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In vitro Activity of Ceftibuten-avibactam Against Enterobacterales from Urinary Tract Infections Collected in the 2022 ATLAS Surveillance Program: A Regional Analysis

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Introduction

Enterobacterales are important etiologic agents of uncomplicated and complicated urinary tract infections (UTIs). Increasing resistance among agents commonly prescribed to treat urinary tract infections indicate that new orally bioavailable agents are needed. Ceftibuten (CTB) is an orally-administered third-generation cephalosporin and is in early clinical development being combined with an oral prodrug of avibactam. Avibactam (AVI) is a non-β-lactam, β-lactamase inhibitor that can restore activity against organisms that possess Class A, C, and some Class D enzymes. The objective of this study was to provide a regional analysis of the *in vitro* activity of ceftibuten combined with avibactam (CTB-AVI) and comparators against a recent collection of Enterobacterales from UTIs.

Methods

The 2,906 non-duplicate, clinically isolated Enterobacterales analyzed in this study were collected through the Antimicrobial Testing Leadership and Surveillance (ATLAS) surveillance program during 2022 by 125 medical centers in 45 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. All isolates were from urinary tract infections. Susceptibility testing was done by broth microdilution according to CLSI guidelines [1] and interpreted using EUCAST 2022 breakpoints [2]. Ceftibuten-avibactam was tested with a fixed concentration of 4 mg/L avibactam. As there are no ceftibuten-avibactam breakpoints, the ceftibuten breakpoint of ≤1 mg/L was applied for comparison purposes only.

Results Summary

- The addition of avibactam restored the *in vitro* activity of ceftibuten against global Enterobacterales by 128-fold, with 96.3% of all isolates inhibited at a ceftibuten-avibactam MIC of ≤1 mg/L (Table 1).
- Ceftibuten-avibactam was the most active of the oral compounds tested, with the MIC_{90} value decreasing from 16 mg/L for ceftibuten to 0.12 mg/L for ceftibuten-avibactam (Table 1, Figure 3). The percent susceptible of comparators ranged from 58.4% to 74.1% globally (Table 1, Figure 5).
- Ceftibuten-avibactam activity was consistent across geographic regions (MIC_{90} = 0.12 mg/L), with the exception of Africa/Middle East isolates (MIC_{90} = 1 mg/L), where there was decreased *in vitro* activity to all the antimicrobials tested (Table 1, Figure 4).

Conclusions

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

References

1. Clinical and Laboratory Standards Institute (CLSI) 2018. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*. Approved Standards-Eleventh Edition. CLSI Document M07-A11. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
2. Clinical and Laboratory Standards Institute, (CLSI) 2022. *Performance Standards for Antimicrobial Susceptibility Testing*. 32nd Edition. CLSI Supplement M100. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA.

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.

Results

Figure 1. Distribution of isolates by region

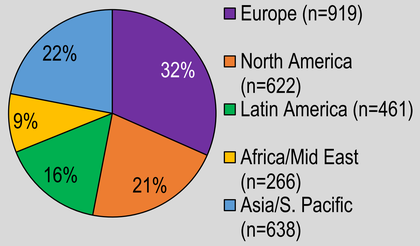


Figure 2. Distribution of isolates by species

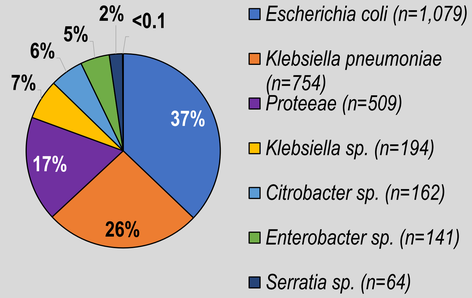


Table 1. *In vitro* activity of ceftibuten-avibactam and comparators against 2,906 Enterobacterales from urinary tract infections in 2022

