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Antimicrobial susceptibility of enterobacterales causing bloodstream infection in United States medical centres: comparison of aztreonam-avibactam with beta-lactams active against carbapenem-resistant enterobacterales

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Abstract

Background Bloodstream infection (BSI) is associated with poor outcomes especially when effective antimicrobial therapy and control of infection source are delayed. As the frequency of Enterobacterales producing metallo-β-lactamases (MBL) and/or OXA-48–like carbapenemases is increasing in some United States (US) medical centres, effective antimicrobials to treat the infections caused by these organisms are urgently needed. Aztreonam-avibactam is under clinical development for treatment of infections caused by Gram-negative bacteria, including MBL producers.

Objectives To evaluate the antimicrobial susceptibility of Enterobacterales causing BSI in US medical centres and compare the activity of aztreonam-avibactam with ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, and other antimicrobials used to treat BSI.

Methods 4,802 Enterobacterales were consecutively collected (1/patient) from 72 US medical centres in 2020–2022 and susceptibility tested by broth microdilution. Aztreonam-avibactam was tested with avibactam at a fixed concentration of 4 mg/L. A pharmacokinetic/pharmacodynamic susceptible breakpoint of ≤ 8 mg/L was applied for aztreonam-avibactam for comparison. Carbapenem-resistant Enterobacterales (CRE) isolates were tested for β-lactamase–encoding genes using Next-generation sequencing.

Results Aztreonam-avibactam was highly active against Enterobacterales; only 2 isolates showed aztreonam-avibactam MICs > 8 mg/L: 1 meropenem-susceptible *E. coli* and 1 *K. aerogenes* (CRE). All carbapenemase producers and 98.0% of CRE were inhibited at an aztreonam-avibactam MIC of ≤ 8 mg/L. CRE susceptibility rates were 81.6% for ceftazidime-avibactam, 65.3% for meropenem-vaborbactam, 61.2% for imipenem-relebactam, and 87.8% for cefiderocol. Aztreonam-avibactam retained activity (MIC, ≤ 8 mg/L) against all (100.0%) meropenem-vaborbactam

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nonsusceptible ($n=17$), 99.5% of imipenem-relebactam nonsusceptible ($n=206$), and 90.0% of ceftazidime-avibactam nonsusceptible ($n=10$) isolates. The most common carbapenemases were KPC-2/3 (57.1% of CREs), OXA-48–like (16.3%), and NDM (14.3%). A carbapenemase gene was not observed in 12.3% of CREs. Ceftazidime-avibactam and meropenem-vaborbactam were active against 100.0% of KPC producers, but ceftazidime-avibactam showed limited activity against MBL producers and meropenem-vaborbactam showed limited activity against OXA-48–like and MBL producers. The most active non–β-lactam comparators against CRE were gentamicin (49.0% susceptible) and amikacin (44.9% susceptible).

Conclusions Aztreonam-avibactam demonstrated potent activity against a large collection of Enterobacterales isolated from patients with BSI in US hospitals, including CRE, MBL producers, and isolates resistant to recently approved β-lactamase inhibitor combinations.

Keywords Bacteraemia, MBL, Ceftazidime-avibactam, Cefiderocol, Enterobacterales, Bloodstream infection

Introduction

Bloodstream infection (BSI) is defined by positive blood cultures in a patient with systemic signs of infection. It can be either secondary to a documented source of infection or a primary infection, i.e., without an identified origin. BSI represents approximately 40% of cases of community-acquired and healthcare-associated sepsis and around 20% of the intensive care unit-acquired cases [1]. BSI is associated with poor outcomes, especially when effective antimicrobial therapy and control of infection source are delayed [2].

