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Antimicrobial Activity of Ceftibuten-Avibactam against Clinical Isolates of *Enterobacterales* Producing Clinically Relevant Beta-Lactamases

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Introduction

- Ceftibuten is an oral cephalosporin active against *Enterobacterales*, which was approved by the US Food and Drug Administration in 1995.
- Avibactam is a potent inhibitor of extended-spectrum β-lactamases (ESBLs), serine carbapenemases, and AmpCs that can be administered orally as a prodrug.
- We evaluated the *in vitro* activity of ceftibuten-avibactam against molecularly characterized *Enterobacterales* that produced the most common β-lactamases and assessed the avibactam concentration to be combined with ceftibuten for susceptibility testing.

Methods

- The organism collection included 71 *Enterobacterales* isolates producing ESBLs (28; CTX-M, SHV, and TEM), KPCs (8), MBLs (7; NDM, VIM, and IMP), AmpC derepressed (3), plasmid AmpC (3), OXA-48-like (2), and SME (2) as well as isolates with porin alterations (5) and wild-type organisms (13).
- Ceftibuten was tested alone and with avibactam at fixed concentrations of 2 mg/L, 4 mg/L, or 8 mg/L and a fixed ratio of 2:1 and 1:1.
- Resistance mechanisms were evaluated by whole genome sequencing, as previously described.
- Organisms were predefined for the susceptibility to ceftibuten-avibactam category based on produced β-lactamases and the known spectrum of avibactam β-lactamase inhibition.
- Ceftibuten-avibactam MIC distributions for the various combinations were grouped as follows (Figures 1 to 5):
  - Organisms that expressed β-lactamases that were completely inhibited by avibactam (labeled as “Inhibited”)
  - Organisms that contained at least one β-lactamase that was not inhibited by avibactam and/or expressed other resistance mechanisms to ceftibuten that were not affected by avibactam (labeled as “not inhibited”)
  - Wild type organisms

Results

- The fixed avibactam concentration of 4 mg/L best separated ceftibuten-avibactam-susceptible from ceftibuten-avibactam-resistant isolates (Figure 2).
- Ceftibuten-avibactam (fixed 4 mg/L) was very active against *Enterobacterales* producing ESBLs ($MIC_{50/90}$, 0.03/0.12 mg/L), including CTX-M-15 ($MIC_{50/90}$, 0.03/0.12 mg/L), KPC (MIC_{50}, 0.06 mg/L), derepressed AmpC (MIC range, 1–2 mg/L), plasmidic AmpC (MIC range, 0.12–0.5 mg/L), SME (MIC range, 0.06–0.12 mg/L), and OXA-48-like (MIC range, 0.5–4 mg/L; Table 1 and Figure 6).
- Ceftibuten-avibactam exhibited limited activity against MBL producers (MIC_{50}, >32 mg/L) and isolates with porin alterations (MIC_{50}, 32 mg/L; Table 1 and Figure 6).
- Ceftibuten was highly active against SME producers (MIC, 0.12-0.25 mg/L) and showed some activity against KPC producers (MIC_{50}, 4 mg/L; MIC range, 2–16 mg/L) and ESBL producers ($MIC_{50/90}$, 4/64 mg/L), but it exhibited very limited activity against MBL, AmpC derepressed, plasmidic AmpC, and OXA-48-like producers (MIC_{50} values of 128 to >128 mg/L; Figure 7).

Conclusions

- Ceftibuten-avibactam showed potent *in vitro* activity against *Enterobacterales* producing most clinically relevant β-lactamases, including ESBLs, KPCs, OXA-48-like, and AmpC, for which limited oral treatment options are available.
- The results of this study demonstrated that the best method for determining ceftibuten-avibactam MIC values was to use doubling dilutions of ceftibuten in the presence of a fixed concentration of 4 mg/L of avibactam.
- These *in vitro* results support further clinical development of oral ceftibuten-avibactam.

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Figure 1. MIC distributions of ceftibuten combined with avibactam at fixed concentration of 2 mg/L

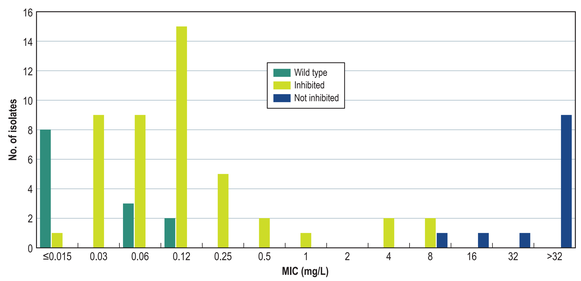

Figure 2. MIC distributions of ceftibuten combined with avibactam at fixed concentration of 4 mg/L

