avibactam is 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. Ceftibuten-avibactam is in early clinical development as a potential oral treatment for complicated urinary tract infections including acute pyelonephritis caused by multidrug-resistant (MDR) and serine β-lactamase-producing Enterobacterales. The objective of this study was to provide an analysis of the *in vitro* activity of ceftibuten-avibactam and comparators against a recent collection of Enterobacterales stratified by site of infection.

Methods

The 23,027 non-duplicate, clinically isolated Enterobacterales analyzed in this study were collected through the Antimicrobial Testing Leadership and Surveillance (ATLAS) program during 2022 by 217 medical centers in 56 countries. 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. 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 isolates by infection source

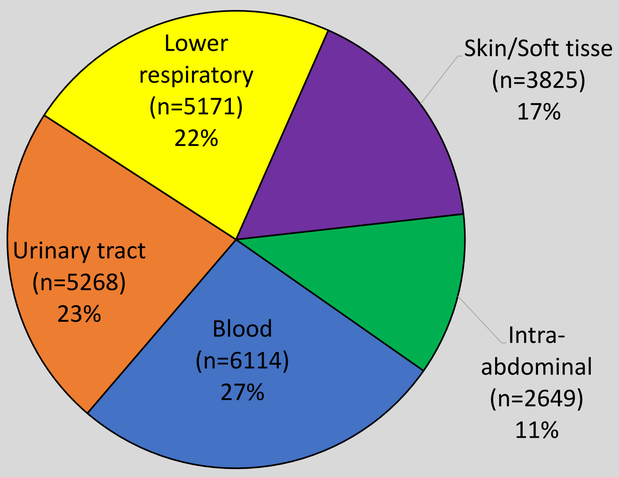
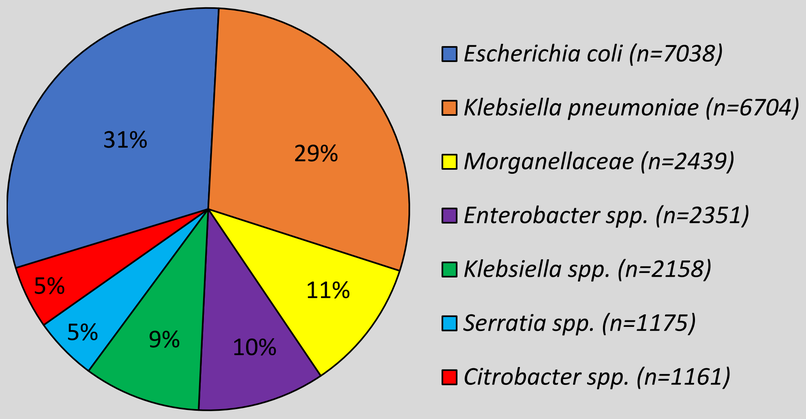


Figure 2. Distribution of isolates by species



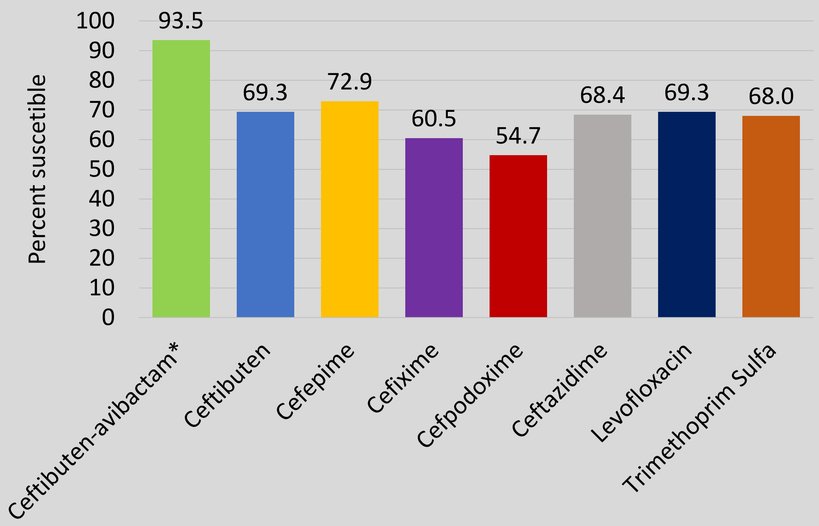
Other (n=68) <0.1%

Table 1. *In vitro* activity of ceftibuten-avibactam and comparators against 23,027 Enterobacterales collected in 2022 stratified by infection source

