Searching for the Optimal Treatment Regimen for Metallo-ß-Lactamase-Producing *Enterobacteriaceae*: Aztreonam + Ceftazidime-Avibactam vs. Aztreonam + Meropenem-Vaborbactam

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Introduction

- Metallo-ß-lactamases (MBL) are Ambler class B enzymes capable of hydrolyzing nearly all ß-lactams, including carbapenems
- Treatment options for infections caused by MBL-producing organisms are limited to agents plagued by toxicities and suboptimal pharmacokinetics
- Aztreonam remains stable to MBL-mediated hydrolysis
  - MBL-producers typically co-harbor additional serine ß-lactamases capable of hydrolyzing aztreonam
- Combining aztreonam with a ß-lactamase inhibitor may produce a therapeutically efficacious combination
- Existing data suggests the combination of aztreonam and ceftazidime/avibactam may be effective against MBL-producing *Enterobacteriaceae*
- The combination of aztreonam with another newly approved novel BLI, vaborbactam, against MBL-producing *Enterobacteriaceae* has not been studied

Objectives

- The primary objective of this study was to evaluate interactions between aztreonam + ceftazidime/avibactam vs. aztreonam + meropenem/ vaborbactam against clinical isolates of *Escherichia coli* co-producing NDM and serine ß-lactamases
- The secondary objective of this study was to evaluate interactions between dual ß-lactam combination (aztreonam + ceftazidime or meropenem) with or without a ß-lactamase inhibitor (avibactam or vaborbactam)

Methods

- Minimum inhibitory concentrations (MICs) were determined in triplicate and reported as the modal MIC
- Time kill experiments performed in triplicate with each agent alone and in combination using the highest concentration of the drug alone with no activity
  - Starting inoculum: 10^6 CFU/mL
  - Time points: 0, 2, 4, 6, and 24 hours
- ß-lactams were tested in time kill experiments using multiplicatives of the MIC or fC_{max} when the MIC (or its multiplicative) exceeded fC_{max}
- fC_{max} values were chosen to simulate a 2 g dose of each respective ß-lactam
  - Aztreonam: 112 µg/mL
  - Ceftazidime: 80 µg/mL
  - Meropenem: 45 µg/mL
- ß-lactamase inhibitors were tested at static concentrations in all experiments
  - Avibactam: 4 µg/mL
  - Vaborbactam: 8 µg/mL
- Definitions:
  - Bactericidal: ≥3 $\log_{10}$ decrease in CFU/mL at 24 hours compared to the starting inoculum
  - Synergy: ≥2 $\log_{10}$ decrease in CFU/mL between the combination and most active single agent alone
  - Indifference: 1-2 $\log_{10}$ decrease in CFU/mL between the combination and most active single agent alone
  - Antagonism: ≥2 $\log_{10}$ increase in CFU/mL compared to the most active agent alone

Results

Table 1. Broth microdilution susceptibilities (µg/mL)

Isolate (genotypic profile)	ATM	ATM + AVI	ATM + VBR	CAZ	CAZ/AVI	MER	MER/VBR
EC-1 (NDM, CMY-2/FOX, CTX-M-1, TEM)	>256	16	128	>256	>256	64	128
EC-2 (NDM-5, OXA-1)	0.25	0.25	0.25	>256	>256	256	>256

Abbreviations: AVI: avibactam; ATM: aztreonam; CAZ: ceftazidime; MER: meropenem; VBR: vaborbactam

Table 2. Change in $\log_{10}$ CFU/mL at 24 hours

Isolate	ATM	ATM + AVI	ATM + VBR	CAZ	CAZ/AVI	MER	MER/VBR	ATM + CAZ	ATM + MER	ATM + CAZ/AVI	ATM + MER/VBR
EC-1	4.65	-6.04	-4.22	4.05	3.51	1.99	4.04	5.52	3.26	-3.92	-5.04
EC-2	2.00	-2.37	5.20	4.94	2.60	5.18	4.01	5.09	6.25	1.93	5.32

Figure 1. Activities of (A) single agents and commercially available dual-combinations, (B) aztreonam-based dual combinations, and (C) aztreonam-based triple combinations against EC-1.