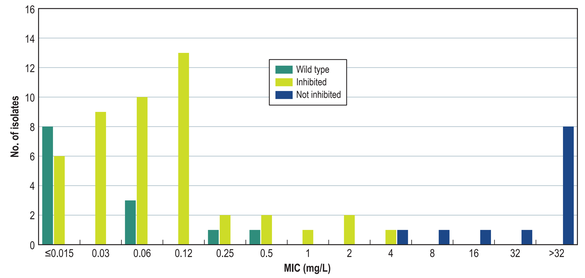

Figure 3. MIC distributions of ceftibuten combined with avibactam at fixed concentration of 8 mg/L

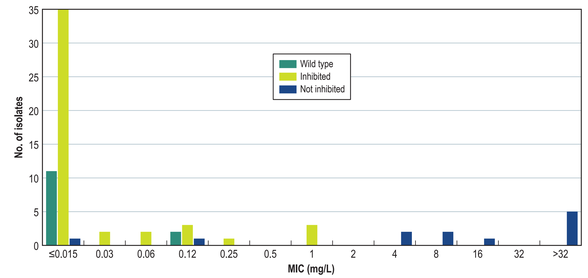

Figure 4. MIC distributions of ceftibuten combined with avibactam at a 1:1 ratio

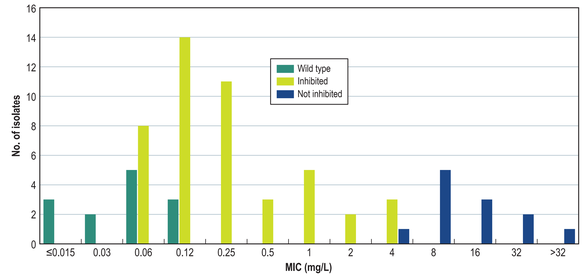

Figure 5. MIC distributions of ceftibuten combined with avibactam at a 2:1 ratio

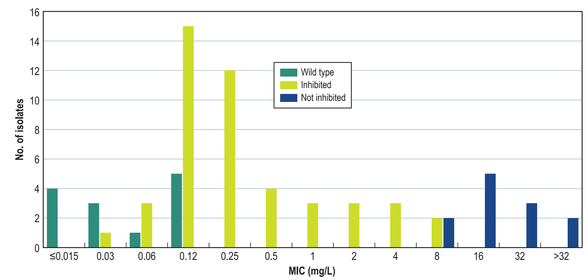

Figure 6. Antimicrobial activity of ceftibuten-avibactam (fixed 4 mg/L) against well-characterized organisms stratified by resistance mechanism

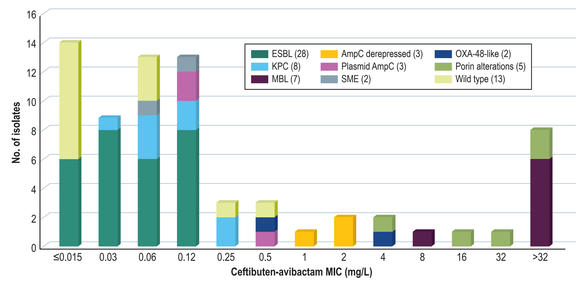

Figure 7. Antimicrobial activity of ceftibuten against well-characterized organisms stratified by resistance mechanism

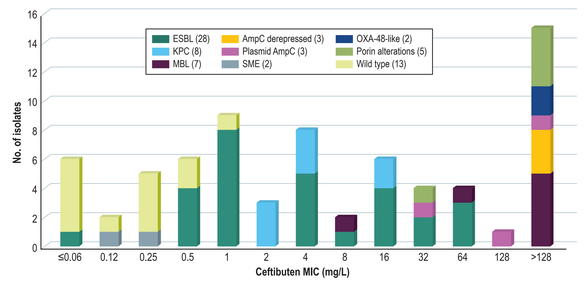

Table 1. Antimicrobial activity of ceftibuten-avibactam (fixed 4 mg/L) against well-characterized organisms stratified by resistance mechanism

Resistance mechanism (no. of isolates)	No. and cumulative % of isolates inhibited at ceftibuten-avibactam (fixed 4 mg/L) MIC (mg/L) of:												
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
ESBL (28)	6 (21.4)	8 (50.0)	6 (71.4)	8 (100.0)									
CTX-M-15 (12)	3 (25.0)	4 (58.3)	3 (83.3)	2 (100.0)									
KPC (8)		1 (12.5)	3 (50.0)	2 (75.0)	2 (100.0)								
MBL (7)										1 (14.3)			6 (100.0)
AmpC derepressed (3)							1 (33.3)	2 (100.0)					
Plasmid AmpC (3)				2 (66.7)	0 (66.7)	1 (100.0)							
SME (2)			1 (50.0)	1 (100.0)									
OXA-48-like (2)						1 (50.0)	0 (50.0)	0 (50.0)	1 (100.0)				
Porin alterations (5)									1 (20.0)	0 (20.0)	1 (40.0)	1 (60.0)	2 (100.0)
Wild type (13)	8 (61.5)	0 (61.5)	3 (84.6)	0 (84.6)	1 (92.3)	1 (100.0)							