A few compounds active against carbapenem-resistant Enterobacterales (CRE) have been recently approved by the United States (US) Food and Drug Administration (FDA), including β-lactamase inhibitor combinations (BLICs) such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, as well as the siderophore cephalosporin cefiderocol [3]. The new BLICs have shown potent in vitro activity and clinical efficacy against KPC-producing Enterobacterales; however, meropenem-vaborbactam and imipenem-relebactam have limited activity against OXA-type carbapenemases and all three BLICs listed above are virtually inactive against MBL producers [4]. Additionally, a decrease in the prevalence of KPC and a proportional increase of CRE carrying OXA-48–like and MBL enzymes has been observed in US medical centres in the last years [5].

Cefiderocol is a novel siderophore cephalosporin with improved stability against β-lactamases and improved transport across the outer membrane of Gram-negative bacteria. Cefiderocol has demonstrated potent in vitro activity and a broad spectrum of activity against Enterobacterales, including CRE; however, there have been increasing reports of resistance recently [6]. Reported mechanisms of resistance to cefiderocol include β-lactamase production, mutations on siderophore receptors, membrane porins and/or PBP3, and overexpression of efflux pumps. It seems that multiple mechanisms are required to confer MIC values above susceptible breakpoint. Moreover, cefiderocol MIC may increase when the organism produces some β-lactamases, mainly some NDM types (NDM-1, -5, -7, and −9), some PER types (PER-1, -6, and −7), KPC variants conferring resistance to ceftazidime-avibactam, and OXA-427 [7]. VIM-1 may also be able to hydrolyse cefiderocol and can increase MIC to borderline levels in *Enterobacter cloacae* species complex [8]. Therefore, treatment options for infections caused by MBL producers are very limited.

Aztreonam-avibactam is under clinical development for treatment of infections caused by Gram-negative bacteria, including MBL producers, and it has recently (April 2024) been granted marketing authorization by the European Medicines Agency (EMA) in the European Union (https://www.ema.europa.eu/en/news/new-antibioticfight-infections-caused-multidrug-resistant-bacteria; accessed on 1 Jul 2024). In this investigation, we evaluated the activities of aztreonam-avibactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, and other antimicrobials against Enterobacterales isolated from patients with BSI.

Materials and methods

Organism collection

A total of 4,802 Enterobacterales were consecutively collected (1/patient) from patients with BSI in 72 US medical centres in 2020–2022 through the International Network for Optimal Resistance Monitoring (INFORM) surveillance program [9]. Medical records were not available to make clinical inferences about the infection source or to differentiate between community-acquired or healthcare-associated BSI. The participating laboratory identified isolates and then the reference monitoring laboratory (Element Iowa City [JMI Laboratories]; North Liberty, Iowa, USA) confirmed bacterial identifications by standard algorithms and/or by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany). CRE was defined as any isolate displaying MIC values of >2 mg/L for imipenem and/or meropenem. Imipenem was not applied

for *Proteus mirabilis* or indole-positive Proteeae due to their intrinsically elevated MIC values. Species distributions are provided in supplemental material.

Susceptibility methods

Isolates were susceptibility tested by the reference broth microdilution method specified by Clinical and Laboratory Standard Institute (CLSI) standards [10]. Validated frozen-form MIC panels were manufactured at Element Iowa City (JMI Laboratories). Aztreonam-avibactam and ceftazidime-avibactam were tested with avibactam at a fixed concentration of 4 mg/L, meropenem-vaborbactam was tested with vaborbactam at fixed concentration of 8 mg/L, and imipenem-relebactam was tested with relebactam at fixed concentration of 4 mg/L [10]. All tests were conducted in a central monitoring laboratory (Element Iowa City [JMI Laboratories]). MIC values were validated by concurrently testing the following quality control strains: *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-2814, *Pseudomonas aeruginosa* ATCC 27853, and *Acinetobacter baumannii-calcoaceticus* species complex NCTC 13304. Both the tentative aztreonam-avibactam pharmacokinetic/pharmacodynamic (PK/PD) susceptible breakpoint of ≤8 mg/L and the recently published EUCAST breakpoint criteria (<4 mg/L for susceptible and >4 mg/L for resistant) were applied for comparison [11] (https://www.ema.europa.eu/en/news/new-antibioticfight-infections-caused-multidrug-resistant-bacteria; accessed on 1 Jul 2024). CLSI / US Food and Drug Administration (FDA) and EUCAST breakpoints were applied for comparators when available [12–14].