Region (n)	Antimicrobial	mg/L			%S	%I	%R
		MIC_{50}	MIC_{90}	Range			
Global (2,906)	CTB-AVI (≤1 mg/L)	≤0.06	0.12	≤0.06 – >64	96.3	--	3.7
	CTB	0.25	16	≤0.06 – >64	71.9	--	28.1
	FEP	≤0.12	32	≤0.12 – >32	74.1	5.3	20.6
	CFM	0.5	>64	≤0.12 – >64	63.7	--	36.3
	CPD	1	>16	≤0.12 – >16	58.4	--	41.6
	CAZ	0.25	64	≤0.03 – >64	70.0	5.1	24.9
	LVX	≤0.25	>8	≤0.25 – >8	67.1	4.7	28.1
	MEM	≤0.06	≤0.06	≤0.06 – >16	96.3	0.8	2.9
	SXT	≤1	>32	≤1 – >32	65.0	1.1	33.9
Europe (919)	CTB-AVI (≤1 mg/L)	≤0.06	0.12	≤0.06 – >64	97.2	--	2.8
	CTB	0.25	16	≤0.06 – >64	71.3	--	28.7
	FEP	≤0.12	32	≤0.12 – >32	75.5	4.9	19.6
	CFM	0.5	>64	≤0.12 – >64	62.4	--	37.6
	CPD	1	>16	≤0.12 – >16	56.9	--	43.1
	CAZ	0.25	64	≤0.03 – >64	69.9	5.4	24.7
	LVX	≤0.25	>8	≤0.25 – >8	71.7	4.5	23.8
	MEM	≤0.06	0.12	≤0.06 – >16	95.9	0.5	3.6
	SXT	≤1	>32	≤1 – >32	66.4	0.8	32.9
N. America (622)	CTB-AVI (≤1 mg/L)	≤0.06	0.12	≤0.06 – >64	96.8	--	3.2
	CTB	0.12	8	≤0.06 – >64	80.7	--	19.3
	FEP	≤0.12	4	≤0.12 – >32	86.8	4.3	8.8
	CFM	0.5	>64	≤0.12 – >64	74.0	--	26.0
	CPD	0.5	>16	≤0.12 – >16	69.0	--	31.0
	CAZ	0.25	16	≤0.03 – >64	81.3	3.5	15.1
	LVX	≤0.25	8	≤0.25 – >8	80.7	4.0	15.3
	MEM	≤0.06	≤0.06	≤0.06 – >16	98.7	0.5	0.8
	SXT	≤1	>32	≤1 – >32	81.2	0.6	18.2
Latin America (461)	CTB-AVI (≤1 mg/L)	≤0.06	0.12	≤0.06 – >64	96.5	--	3.5
	CTB	0.25	32	≤0.06 – >64	69.0	--	31.0
	FEP	≤0.12	>32	≤0.12 – >32	70.1	4.3	25.6
	CFM	0.5	>64	≤0.12 – >64	63.8	--	36.2
	CPD	1	>16	≤0.12 – >16	58.4	--	41.6
	CAZ	0.25	64	≤0.03 – >64	67.0	4.6	28.4
	LVX	≤0.25	>8	≤0.25 – >8	60.3	4.3	35.4
	MEM	≤0.06	0.12	≤0.06 – >16	95.0	0.9	4.1
	SXT	≤1	>32	≤1 – >32	55.5	2.0	42.5
Asia/Pacific (638)	CTB-AVI (≤1 mg/L)	≤0.06	0.12	≤0.06 – >64	96.9	--	3.1
	CTB	0.25	32	≤0.06 – >64	73.7	--	26.3
	FEP	≤0.12	32	≤0.12 – >32	71.8	7.4	20.8
	CFM	0.5	>64	≤0.12 – >64	62.2	--	37.8
	CPD	1	>16	≤0.12 – >16	56.6	--	43.4
	CAZ	0.25	32	≤0.03 – >64	68.8	6.7	24.5
	LVX	0.5	>8	≤0.25 – >8	61.3	5.0	33.7
	MEM	≤0.06	0.12	≤0.06 – >16	97.5	0.6	1.9
	SXT	≤1	>32	≤1 – >32	62.5	1.1	36.4
Mid East/Africa (266)	CTB-AVI (≤1 mg/L)	≤0.06	1	≤0.06 – >64	90.2	--	9.8
	CTB	0.5	>64	≤0.06 – >64	54.1	--	45.9
	FEP	1	>32	≤0.12 – >32	51.9	6.0	42.1
	CFM	4	>64	≤0.12 – >64	47.4	--	52.6
	CPD	8	>16	≤0.12 – >16	42.9	--	57.1
	CAZ	1	>64	≤0.03 – >64	51.9	4.9	43.2
	LVX	1	>8	≤0.25 – >8	45.1	7.5	47.4
	MEM	≤0.06	0.5	≤0.06 – >16	91.7	2.7	5.6
	SXT	32	>32	≤1 – >32	44.4	1.9	53.8

%S/I/R, percent susceptible/intermediate/resistant based on EUCAST 2022 v12.0 (ceftibuten-avibactam breakpoint of ≤1 mg/L was applied for comparison purposes only); CTB-AVI, ceftibuten-avibactam; CTB, ceftibuten; FEP, cefepime; CFM, cefixime; CPD, cefpodoxime; CAZ, ceftazidime; LVX, levofloxacin; MEM, meropenem; SXT, trimethoprim-sulfamethoxazole

