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Activity of Novel β-Lactam/β-Lactamase Inhibitor Combinations Against AmpC-Producing Species Collected in United States Hospitals

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Introduction

- Inducible AmpC resistance is caused by the derepression of the chromosomal AmpC in the presence of a β-lactam and limits the use of these agents to treat infections caused by Enterobacterales species known to produce these enzymes (AmpC producers).
- Novel β-lactam/β-lactamase inhibitors (BL/BLIs), such as meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-relebactam, display activity against isolates producing serine-carbapenemases, extended-spectrum β-lactamases, and AmpC enzymes.
- In this study, we evaluated the activity of novel BL/BLIs against a collection of AmpC producers collected in US hospitals during 2021.

Materials and Methods

- A total of 1,252 organisms of Enterobacterales species known to overexpress AmpC enzymes were consecutively collected in 31 US hospitals during 2021.
  - AmpC-producing species included in this study are displayed in Figure 1.
  - Isolate frequency by infection source is displayed in Figure 2.
  - Only 1 isolate per patient episode was included.
- Isolates were susceptibility tested against meropenem-vaborbactam, ceftazidime-avibactam, and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) document.
  - Vaborbactam was tested at a fixed concentration of 8 mg/L.
  - Avibactam and relebactam were tested at a fixed concentration of 4 mg/L.
- Quality control (QC) was performed according to the CLSI M100 (2022) criteria.
  - All QC MIC results were within acceptable ranges.
- Categorical interpretations for all comparator agents were those criteria found in the CLSI M100 (2022), or the US Food and Drug Administration (FDA) website.

Results

- Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.06 mg/L; Figure 3) and amikacin were the most active agents tested against isolates belonging to AmpC producing species, inhibiting 99.8% (Figure 4).
- Ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5 mg/L) inhibited 99.5% and imipenem-relebactam ($MIC_{50/90}$, 0.12/1 mg/L) inhibited 95.9% of all AmpC producers (Figures 3 and 4).
- Cefepime and meropenem, the recommended agents to treat infections caused by AmpC-producing species, were active against 92.0% and 97.6% of these isolates, respectively (Figure 4).
- Piperacillin-tazobactam and ceftolozane-tazobactam ($MIC_{50/90}$, 0.5/8 mg/L; Figure 3) displayed activity against 76.4% and 83.6% of the AmpC producers, respectively (Figure 4).
- Tigecycline was active against 96.8% of the isolates; only 53.8% of the isolates had a colistin MIC of ≤2 mg/L (Figure 4).
- A total of 39 (3.1%) AmpC producers were nonsusceptible to imipenem and/or meropenem (Figure 4) (carbapenem non-susceptible Enterobacterales [CNSE]).
  - Meropenem-vaborbactam ($MIC_{50/90}$, 0.25/2 mg/L; data not shown) was active against 92.3% of the CNSE AmpC producers and displayed higher potency than other agents (Figure 3).
  - Imipenem-relebactam ($MIC_{50/90}$, 0.25/2 mg/L) and ceftazidime-avibactam ($MIC_{50/90}$, 1/>32 mg/L) were active against 89.7% of the CNSE AmpC producers.
- Against cefepime-resistant AmpC producers (*n*=45; 3.6%), meropenem-vaborbactam, imipenem-relebactam, and ceftazidime-avibactam exhibited 93.3%, 88.9%, and 86.7% activity when current CLSI breakpoints were applied.