Screening for β-lactamases

CRE isolates were tested for β-lactamase–encoding genes using Next-generation sequencing (NGS). Total genomic DNA was prepared using the KingFisher Cell and Tissue DNA kit (ThermoFisher Scientific, Waltham, MA, USA) or the MagMax DNA Multi-Sample Ultra 2.0 extraction kit (ThermoFisher) on a KingFisher Flex Magnetic Particle Processor (ThermoFisher). DNA libraries were constructed using either the Nextera XT library construction protocol and index kit or the Illumina DNA prep (Illumina, San Diego, CA, USA) with sequencing performed on either a MiSeq Sequencer with a MiSeq Reagent Kit v3 (600 cycles) or a NextSeq 1000 Sequencer using NextSeq1000/2000 P2 Reagents (300 cycles). The generated FASTQ files were assembled using SPAdes Assembler and subjected to proprietary software (Element Iowa City [JMI Laboratories]) for screening of β-lactamase genes [15].

Results

Aztreonam-avibactam was highly active against Enterobacterales causing BSI in US medical centres. Overall, aztreonam-avibactam inhibited >99.9% (99.96% or 4,800/4,802) of isolates at ≤8 mg/L and 99.9% (4,796/4,802) at ≤4 mg/L ($MIC_{50/90}$, ≤0.03/0.12 mg/L; Table 1; Fig. 1). Additionally, aztreonam-avibactam demonstrated potent activity against CRE (n=49; $MIC_{50/90}$, 0.25/1 mg/L; 98.0% [48/49] inhibited at ≤8 mg/L; Table 1; Figs. 1 and 2). Ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.25 mg/L; 99.8% susceptible) and meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.06 mg/L; 99.6% susceptible) were also very active against Enterobacterales; however, these compounds exhibited partial activity against CRE with susceptibility rates of 81.6% for ceftazidime-avibactam ($MIC_{50/90}$, 1/>32 mg/L) and 65.3% for meropenem-vaborbactam ($MIC_{50/90}$, 0.25/32 mg/L; Table 1; Fig. 2). Imipenem-relebactam was active against 95.0% of Enterobacterales ($MIC_{50/90}$, 0.12/0.5 mg/L) and 61.2% of CRE ($MIC_{50/90}$, 0.5/8 mg/L; Table 1). Notably, aztreonam-avibactam retained activity (MIC, ≤8 mg/L) against all meropenem-vaborbactam nonsusceptible (n=17), 99.4% of imipenem-relebactam nonsusceptible (n=156), and 90.0% of ceftazidime-avibactam nonsusceptible (n=10) isolates (data not shown).

Cefiderocol was only tested against CRE isolates and inhibited 87.8% of isolates at ≤4 mg/L (CLSI and US FDA susceptible breakpoint) and 81.6% of isolates at ≤2 mg/L (EUCAST susceptible breakpoint; Table 1; Fig. 2).

Other agents active against >90% of Enterobacterales were meropenem ($MIC_{50/90}$, 0.03/0.06 mg/L; 98.9% susceptible), ceftolozane-tazobactam ($MIC_{50/90}$, 0.25/1 mg/L; 94.8% susceptible), and imipenem ($MIC_{50/90}$, ≥0.12/1 mg/L; 92.9% susceptible). The aminoglycosides gentamicin ($MIC_{50/90}$, 0.5/2 mg/L) and amikacin ($MIC_{50/90}$, 2/4 mg/L) were also very active against Enterobacterales with susceptibility rates of 90.2% and 93.4%, respectively; however, these compounds showed limited activity against CRE with susceptibility rates of 49.0% for gentamicin ($MIC_{50/90}$, 4/>16 mg/L) and 44.9% for amikacin ($MIC_{50/90}$, 8/32 mg/L) (Table 1).

