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# Activity of aztreonam-avibactam and comparator agents against a global collection of metallo-β-lactamase-producing Enterobacterales

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## Introduction

- Carbapenem-resistant Enterobacterales (CRE) isolates have been highlighted as a threat to human health.
- Therapies to treat CRE isolates that produce serine carbapenemases are in clinical use, but the options for the treatment of metallo-β-lactamases (MBL)-producing Enterobacterales isolates are still limited.
- MBL-producers are often multidrug-resistant due to the presence of resistance genes carried in the same mobile genetic element as the MBL-encoding gene.
- We evaluated the activity of aztreonam-avibactam and comparator agents tested against 490 Enterobacterales isolates producing MBLs collected in a global surveillance program.

## Methods

- A total of 490 MBL-producers were identified during 2019–2022 in hospitals located in Asia-Pacific, Europe, and Latin America.
- Isolates were recovered mainly from patients hospitalized pneumonia (n=146), bacteremia (n=112), and urinary tract infections (n=102).
- Susceptibility testing was performed by reference broth microdilution method in a central laboratory.
  - Avibactam was tested at 4 mg/L.
  - A pharmacokinetic/pharmacodynamic (PK/PD) susceptible breakpoint of ≤8 mg/L was applied for aztreonam-avibactam for comparison purposes.
  - EUCAST or US FDA breakpoints were applied for comparator agents.
- MBL genes were identified by whole genome sequencing analysis using Illumina short reads and a custom developed analysis pipeline.

## Results

- The most common MBL was NDM-1 that was detected alone among 307 isolates or with other MBL genes (3 isolates, Figure 1).
- The genes encoding NDM-5 and VIM-1 were detected among 68 and 53 isolates, respectively.
  - 11 other MBL-encoding gene variants were detected among 59 isolates.
- Aztreonam-avibactam ($MIC_{50/90}$, 0.12/0.5 mg/L) inhibited all 490 isolates at ≤4 mg/L and all isolates would be categorised as susceptible using the tentative PK/PD breakpoint (Table 1).
- Cefepime-taniborbactam ($MIC_{50/90}$, 2/32 mg/L) inhibited 36.7% and 55.5% of the isolates when applying the EUCAST and US FDA breakpoints for cefepime alone for comparison purposes only, respectively.
- Cefiderocol ($MIC_{50/90}$, 2/4 mg/L) inhibited 66.6% and 90.8% of the MBL-producing isolates using the EUCAST and US FDA breakpoints, respectively.
- Tigecycline inhibited 94.1% of the isolates applying the US FDA breakpoint and 76.6% of the isolates were susceptible to colistin using the EUCAST breakpoint.
- Gentamicin was active against 34.1% of these isolates while amikacin inhibited 32.4%.
- All other agents tested inhibited <17% of the MBL-producing isolates.

## Conclusions

- Aztreonam-avibactam was active against this large collection of MBL-producing isolates that had elevated MIC values for many comparator agents, inhibiting all isolates at ≤4 mg/L.
- Other agents recently approved or under evaluation that potentially have MBL activity inhibited 36.7% to 90.8% of the MBL-producing isolates, depending on the breakpoint applied.
- MBL-producing organisms are still considered an unmet medical need and the development of agents active against these isolates is of utmost importance.

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## References

CLSI. M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. Wayne, PA, Clinical and Laboratory Standards Institute, 2018.

EUCAST. 2023. Breakpoint tables for interpretation of MICs and zone diameters. Available at https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.1_Breakpoint_Tables.pdf

Mackow NA, van Duin D. Reviewing novel treatment options for carbapenem-resistant Enterobacterales. Expert Rev Anti Infect Ther. 2024 Jan-Jun;22(1-3):71-85. doi: 10.1080/14787210.2024.2303028. Epub 2024 Feb 12. PMID: 38183224.