Infection source (n)	Antimicrobial	mg/L MIC_{50}	mg/L MIC_{90}	mg/L Range	%S	%I	%R
Blood (6114)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.25	≤0.06 – >64	94.1	na	na
	Ceftibuten	0.25	64	≤0.06 – >64	69.7	--	30.3
	Cefepime	≤0.12	>32	≤0.12 – >32	72.2	4.6	23.2
	Cefixime	0.5	>64	≤0.12 – >64	61.8	--	38.2
	Cefpodoxime	1	>16	≤0.12 – >16	56.9	--	43.1
	Ceftazidime	0.25	>64	≤0.03 – >64	68.4	4.2	27.4
	Ceftazidime-avibactam	0.12	0.5	≤0.03 – >64	96.1	--	3.9
	Levofloxacin	≤0.25	>8	≤0.25 – >8	70.0	5.3	24.6
	Trimethoprim Sulfa	≤1	>32	≤1 – >32	67.1	0.9	32.0
LRTI (5171)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.5	≤0.06 – >64	92.8	na	na
	Ceftibuten	0.25	>64	≤0.06 – >64	68.0	--	32.0
	Cefepime	≤0.12	>32	≤0.12 – >32	72.9	4.5	22.6
	Cefixime	0.5	>64	≤0.12 – >64	60.3	--	39.7
	Cefpodoxime	1	>16	≤0.12 – >16	52.3	--	47.7
	Ceftazidime	0.25	>64	≤0.03 – >64	67.8	3.5	28.7
	Ceftazidime-avibactam	0.12	1	≤0.03 – >64	95.7	--	4.3
	Levofloxacin	≤0.25	>8	≤0.25 – >8	72.2	5.9	21.9
	Trimethoprim Sulfa	≤1	>32	≤1 – >32	71.9	1.3	26.8
UTI (5268)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.25	≤0.06 – >64	93.9	na	na
	Ceftibuten	0.25	64	≤0.06 – >64	68.9	--	31.1
	Cefepime	≤0.12	>32	≤0.12 – >32	71.3	5.5	23.2
	Cefixime	0.5	>64	≤0.12 – >64	60.5	--	39.5
	Cefpodoxime	1	>16	≤0.12 – >16	55.9	--	44.1
	Ceftazidime	0.25	64	≤0.03 – >64	67.0	5.4	27.7
	Ceftazidime-avibactam	0.12	0.5	≤0.03 – >64	96.2	--	3.8
	Levofloxacin	≤0.25	>8	≤0.25 – >8	64.2	4.8	31.0
	Trimethoprim Sulfa	≤1	>32	≤1 – >32	63.5	1.2	35.3
SSTI (3825)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.5	≤0.06 – >64	92.7	na	na
	Ceftibuten	0.25	64	≤0.06 – >64	69.0	--	31.0
	Cefepime	≤0.12	>32	≤0.12 – >32	73.6	5.1	21.2
	Cefixime	1	>64	≤0.12 – >64	57.1	--	42.9
	Cefpodoxime	1	>16	≤0.12 – >16	51.1	--	48.9
	Ceftazidime	0.25	>64	≤0.03 – >64	69.2	3.6	27.2
	Ceftazidime-avibactam	0.12	1	≤0.03 – >64	95.3	--	4.7
	Levofloxacin	≤0.25	>8	≤0.25 – >8	69.6	6.3	24.1
	Trimethoprim Sulfa	≤1	>32	≤1 – >32	67.4	1	31.6
IAI (2649)	Ceftibuten-avibactam (≤1 mg/L)	≤0.06	0.25	≤0.06 – >64	93.5	na	na
	Ceftibuten	0.25	64	≤0.06 – >64	72.1	--	27.9
	Cefepime	≤0.12	32	≤0.12 – >32	76.7	4.9	18.4
	Cefixime	0.5	>64	≤0.12 – >64	63.0	--	37.0
	Cefpodoxime	1	>16	≤0.12 – >16	57.4	--	42.6
	Ceftazidime	0.25	64	≤0.03 – >64	71.5	4.2	24.3
	Ceftazidime-avibactam	0.12	0.5	≤0.03 – >64	96.9	--	3.1
	Levofloxacin	≤0.25	>8	≤0.25 – >8	71.8	4.7	23.5
	Trimethoprim Sulfa	≤1	>32	≤1 – >32	72.1	0.6	27.3