It worth noting that all isolates with decreased susceptibility (MIC≥8 mg/L) to aztreonam-avibactam exhibited aztreonam MIC of >16 mg/L. Moreover, only one CRE isolate were susceptible to aztreonam, an IMP producer *P. mirabilis* with aztreonam and aztreonam-avibactam MIC of ≤0.03 mg/L.

A carbapenemase-encoding gene was identified in 87.8% (43/49) of CRE isolates, including 1 isolate that produced 2 carbapenemases, an OXA-181 and an NDM-1. The most common carbapenemase-encoding genes identified among CRE isolates were bla_{KPC} (57.1% of CRE isolates), $bla_{OXA\text{-}48\text{-}like}$ (16.3%; including the isolate with $bla_{OXA\text{-}181}$ plus $bla_{NDM\text{-}1}$), bla_{NDM} (14.3%; including the

Table 1 Antimicrobial susceptibility of organisms from patients with bloodstream infections in US medical centres (2020–2022)

Antimicrobial agent	mg/L		CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	%S	%I	%*R*	%S	%I	%*R*
Enterobacterales (4,802)								
Aztreonam-avibactam	≤ 0.03	0.12	> 99.9 [b]			99.9		0.1
Ceftazidime-avibactam	0.12	0.25	99.8		0.2	99.8		0.2
Meropenem-vaborbactam	0.03	0.06	99.6	< 0.1	0.3	99.7		0.3
Imipenem-relebactam	0.12	0.5	95.0 [c]	3.9	1.1	98.9 [c]		1.1
Ceftolozane-tazobactam	0.25	1	94.8	1.1	4.1	94.8		5.2
Piperacillin-tazobactam	2	16	88.7	3.5	7.8	88.7		11.3
Aztreonam	0.12	> 16	84.3	1.5	14.3	82.6	1.7	15.7
Ceftriaxone	≤ 0.06	> 8	81.4	0.9	17.7	81.4 [d]	0.9	17.7
Ceftazidime	0.25	32	84.7	1.8	13.5	82.1	2.6	15.3
Cefepime	0.06	16	86.9	2.3	10.7	85.9	2.3	11.8
Meropenem	0.03	0.06	98.9	0.2	0.9	99.1 [d]	0.3	0.6
Imipenem	≤ 0.12	1	92.9	5.1	2.0	98.0	1.2	0.8
Levofloxacin	0.06	16	79.5	3.0	17.5	79.5	3.0	17.5
Gentamicin	0.5	2	90.2	0.5	9.3	90.2 [e]		9.8
Amikacin	2	4	93.4	4.9	1.7	98.3 [e]		1.7
CRE (49)								
Aztreonam-avibactam	0.25	1	98.0 [b]			95.9		4.1
Ceftazidime-avibactam	1	> 32	81.6		18.4	81.6		18.4
Meropenem-vaborbactam	0.25	32	65.3	4.1	30.6	69.4		30.6
Imipenem-relebactam	0.5	8	61.2 [c]	6.1	32.7	67.3 [c]		32.7
Ceftolozane-tazobactam	> 16	> 16	2.0	4.1	93.9	2.0		98.0
Piperacillin-tazobactam	> 128	> 128	2.0	4.1	93.9	2.0		98.0
Aztreonam	> 16	> 16	2.0	2.0	95.9	2.0	0.0	98.0
Cefiderocol	1	8	87.8	6.1	6.1	81.6		18.4
Ceftriaxone	> 8	> 8	0.0	0.0	100.0	0.0 [d]	0.0	100.0
Ceftazidime	> 32	> 32	2.0	2.0	95.9	0.0	2.0	98.0
Cefepime	> 32	> 32	2.0	14.3	83.7	2.0	8.2	89.8
Meropenem	16	> 32	2.0	10.2	87.8	12.2 [d]	30.6	57.1
Imipenem	8	> 8	4.1	0.0	95.9	4.1	16.3	79.6
Levofloxacin	8	> 32	16.3	14.3	69.4	16.3	14.3	69.4
Gentamicin	4	> 16	49.0	8.2	42.9	49.0 [e]		51.0
Amikacin	8	32	44.9	12.2	42.9	57.1 [e]		42.9
Carbapenemase producers (43)								
Aztreonam-avibactam	0.25	0.5	100.0 [b]			100.0		0.0
Ceftazidime-avibactam	1	> 32	83.7		16.3	83.7		16.3
Meropenem-vaborbactam	0.12	32	67.4	0.0	32.6	67.4		32.6
Imipenem-relebactam	0.5	8	62.8 [c]	2.3	34.9	65.1 [c]		34.9