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**Figure 1. Distribution of MBL genes among 490 Enterobacterales isolates**

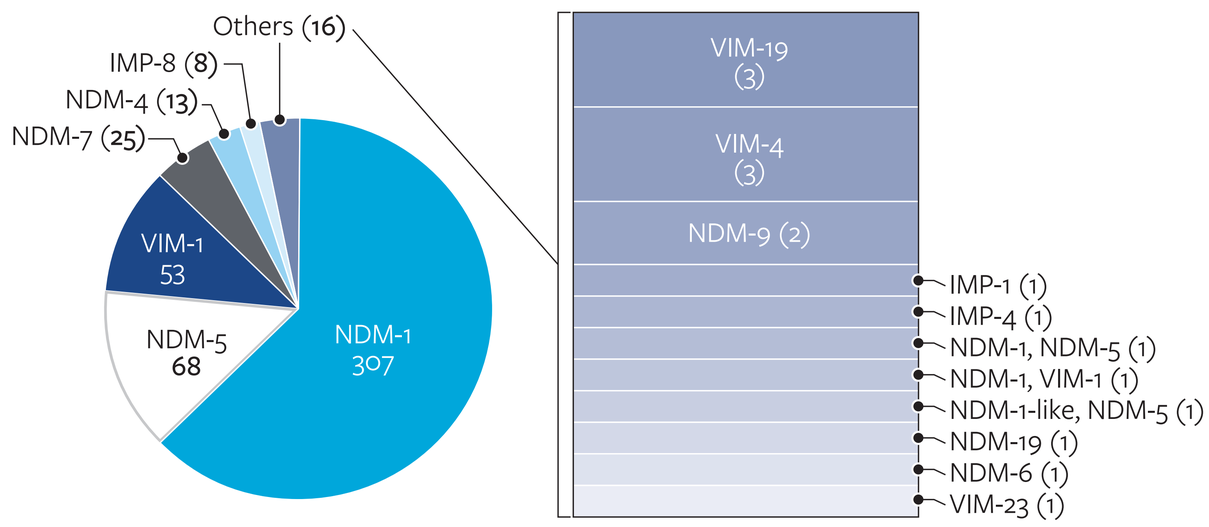


**Table 1. Activity of aztreonam-avibactam and comparator agents against 490 MBL-producing isolates**

| Antimicrobial Agent | % of isolates inhibited at MIC (mg/L) | | | | | | $MIC_{50}$ (mg/L) | $MIC_{90}$ (mg/L) | EUCAST %Susceptible | US FDA %Susceptible |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≤0.5 | 1 | 2 | 4 | 8 | 16 | | | | |
| Aztreonam-avibactam | 93.9 | 96.9 | 99.2 | 100.0 | | | 0.12 | 0.5 | [100][a] | [100][a] |
| Cefepime-taniborbactam | 19.4 | 36.7 | 55.5 | 65.7 | 73.1 | 80.8 | 2 | 32 | [36.7][b] | [55.5][b] |
| Cefiderocol | 12.9 | 32.4 | 66.7 | 90.8 | 96.3 | 99.0 | 2 | 4 | 66.7 | 90.8 |
| Ceftazidime-avibactam | 1.8 | 1.8 | 1.8 | 2.0 | 2.2 | 2.7 | >32 | >32 | 2.2 | 2.2 |
| Aztreonam | 12.7 | 14.7 | 15.5 | 17.1 | 18.4 | 22.2 | >16 | >16 | 14.7 | 17.1 |
| Cefepime | 0.0 | 0.2 | 0.4 | 0.8 | 1.0 | 5.1 | >32 | >32 | 0.2 | 0.4 |
| Piperacillin-tazobactam | | | 0.0 | 0.2 | 1.0 | 1.2 | >128 | >128 | 1.0 | 1.2 |
| Meropenem | 1.0 | 2.4 | 6.3 | 12.4 | 20.8 | 33.3 | 32 | >32 | 6.3 | 2.4 |
| Levofloxacin | 12.7 | 23.9 | 28.0 | 32.5 | 40.5 | 61.6 | 16 | >32 | 12.7 | 12.7 |
| Gentamicin | 22.0 | 31.2 | 34.1 | 37.8 | 42.9 | 47.1 | >16 | >16 | 34.1 | 34.1 |
| Amikacin | 0.2 | 7.1 | 16.9 | 32.4 | 47.1 | 62.4 | 16 | >32 | 47.1 | 32.4 |
| Trimethoprim-sulfamethoxazole | 9.4 | 13.7 | 15.7 | 17.1 | | | >4 | >4 | 15.7 | 15.7 |
| Tigecycline | 60.2 | 81.6 | 94.1 | 99.2 | 99.6 | | 0.5 | 2 | NA | 94.1 |
| Colistin | 75.2 | 75.8 | 76.6 | 77.0 | 79.5 | | 0.25 | >8 | 76.6 | NA |

Susceptibility percentages in brackets are not approved and are based on (a) a pharmacokinetic/pharmacodynamic (PK/PD) susceptible breakpoint of ≤8 mg/L or (b) in the breakpoints for cefepime alone.