Figure 3. MIC distribution of ceftibuten and ceftibuten-avibactam for 2,906 Enterobacterales from urinary tract infections collected globally in 2022

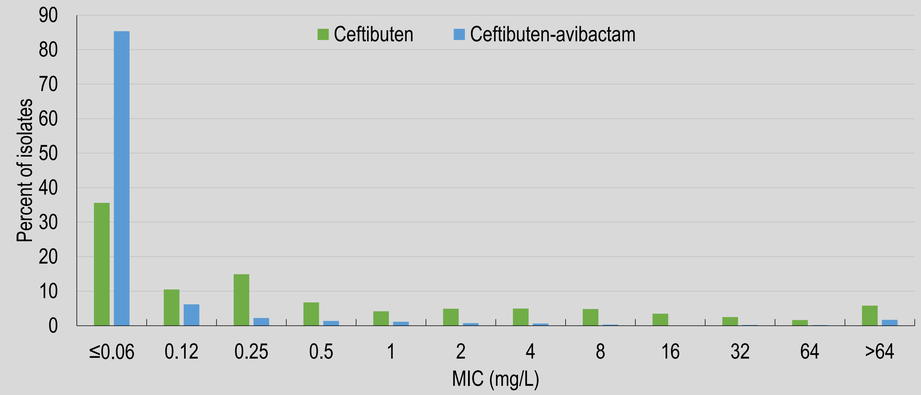


Figure 4. MIC distribution of ceftibuten and ceftibuten-avibactam for 2,906 Enterobacterales from urinary tract infections collected in 2022 by region

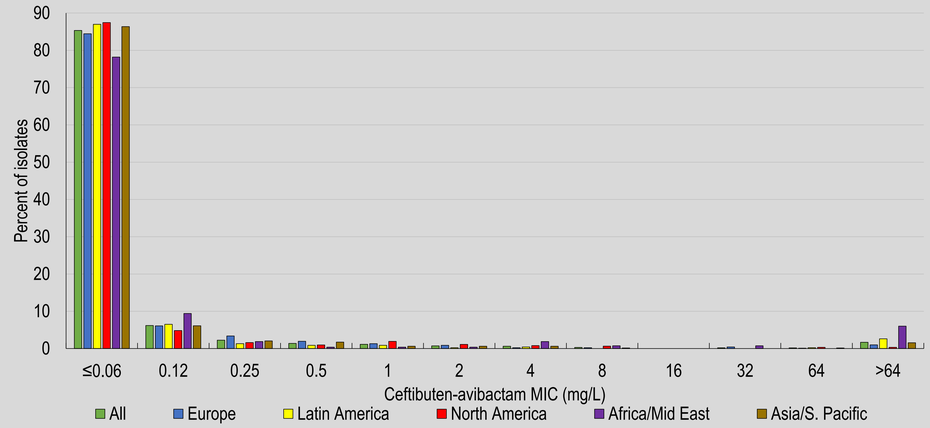
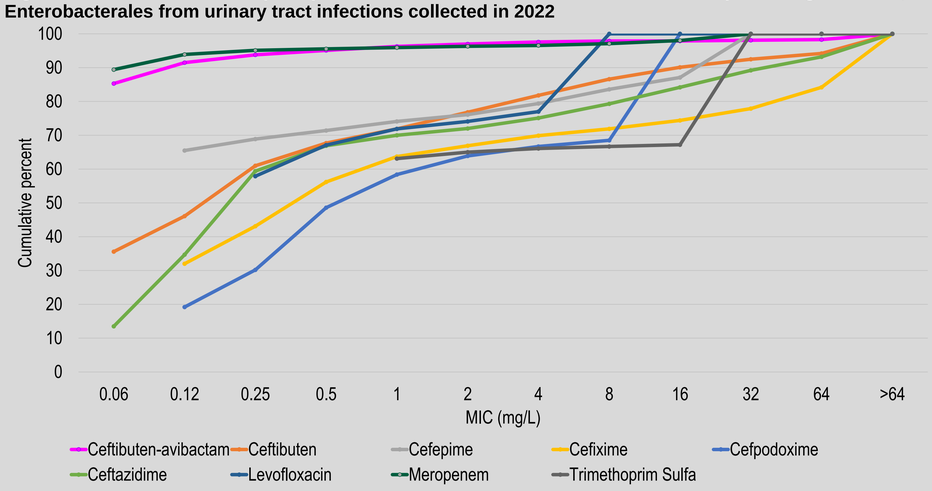


Figure 5. Cumulative MIC frequency distribution of ceftibuten-avibactam and comparator agents for 2,906 Enterobacterales from urinary tract infections collected in 2022



Presented at ECCMID 2023 on April 15 - 18, 2023 in Copenhagen, Denmark