Figure 1. AmpC-producing bacterial species collected from US hospitals in 2021

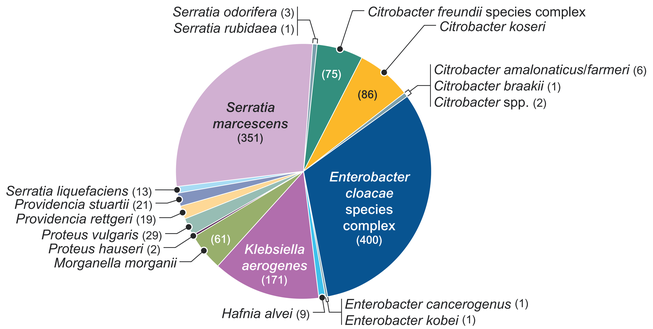


Figure 2. AmpC-producing isolates by infection site

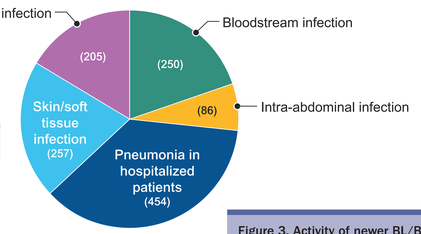


Figure 3. Activity of newer BL/BLI combinations against AmpC producers

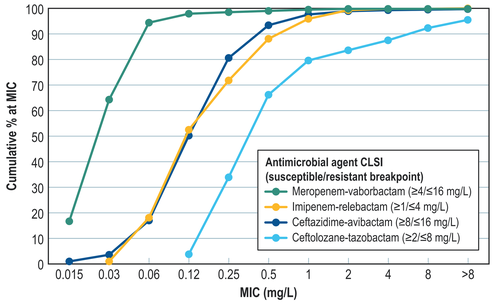
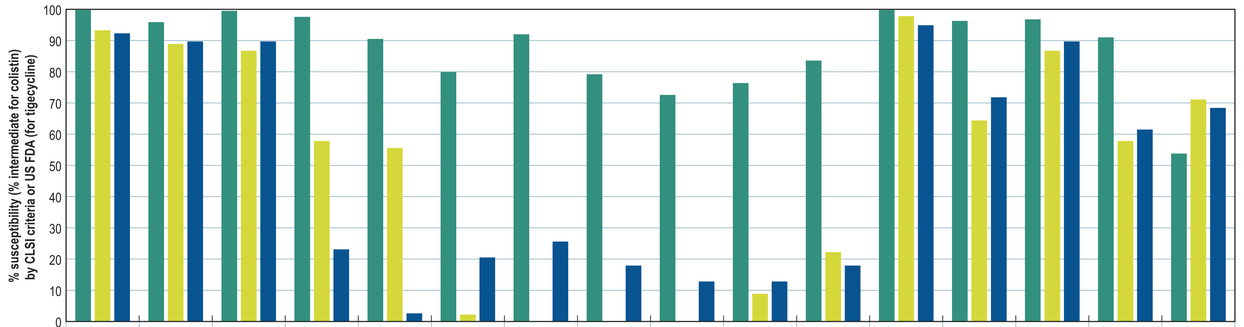


Figure 4. Activity of BL/BLI and other agents against AmpC-producing isolates



	Meropenem-vaborbactam	Imipenem-relebactam	Ceftazidime-avibactam	Meropenem	Imipenem	Aztreonam	Cefepime	Ceftazidime	Ceftriaxone	Piperacillin-tazobactam	Ceftolozane-tazobactam	Amikacin	Gentamicin	Tigecycline	Levofloxacin	Colistin
All AmpC-producers (*n*=1,252)	99.8	95.9	99.5	97.6	90.5	79.9	92.0	79.2	72.6	76.4	83.6	99.8	96.3	96.8	91.0	53.8
Cefepime-resistant (*n*=45)	93.3	88.9	86.7	57.8	55.6	2.2	0.0	0.0	0.0	8.9	22.2	97.8	64.4	86.7	57.8	71.1
CNSE (*n*=39)	92.3	89.7	89.7	23.1	2.6	20.5	25.6	17.9	12.8	12.8	17.9	94.9	71.8	89.7	61.5	68.4

Conclusions

- Infections caused by AmpC-producing species often are challenging to treat.
- Understanding the activity of new BL/BLIs is critical, as the use of cefepime and meropenem can lead to resistance.
- Meropenem-vaborbactam, imipenem-relebactam, and ceftazidime-avibactam displayed good activity against AmpC producers.
  - When analyzing carbapenem-nonsusceptible or cefepime-resistant isolates, meropenem-vaborbactam was slightly more active and also more potent than other BL/BLI combinations.

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