B-lactamase Characterization of Enterobacteriaceae Baseline Pathogens from Two Phase III Trials of Ceftazidime-Avibactam

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Abstract

Background: Ceftazidime-avibactam (CAZ-AVI) is a novel β-lactam-β-lactam inhibitor combination for the treatment of Gram-negative bacterial infections. This study characterized the β-lactamase content of Enterobacteriaceae from patients with complicated intra-abdominal infections (cIAI) in Phase II trials of CAZ-AVI (NCT01483080; NCT01505209).

Methods: Susceptibility testing of clinical Enterobacteriaceae isolates was centrally performed based on CLSI (M100-S25). MIC criteria were pre-established for selecting Enterobacteriaceae for screening of extended-spectrum β-lactamases (ESBLs) and/or carbapenemases genes. Selected isolates underwent microarray-based assay, complemented by PCR/sequencing. Relative β-lactamase expression levels were determined.

Results: 1516 ESBL-producing Enterobacteriaceae were screened for a total of 15 different β-lactamase-encoding genes (ESBLs/CES/BES/CIM/OXA/NDM/IMP/KPC/CMY/SVH/SAT/EXT/IMI/AmpC). Overall CTX-M, OXA-1/30 and AmpC were the most prevalent enzymes, representing 87.7% (71/81) and 52.1% (42/81) respectively. CTX-M enzymes (73.3%; 11/15) also prevailed among carbapenemase-producing Enterobacteriaceae. Screening for CRE clinical trial isolates often carried a 5-fold greater difference of MIC (MIC susceptible > MIC resistant). Among screen-positive Enterobacteriaceae, AmpC, OXA-48 and CMY enzymes showed plasmid-encoded expression, with AmpC, CMY and OXA-48 genes being most frequently identified (46.9%, 25.6%, 24.7% respectively).

Conclusions: The β-lactamase content of Enterobacteriaceae from patients with cIAI in Phase II trials of CAZ-AVI indicates the need for combination therapy to cover β-lactamase-producing Enterobacteriaceae, and underscores the importance of performing susceptibility testing by clinical laboratories.

Materials and Methods

Patients and clinical isolates

Isolates were recovered from patients enrolled in two Phase E trials randomized, multi-center, double-blind, parallel-group, comparative trials (two Phase II trials) for the treatment of complicated intra-abdominal infections (IAI) based on combination with metronidazole and compared urinary tract infections (UTIs), including pyelonephritis, in patients with limited or no treatment options. Clinical specimens were collected from 710 patients (five Phase II trials); each Phase II trial had several Phase III trials that followed. Several Phase III trials have now completed. The present study characterizes the β-lactam content of Enterobacteriaceae from patients with cIAI enrolled in two Phase III trials of ceftazidime-avibactam.

Conclusions

This study clearly shows the spread of CTX-M and CTX-M + OXA-130-carrying plasmids among clinical isolates of Enterobacteriaceae. This enzyme profile has been established among ESBL-producing Enterobacteriaceae (5%), and even more recently, even as the last decade, but it has also become common in other Enterobacteriaceae species, such as K. pneumoniae. Furthermore, NDM variants predominated among CRE clinical isolates.

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