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Characterization of *Enterobacter cloacae* and *Citrobacter freundii* species complex isolates with decreased susceptibility to cephalosporins from United States hospitals and activity of aztreonam-avibactam and comparator agents (2019–2023)

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CONCLUSIONS

ATM-AVI was highly active against CFC and ECLC isolates with decreased susceptibility to 3rd and/or 4th generation cephalosporins and retained complete activity against carbapenem-resistant isolates, including MBL producers.

The activities of CAZ-AVI, MEM-VAB, and cefiderocol were compromised against carbapenem-resistant isolates due to the high frequency of NDM producers.

Our results indicated that ATM-AVI may represent a valuable option to treat infections caused by multidrug-resistant CFC and ECLC.

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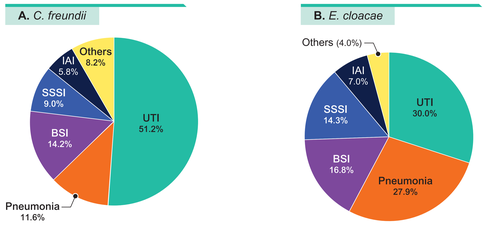
INTRODUCTION

- Aztreonam-avibactam (ATM-AVI) is under development in the United States (US) to treat infections caused by Gram-negative bacteria, including metallo-β-lactamase (MBL) producers.
- Phase 3 clinical trials REVISIT (NCT03329092) and ASSEMBLE (NCT03580044) evaluated the efficacy, safety, and tolerability of ATM-AVI in treating serious bacterial infections due to Gram-negative bacteria, including MBL-producing multidrug-resistant pathogens for which there are limited or no treatment options.
- Moreover, ATM-AVI has been recently approved by the European Medicine Agency (Emblaveo®) to treat adults who have complicated intra-abdominal infections (IAI), hospital-acquired pneumonia (including ventilator-associated pneumonia), and complicated urinary tract infections (UTI; including pyelonephritis), as well as infections caused by aerobic Gram-negative organisms in patients who have limited treatment options.
- We evaluated the *in vitro* activities of ATM-AVI and comparators against cephalosporin non-susceptible (S) *E. cloacae* (ECLC) and *C. freundii* species complex (CFC) from patients hospitalized in US medical centers.

METHODS

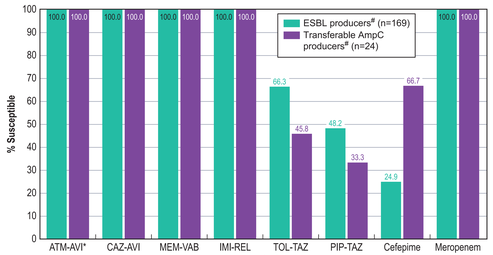
- A total of 43,235 Enterobacterales (1/patient) were collected via the INFORM Surveillance Program from 80 US medical centers in 2019–2023.
- Among those, 5,106 (11.8%) were ECLC (n=3,732) or CFC (n=1,374).
- Susceptibility testing was performed by CLSI broth microdilution.
- We evaluated the antimicrobial susceptibility and β-lactamase production of ECLC and CFC isolates that were resistant to ceftazidime (MIC ≥16 mg/L) or non-S to cefepime (MIC ≥2 mg/L).
- The collection includes 1,065 ECLC and 379 CFC.
- ATM-AVI was tested with avibactam at fixed 4 mg/L and a pharmacodynamic/pharmacokinetic susceptible breakpoint of ≤8 mg/L was applied for comparison.
- Comparators included ceftazidime-avibactam (CAZ-AVI), meropenem-vaborbactam (MEM-VAB), and cefiderocol, among others.
- Cefiderocol was only tested against carbapenem-resistant Enterobacterales (CRE) isolates in iron-depleted media.
- All isolates (n=1,444) were characterized by whole genome sequencing.

