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Comparative Activity of Meropenem-Vaborbactam and Ceftazidime-Avibactam Against Multidrug-Resistant *Enterobacter cloacae* from Hospitals in Europe and United States

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Introduction

- Among *Enterobacter* species, *E. cloacae* is the most common cause of human infections.
- *E. cloacae* isolates are resistant to many β-lactam agents due to the constitutive expression of chromosomal AmpC.
  - Additionally, resistance against beta-lactams and other antimicrobial classes can occur due to alterations in gene regulatory pathways.
- Therapeutic options for the treatment of *E. cloacae* include cefepime and meropenem.
- Resistance to cefepime and meropenem in *E. cloacae* can occur due to combinations of resistance mechanisms, including overexpression of β-lactamases, alterations in the outer membrane protein, or decreased expression and upregulation of efflux systems.
  - Resistance to these agents limits the available treatment choices for these isolates.
- We evaluated the activity of meropenem-vaborbactam, ceftazidime-avibactam, and comparator agents against 235 multidrug resistant (MDR) *E. cloacae* isolates collected in Europe and the US during 2017–2019.

Materials and Methods

- A total of 2,459 *E. cloacae* clinical isolates were collected in 40 European and 33 US hospitals during 2017, 2018, and 2019.
- Isolates were collected from bloodstream, intra-abdominal, skin/soft tissue, urinary tract infections, or patients hospitalized with pneumonia.
- 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 M07 (2018) and M100 (2021) documents.
  - Vaborbactam was tested at a fixed concentration of 8 mg/L.
  - Avibactam was tested at fixed 4 mg/L.
- Quality control (QC) was performed according to the CLSI M100 (2021) criteria.
  - All QC MIC results were within acceptable ranges.
- Categorical interpretations for all comparator agents were those criteria found in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (2021), the CLSI M100 (2021), or the US Food and Drug Administration (FDA) website.
- Multidrug-resistant (MDR) isolates were identified as nonsusceptible to 3 or more antimicrobial classes using the following antimicrobial class representative agents and CLSI interpretive criteria for *Enterobacterales*: ceftriaxone (≥2 mg/L), meropenem (≥2 mg/L), piperacillin-tazobactam (≥32/4 mg/L), levofloxacin (≥4 mg/L), gentamicin (≥8 mg/L), tigecycline (≥4 mg/L), and colistin (≥4 mg/L).

Results

- An MDR phenotype was observed among 9.6% of the *E. cloacae* isolates.
  - MDR rates in Europe (12.0%; 155/1,295) were considerably higher than in the US (6.9%; 80/1,164).
- Meropenem-vaborbactam inhibited 94.5% and 97.4% of the MDR *E. cloacae* isolates applying CLSI and EUCAST breakpoints, respectively (Figures 1A and 2A).
- Ceftazidime-avibactam was the second most active beta-lactam agent/combination against these isolates and inhibited 93.6% of the MDR *E. cloacae* isolates (Figure 2A).
- Meropenem alone inhibited 77.9%/85.5% of the isolates (CLSI/EUCAST breakpoints).
- A total of 26.0%/16.2% of the MDR *E. cloacae* isolates were inhibited by cefepime at the current CLSI/EUCAST breakpoints.
- Piperacillin-tazobactam was active against only 13.2%/6.4% of the MDR *E. cloacae* using the CLSI/EUCAST breakpoints.
- Amikacin and tigecycline were the most active non-beta-lactam comparators, inhibiting 91.9% and 80.0% of these isolates using CLSI/US FDA breakpoints.
- 93.1% of the isolates were intermediate to colistin when applying CLSI breakpoints or susceptible using the EUCAST criteria.
- When analyzing the MDR *E. cloacae* isolates nonsusceptible to meropenem and cefepime—the main therapeutic options against *E. cloacae*-caused infections—meropenem-vaborbactam inhibited 73.5% at 4 mg/L (Figures 1B and 2B).
- At the EUCAST breakpoint of 8 mg/L, 87.8% of the isolates were inhibited by meropenem-vaborbactam (Figures 1B and 2B).
- Ceftazidime-avibactam inhibited 73.5% of these isolates using CLSI or EUCAST breakpoints.
- Meropenem was active against 37.5% of the isolates when applying the EUCAST breakpoint criteria.
- Other β-lactam agents had no activity against the MDR *E. cloacae* isolates nonsusceptible to meropenem and cefepime.