Table 1 (continued)

Antimicrobial agent	mg/L		CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R	%S	%I	%R
Ceftolozane-tazobactam	> 16	> 16	2.3	2.3	95.3	2.3		97.7
Piperacillin-tazobactam	> 128	> 128	2.3	4.7	93.0	2.3		97.7
Aztreonam	> 16	> 16	2.3	2.3	95.3	2.3	0.0	97.7
Cefiderocol	1	4	90.7	4.7	4.7	83.7		16.3
Ceftriaxone	> 8	> 8	0.0	0.0	100.0	0.0[d]	0.0	100.0
Ceftazidime	> 32	> 32	2.3	2.3	95.3	0.0	2.3	97.7
Cefepime	> 32	> 32	2.3	14.0	83.7	2.3	7.0	90.7
Meropenem	16	> 32	2.3	9.3	88.4	11.6[d]	27.9	60.5
Imipenem	8	> 8	0.0	0.0	100.0	0.0	11.6	88.4
Levofloxacin	8	> 32	14.0	14.0	72.1	14.0	14.0	72.1
Gentamicin	4	> 16	44.2	9.3	46.5	44.2[e]		55.8
Amikacin	8	32	41.9	11.6	46.5	53.5[e]		46.5

[a] According to CLSI (2023) and EUCAST (2023)

[b] % inhibited at ≤ 8 mg/L

[c] All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species and EUCAST excludes *Morganellaceae*

[d] Indications other than meningitis

[e] For infections originating from the urinary tract

isolate with $bla_{\text{OXA-181}}$ plus $bla_{\text{NDM-1}}$), and bla_{IMP} (2.0%; Fig. 3).

The antimicrobial susceptibility of carbapenemase-producing CRE isolates (n=43), i.e. excluding isolates that were resistant to carbapenems due to other resistant mechanisms not related to the production of carbapenemases, were analysed separately in Table 1. The most active compounds against this group of CREs were aztreonam-avibactam ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0% inhibited at ≤8 mg/L), followed by cefiderocol ($MIC_{50/90}$, 1/4 mg/L; 90.7% susceptible), ceftazidime-avibactam ($MIC_{50/90}$, 1/>32 mg/L; 83.7% susceptible), meropenem-vaborbactam ($MIC_{50/90}$, 0.12/32 mg/L; 67.4% susceptible), and imipenem-relebactam ($MIC_{50/90}$, 0.5/8 mg/L; 62.8% susceptible; Table 1). The highest aztreonam-avibactam MIC value among carbapenemase-producing CRE was only 2 mg/L (Fig. 1).