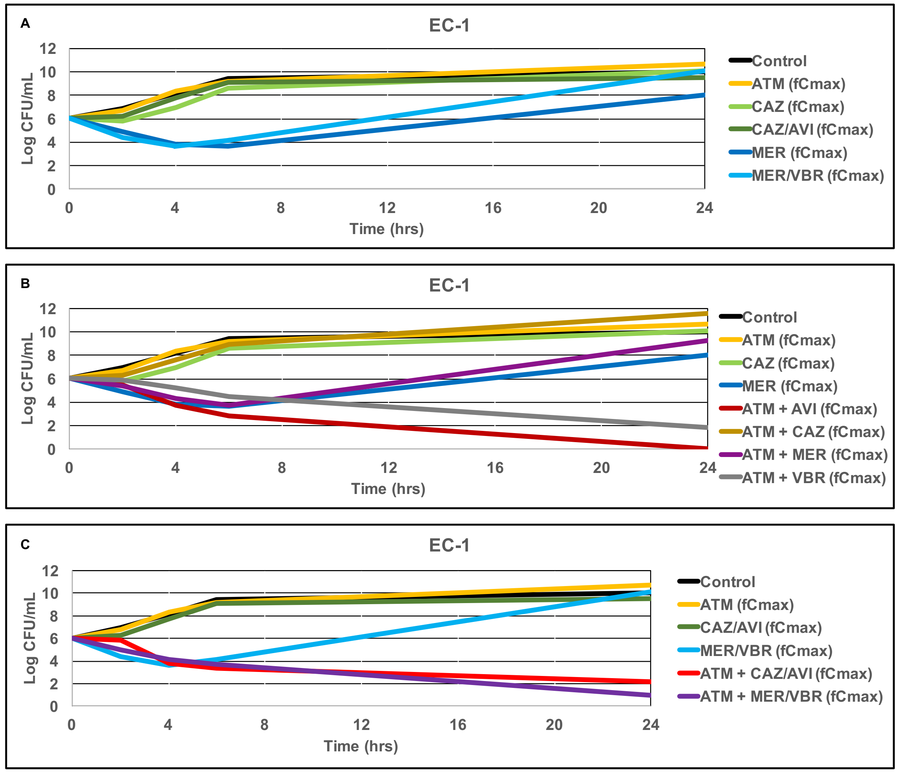
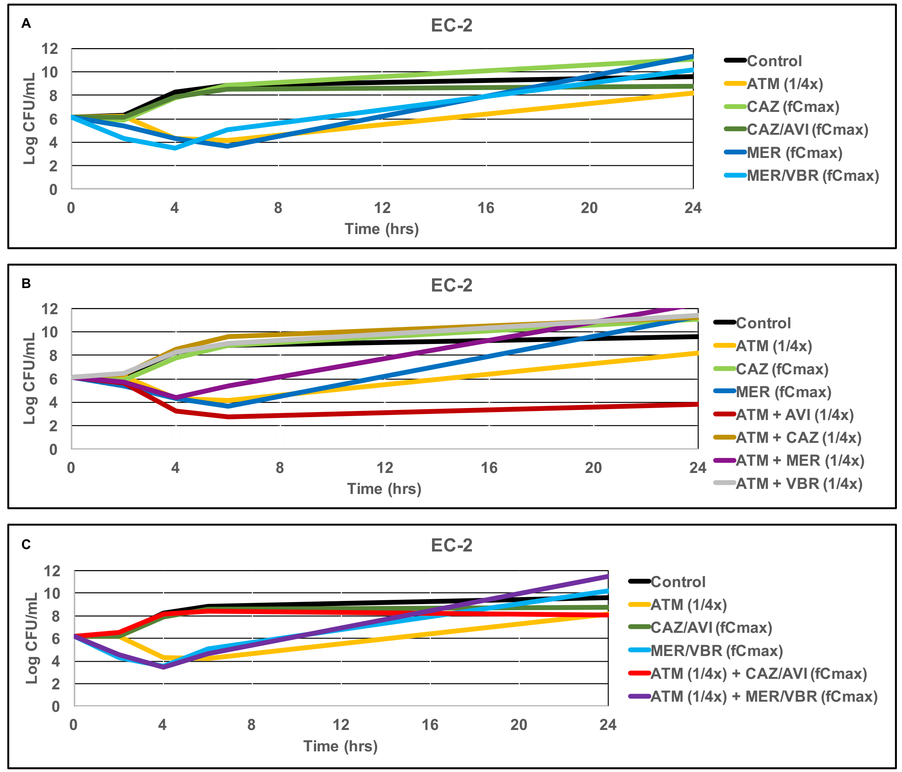


Figure 2. Activities of (A) single agents and commercially available dual-combinations, (B) aztreonam-based dual combinations, and (C) aztreonam-based triple combinations against EC-2.



Conclusions

- No single agent demonstrated bactericidal activity against either isolate
- Synergy was observed for both aztreonam + ceftazidime/avibactam and aztreonam + meropenem/vaborbactam against the aztreonam-resistant isolate but not for the aztreonam-susceptible isolate
- Synergy appeared to be driven by the aztreonam and beta-lactamase inhibitor combination
- Aztreonam-based combination therapy may be a potential therapeutic option for MBL-producing infections and future studies including more isolates and combinations are warranted

Disclosures

- The authors declare no actual or potential disclosures of interest

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