ECCMID 2024 | Poster #P1824

β-lactam resistance mechanisms in baseline Enterobacterales from the REVISIT and ASSEMBLE aztreonam-avibactam Phase 3 clinical trials

RE Mendes[1], C Hubler[1], JH Kimbrough[1], LN Woosley[1], FF Arhin[2], M Castanheira[1]

[1] Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA; [2] Pfizer, Inc., Kirkland, Quebec, Canada

Introduction

- The REVISIT (NCT03329092) and ASSEMBLE (NCT03580044) phase 3 clinical trial studies evaluated the efficacy, safety, and tolerability of the candidate aztreonam-avibactam for treating serious infections caused by Gram-negative bacteria, including metallo-β-lactamase (MBL)-producing multidrug-resistant pathogens.
- Results from these phase 3 clinical trial studies provided the basis for the submission to the European Medicines Agency in seeking approval for the treatment of complicated intra-abdominal and urinary tract infections, hospital-acquired pneumonia and infections caused by certain types of bacteria (aerobic Gram-negative) where treatment options are limited.
- This study characterised the β-lactam resistance mechanisms in Enterobacterales recovered during baseline visits of patients enrolled in the phase 3 clinical trials for aztreonam-avibactam.

Materials and Methods

Patients and bacterial isolates

- A total of 439 randomised patients generated 92 baseline isolates (1 strain/patient) that met the MIC criteria for molecular characterization of β-lactam resistance mechanisms.

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following Clinical and Laboratory Standards Institute (CLSI) M07 and M100 guidelines.

Screening of β-lactam resistance determinants

- *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* with ceftriaxone, ceftazidime, or aztreonam MIC of ≥2 mg/L, and any Enterobacterales displaying MIC ≥2 mg/L for imipenem (excluded for *P. mirabilis*, *P. penneri*, and indole-positive Proteeae) or meropenem were subjected to genome sequencing and screening of β-lactamase genes.
- Relative transcription levels of chromosomal *ampC* (cAmpC) were assessed by RT-PCR, and isolates with elevated aztreonam-avibactam MIC (i.e. 8 mg/L) had the penicillin-binding protein (PBP) evaluated. Isolates from China were evaluated by *in silico* DNA sequence analysis only.

Results

- A total of 85 (19.4%) randomised patients enrolled in the REVISIT and ASSEMBLE trials generated 92 Enterobacterales, which met the MIC criteria for screening of β-lactam resistance determinants.
- Six patients had multiple isolates. *E. coli* (40.2%) and *K. pneumoniae* (44.6%) were similarly represented, followed by smaller number (1.1–4.4%) of isolates from 7 groups/species (Figure 1).
- Most Enterobacterales (43.5%; 40/92) carried CTX-M alone.
  - A small group of isolates carried or bla_{CTX-M} in combination with SHV-12 (1), pAmpC (CMY-4 or DHA-1) or overexpression of cAmpC (2) (Table 1).
  - Also, pAmpC (2) or overexpression of cAmpC (9) alone were observed in 12.0% (11/92) of isolates.
- Carbapenemase genes were detected in 38.0% (35/92) of isolates, most commonly NDM alone (18.5%; 17/92), followed by OXA-48-like alone (14.1%; 13/92) (Figure 2 and Table 1).
  - Three (3.3%) *K. pneumoniae* carried both NDM and OXA-48.
- Aztreonam-avibactam ($MIC_{50/90}$, 0.12/1 mg/L) inhibited all isolates at MIC of ≤2 mg/L, except for 4 *E. coli* with MIC of 8 mg/L (Figure 3).
  - These *E. coli* strains had a 4 amino acid insertion in PBP3, and 1 isolate each had NDM-5/CTX-M-15, NDM-5/CMY-42, NDM-5/CMY-145, or CMY-42/DHA-1 enzymatic profiles (data not shown).

Figure 1. Distribution of bacterial species recovered from patients enrolled in the REVISIT and ASSEMBLE trials that met the MIC criteria for screening of β-lactam resistance determinants

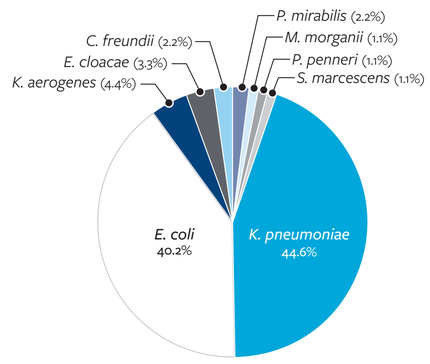
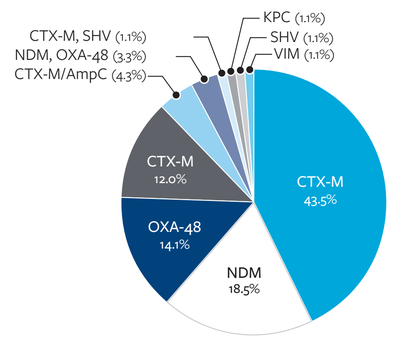


Figure 2. Distribution summary of β-lactamase genes detected among bacterial isolates included in this study



AmpC is represented by isolates overexpressing the choromosomal *ampC* gene or the presence of plasmid AmpC; SHV only includes those with extended-spectrum β-lactamase genes.