Ceftazidime-avibactam ($MIC_{50/90}$, 1/4 mg/L) and meropenem-vaborbactam ($MIC_{50/90}$, 0.03/1 mg/L) were active against all KPC producers, whereas imipenem-relebactam ($MIC_{50/90}$, 0.12/0.5 mg/L) and cefiderocol ($MIC_{50/90}$, 1/2 mg/L) inhibited 96.4% (27/28) of isolates at their respective CLSI susceptible breakpoint (Fig. 2). Ceftazidime-avibactam and cefiderocol were also highly active (100.0% susceptible) against OXA-48–like producers (excluding the MBL co-producer isolate), whereas both meropenem-vaborbactam (14.3% susceptible) and imipenem-relebactam (0.0% susceptible) exhibited limited activity against these organisms (Fig. 2). Notably, 16.3% (8/49) of CREs produced an MBL and only aztreonam-avibactam was highly active against MBL producers ($MIC_{50/90}$, ≤0.03/0.5 mg/L; 100.0% inhibited at ≤8 mg/L; highest MIC, 2 mg/L). Cefiderocol was active against 62.5% (5/8) and ceftazidime-avibactam was active against 12.5% (1/8) of MBL producers. Meropenem-vaborbactam and imipenem-relebactam did not inhibit any MBL-producing isolate at their respective susceptible breakpoint (0.0% susceptible; Fig. 2). Against non-carbapenemase producers (n=6; 12.3% of CREs), the activities of these compounds varied from 66.7% for aztreonam-avibactam, ceftazidime-avibactam, and cefiderocol to 50.0% for meropenem-vaborbactam and imipenem-relebactam (Fig. 2).

Two isolates with aztreonam-avibactam MIC values>8 mg/L were further characterised using NGS and gene expression analysis (Table S1). *E. coli* strain 1,171,261 was susceptible to ceftazidime-avibactam (MIC, 2 mg/L), cefiderocol (MIC, 1 mg/L), meropenem (MIC, 0.03 mg/L), and imipenem (MIC, ≤0.12 mg/L). This strain possessed a plasmid-borne AmpC-encoding gene, $bla_{\text{CMY-42}}$, in addition to genes encoding CTX-M-15 and OXA-1. Alterations in the porins OmpF and OmpC were also identified. Importantly, this isolate bore a YRIK-insertion in PBP3 after residue P333, among