Conclusions

- Meropenem-vaborbactam and ceftazidime-avibactam displayed good activity against MDR *E. cloacae* for which treatment options are limited.
- These β-lactam/β-lactamase inhibitor combinations exhibited activity against MDR *E. cloacae* nonsusceptible to meropenem and cefepime.
- *E. cloacae* is the second most common *Enterobacterales* species/species complex displaying MDR and carbapenem-resistance phenotypes, behind only *Klebsiella pneumoniae*.
- Therapeutic options for serious infections caused by MDR *E. cloacae* are needed.

References

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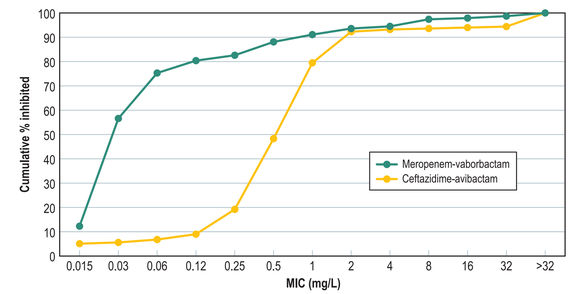
Figure 1. Cumulative percentage of MDR *E. cloacae* isolates inhibited by MIC of meropenem-vaborbactam and ceftazidime-avibactam

A. MDR *E. cloacae* (235 isolates)



B. Meropenem nonsusceptible and cefepime nonsusceptible MDR *E. cloacae* (49 isolates)

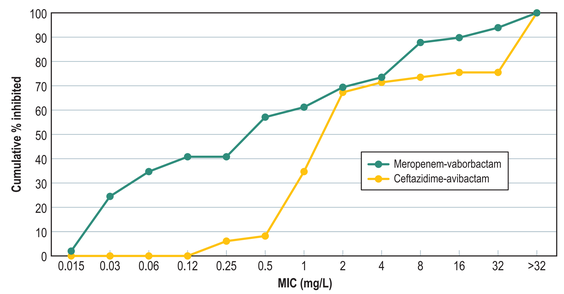
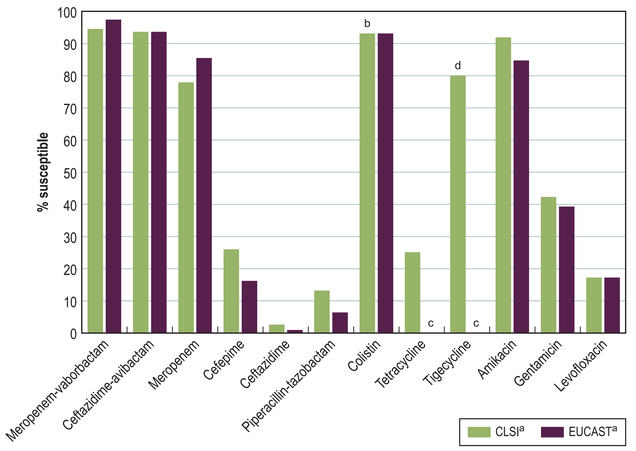


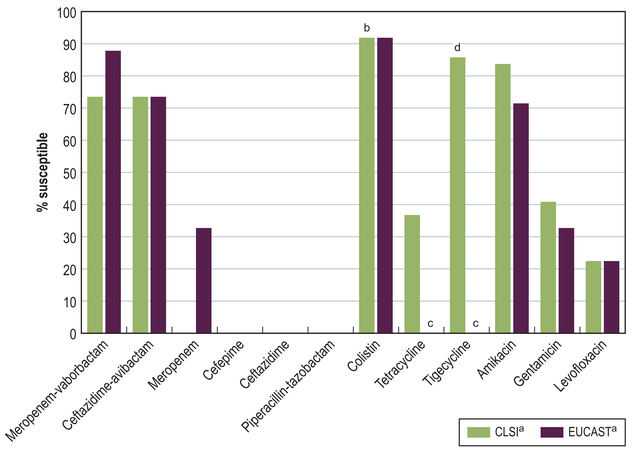
Figure 2. Susceptibility rates for MDR *E. cloacae* isolates

A. MDR *E. cloacae* (235 isolates)



[a] Criteria as published by CLSI (2021) and EUCAST (2021).
[b] Percentage intermediate (no susceptibility breakpoint available).
[c] Breakpoint not available.
[d] US FDA breakpoint applied.

B. Meropenem nonsusceptible and cefepime nonsusceptible MDR *E. cloacae* (49 isolates)



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