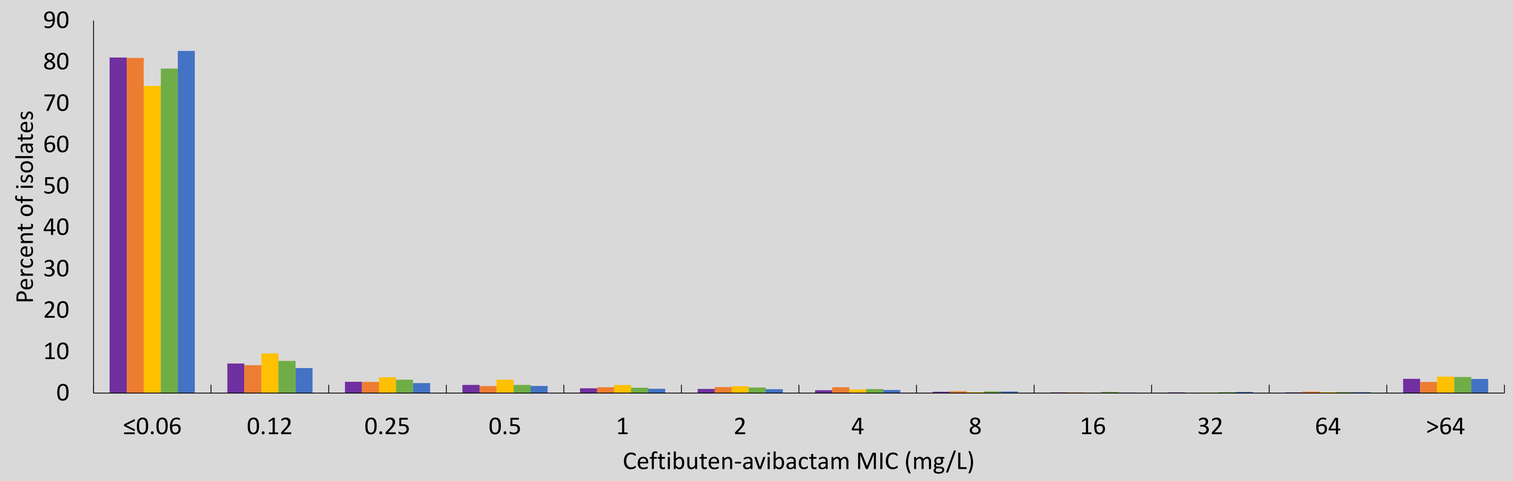
%S/I/R, percent susceptible/intermediate/resistant based on EUCAST 2022 v13.0 (ceftibuten-avibactam susceptible breakpoint of ≤1 mg/L was applied for comparison purposes only); LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSTI, skin/soft tissue infection; IAI, intra-abdominal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

Figure 3. Percent of Enterobacterales collected in 2022 susceptible* to ceftibuten-avibactam and oral comparators



* Corresponds to ceftibuten-avibactam ≤1 mg/L for comparison purposes only

Figure 4. MIC distribution of ceftibuten-avibactam for Enterobacterales collected in 2022 stratified by infection source



LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSTI, skin/soft tissue infection; IAI, intra-abdominal infection.

Results Summary

- The addition of avibactam restored the *in vitro* activity of ceftibuten against Enterobacterales by at least 128-fold and was consistent across infection sources (Table 1, Figure 4).
- Ceftibuten-avibactam was the most active oral compound tested across all infection sources, with MIC_{90} values ranging from 0.25 mg/L to 0.5 mg/L, and >92.7% of all isolates inhibited at an MIC of ≤1 mg/L. Percent susceptible of oral comparators ranged from 54.7% to 72.9% (Figure 3).
- MIC values for ceftibuten-avibactam ranged from ≤0.06 to >64 mg/mL (Figure 4). Of the 818 isolates with a ceftibuten-avibactam MIC >64mg/L, 770 were molecularly characterized, and of those, 757 (98.3%) carried metallo-β-lactamase (MBL) genes.
- Based on MIC_{90} values, *in vitro* activity of ceftibuten-avibactam was comparable to that of ceftazidime-avibactam.

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.
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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

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