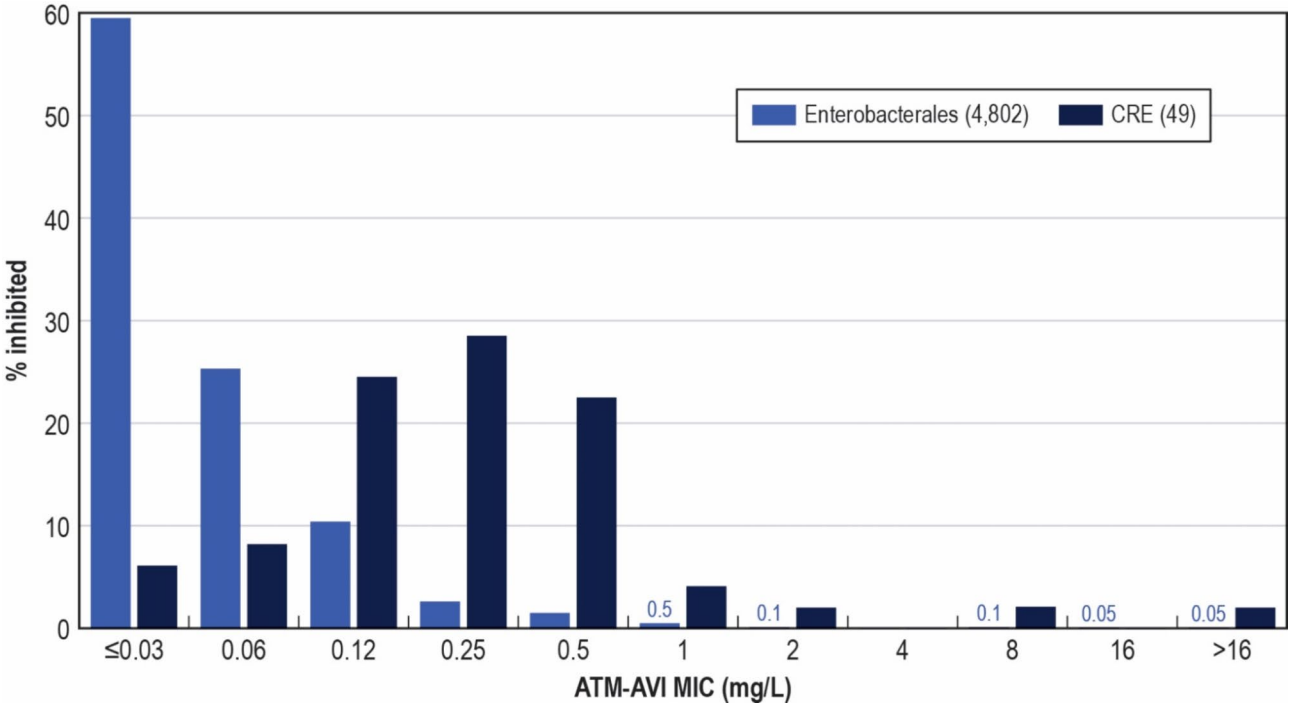

Fig. 1 Aztreonam-avibactam (ATM-AVI) MIC distributions for Enterobacterales and carbapenem-resistant (CRE) isolates from patients with bloodstream infections in United States medical centers (2020–2022)

