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

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Introduction

• Ceftibuten is an oral cephalosporin active against Enterobacteriales, which was approved by the US Food and Drug Administration in 1995.
• Avibactam is a potent inhibitor of extended-spectrum β-lactamases (ESBLs), some carbapenemases, and AmpC that can be administered orally or as a prophylaxis.
• We evaluated in vitro activity of ceftibuten-avibactam against molecularly characterized Enterobacteriales 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 73 Enterobacteriales isolates producing ESBLs (28): CTX-M, SHV, and TEM, AmpC (9): MBC (7): NDM, VIM, and IMP, AmpC demethylase (3); plasmid AmpC (3); OXA-48-like (2); and SME (2) as well as isolates with porin alterations (5) and xanthine organisms (3).
• Ceftibuten was tested alone and with avibactam at fixed concentrations of 2 mg/L, 4 mg/L, and 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 preclassified for the susceptibility to ceftibuten-avibactam category based on produced β-lactamases and the known spectrum of avibactam. 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 expressed other resistance mechanisms to ceftibuten that were not affected by avibactam labeled as “not inhibited”.
  - Wild type organisms.

Results

• The fixed avibactam (4 mg/L) level separated ceftibuten-avibactam-susceptible from ceftibuten-avibactam-resistant isolates (Figure 2).
• Ceftibuten-avibactam (fixed 4 mg/L) was very active against Enterobacteriales producing ESBLs (MIC50/90, 0.03/0.12 mg/L), including CTX-M-15 (MIC50/90, 0.03/0.12 mg/L) and 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, 0.06–0.12 mg/L; Table 1 and Figure 6).
• Ceftibuten-avibactam exhibited limited activity against MBL producers (MICav, >32 mg/L) against well-characterized organisms stratified by resistance mechanism.

Conclusions

• Ceftibuten-avibactam showed potent in vitro activity against Enterobacteriales producing most clinically relevant β-lactamases, including ESBLs, AmpC, 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 MIC values was to use doubling dilutions of ceftibuten in the presence of a fixed concentration of 4 mg/L of avibactam.

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