Figure 3. Cumulative MIC distribution of aztreonam (ATM), aztreonam-avibactam (ATM-AVI) and meropenem (MER) against Enterobacterales included in this study

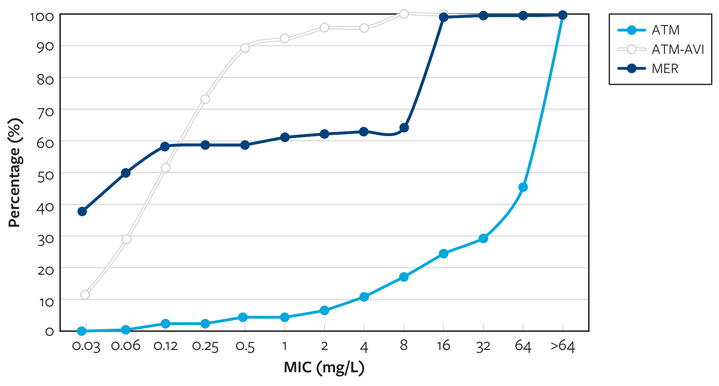


Table 1. Distribution of β-lactamase genes detected among bacterial isolates included in this study

Species/β-lactamase	Number
C. freundii	2
cAmpC	1
CTX-M-15, cAmpC	1
E. cloacae	3
cAmpC	1
CTX-M-9	1
NDM-1, CTX-M-15, cAmpC	1
E. coli	37
cAmpC	2
CMY-2	1
CMY-42, DHA-1	1
CTX-M-1	1
CTX-M-14	3
CTX-M-15	11
CTX-M-15, CMY-4	1
CTX-M-27	4
CTX-M-55	6
CTX-M-65	1
NDM-5, CMY-145	1
NDM-5, CMY-2	1
NDM-5, CMY-42	1
NDM-5, CTX-M-15	2
NDM-5, CTX-M-15, CMY-2	1
K. aerogenes	4
cAmpC	3
NDM-5	1
K. pneumoniae	41
CTX-M-14, DHA-1	1
CTX-M-15	9
CTX-M-15, SHV-12	1
CTX-M-55	2
KPC-2, CTX-M-65, SHV-12	1
NDM-1, CTX-M-15	7
NDM-1, CTX-M-15, CTX-M-3	1
NDM-1, CTX-M-15, SHV-12	1
NDM-1, OXA-48, CTX-M-15	1
NDM-1, OXA-48, CTX-M-15, SHV-12	1
NDM-5, OXA-48, CTX-M-14, CTX-M-15	1
OXA-232	1
OXA-232, CTX-M-15	2
OXA-48, CTX-M-15	6
OXA-48, CTX-M-55	4
SHV-2A	1
VIM-1, VEB-1	1
M. morganii	1
cAmpC	1
P. mirabilis	2
CTX-M-2	1
CTX-M-55	1
P. penneri	1
cAmpC	1
S. marcescens	1
CTX-M-15, cAmpC	1
Total	**92**

Conclusions

- CTX-M prevailed among baseline Enterobacterales meeting the MIC criteria for screening of β-lactam resistance mechanisms.
  - However, a diverse array of potent β-lactamase genes were detected, including carbapenemases.
- Aztreonam-avibactam demonstrated low MIC results (i.e. ≤2 mg/L) against 95.7% of isolates selected for screening of β-lactam resistance, except against 4 *E. coli* (MIC, 8 mg/L) with altered PBP3.
- Further analysis will evaluate the clinical efficacy of aztreonam-avibactam in patients infected with this select group of pathogens.

Disclosures

This study at JMI Laboratories/Element Iowa City was supported by Pfizer.

REVISIT (NCT03329092) and ASSEMBLE (NCT03580044) phase 3 clinical trials were funded by Pfizer. The development of aztreonam-avibactam was supported Pfizer and the U.S. Department of Health and Human Services; Administration for Strategic Preparedness and Response; Biomedical Advanced Research and Development Authority (BARDA) (HHSO100201500029C), and through the EU's Innovative Medicines Initiative—a partnership between the EU and the European pharmaceutical industry, under a project called COMBACTE-CARE (Combating Bacterial Resistance in Europe—Carbapenem Resistance).

References

Clinical and Laboratory Standards Institute (2018). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved Standard: Eleventh Edition. *M07Ed11*. Wayne, PA, USA.

Clinical and Laboratory Standards Institute (2023). Performance standards for antimicrobial susceptibility testing: 33rd Informational Supplement. *M100Ed33*. Wayne, PA, USA.

Mendes RE, Jones RN, Woosley LN, Cattoir V, Castanheira M (2019). Application of next-generation sequencing for characterization of surveillance and clinical trial isolates: Analysis of the distribution of β-lactamase resistance genes and lineage background in the United States. *Open Forum Infect Dis* 6: S69-S78.

Contact

Rodrigo E. Mendes, Ph.D.
Element Iowa City
(JMI Laboratories)
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: rodrigo.mendes@element.com

SCAN ME

To obtain a PDF of this poster:

Scan the QR code or visit https://www.jmilabs.com/data/posters/ECCMID2024_17-PZR-06_P1_ATM-AVI_Molecular_Trial.pdf

Charges may apply. No personal information is stored.