Figure 1. Distribution of isolates by infection sources



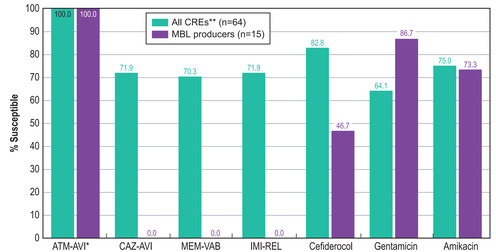
Abbreviations: UTI, urinary tract infection; BSI, bloodstream infection; SSSI, skin and skin structure infection; IAI, intra-abdominal infection.

Figure 2. Susceptibility of ESBL and transferable AmpC producers



Abbreviations: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; TOL-TAZ, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam.
* % inhibited at ≤8 mg/L
# Excluding MBL co-producers

Figure 3. Susceptibility of carbapenem-resistant isolates (CRE) and MBL producers



Abbreviations: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; TOL-TAZ, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam.
* % inhibited at ≤8 mg/L
** Includes MBL producers

RESULTS

- Isolates were mainly from UTI, pneumonia, and bloodstream infection (BSI; Figure 1).
- ATM-AVI inhibited 99.9% of isolates at ≤8 mg/L and showed complete activity (100.0% inhibited at ≤8 mg/L) against ESBL producers and CRE isolates, including MBL (all NDM) producers (Table 1 and Figures 2 and 3).
- CAZ-AVI and MEM-VAB were highly active against ESBL producers but showed limited activity against CRE (70.3–71.9%S), especially MBL producers (0.0%S; Figures 2 and 3).
- Cefiderocol was active against 82.8% of CREs but only 46.7% of MBL (all NDM) producers (Figure 3).
- A carbapenemase was identified in 55 of 64 (85.9%) CRE isolates, including KPC type (40 isolates; 62.5% of CREs) and NDM-1 (15; 23.4% of CREs; Figure 4).
- The most common ESBLs were CTX-M type, SHV type, and OXA type (Figure 4).
- Two or more ESBLs were identified in 70 isolates (34.0% of ESBL producers), mainly OXA-1/30 plus a CTX-M (65 isolates; 31.6% of ESBL producers; Figure 4).
- A transferable AmpC was identified in 27 isolates; 3 of them co-produced a carbapenemase (Figures 3 and 4).

Table 1. Susceptibility of *C. freundii* and *E. cloacae* isolates with decreased susceptibility to 3rd and/or 4th generation cephalosporins

Antimicrobial	All (1,444)		*C. freundii* (379)		*E. cloacae* (1,065)	
	$MIC_{50/90}$	%S[a]	$MIC_{50/90}$	%S[a]	$MIC_{50/90}$	%S[a]
Aztreonam-avibactam	0.25/1	99.9[b]	0.25/0.5	100.0[b]	0.5/1	99.9[b]
Ceftazidime-avibactam	0.5/1	98.2	0.5/1	99.5	0.5/1	97.7
Meropenem-vaborbactam	0.03/0.06	98.5	0.03/0.03	99.7	0.03/0.06	98.2
Ceftolozane-tazobactam	8/>16	20.7	16/>16	17.4	8/>16	21.9
Piperacillin-tazobactam	128/>128	9.2	128/>128	9.2	64/>128	9.1
Aztreonam	>16/>16	2.6	>16/>16	2.9	>16/>16	2.5
Ceftriaxone	>8/>8	0.3	>8/>8	0.3	>8/>8	0.4
Ceftazidime	>32/>32	1.3	>32/>32	1.8	>32/>32	1.1
Cefepime	2/32	65.0	1/8	75.2	2/32	61.3
Meropenem	0.06/0.25	94.7	0.06/0.12	96.3	0.06/0.25	94.2
Levofloxacin	0.06/2	81.0	0.12/2	76.3	0.06/2	82.7
Gentamicin	0.25/4	89.3	0.5/8	88.9	0.25/4	89.5
Amikacin	1/2	96.1	2/4	93.9	1/2	96.8

[a] % susceptible per CLSI criteria.
[b] % inhibited at ≤8 mg/L.

Figure 4. β-lactamases detected among *C. freundii* and *E. cloacae* isolates