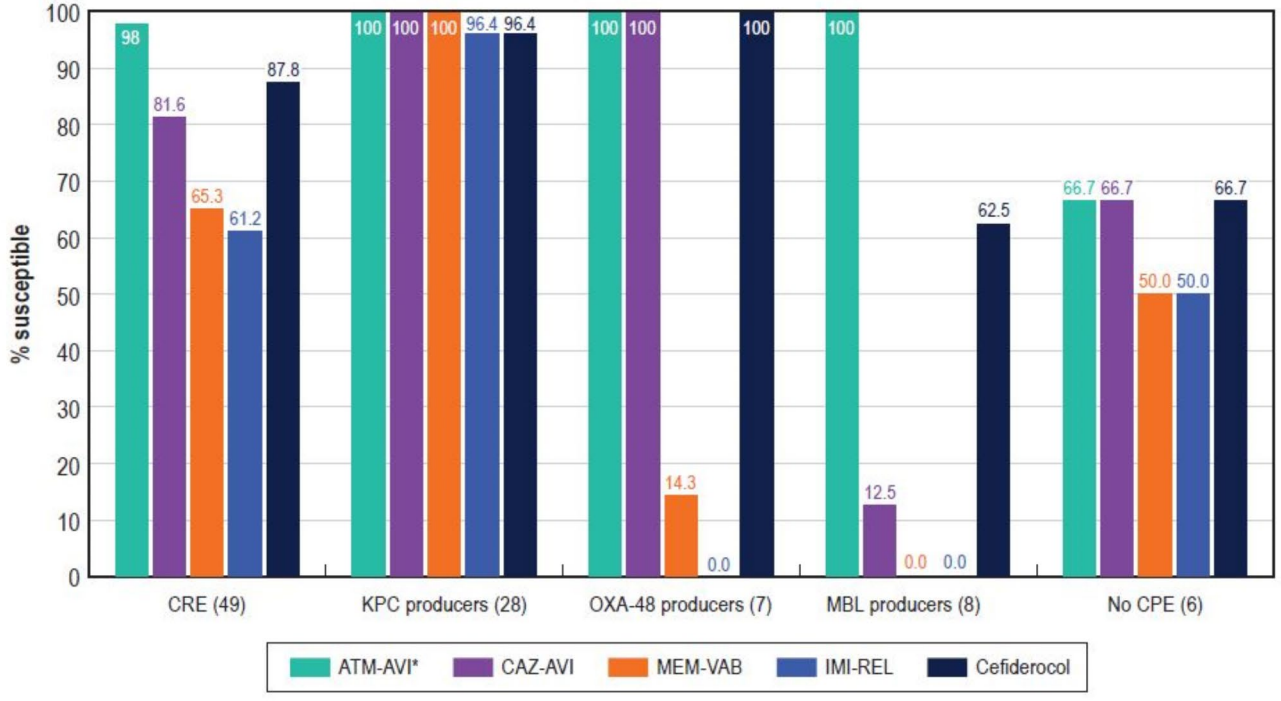

Fig. 2 Antimicrobial activity of aztreonam-avibactam and comparators against carbapenem-resistant Enterobacterales (CRE) isolates stratified by carbapenemase-encoding gene (CPE)

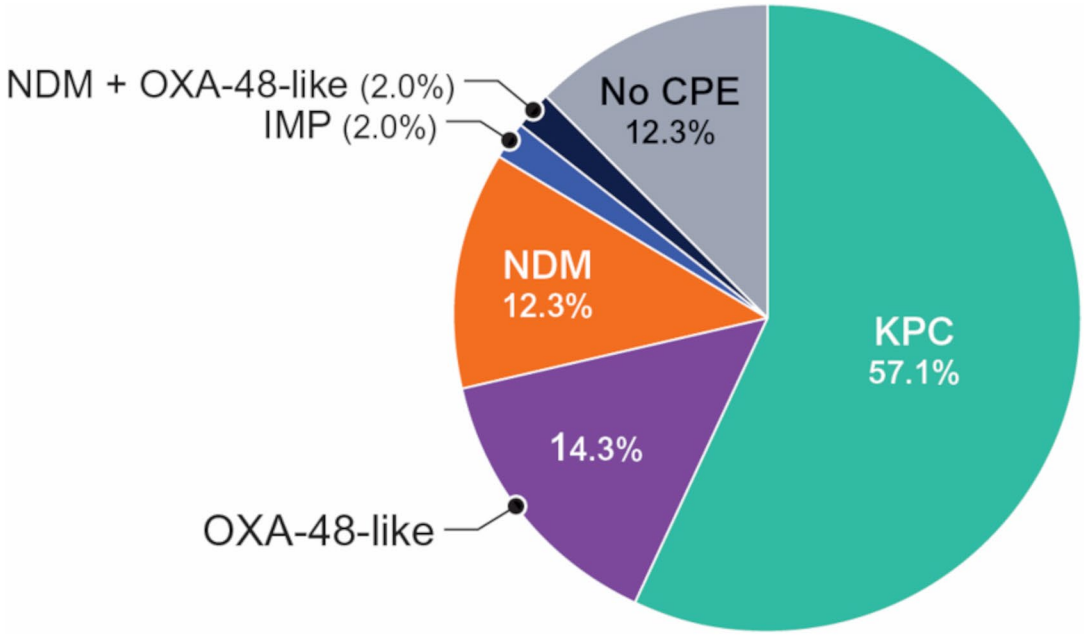

Fig. 3 Frequency of carbapenemase-encoding genes (CPE) among CRE isolates from patients hospitalized with bloodstream infections

other alterations in this protein. The *K. aerogenes* isolate 1,217,700 was resistant to ceftazidime-avibactam (MIC, >32 mg/L), cefiderocol (MIC, >64 mg/L), and imipenem (MIC, 4 mg/L), but susceptible to meropenem (MIC, 2 mg/L), meropenem-vaborbactam (MIC, 2 mg/L), and imipenem-relebactam (MIC, 2 mg/L). NGS identified alterations in *ampC* and a frameshift mutation resulting in the introduction of an early termination codon in OmpC (Table S1). AmpC was >2,000-fold overexpressed in this isolate relative to the susceptible control strain (Table S1).

Discussion

Data on the antimicrobial susceptibility of bacterial isolates causing BSI in US medical centres is very scarce, making it difficult to compare our results with those from other investigators. The National Healthcare Safety Network (NHSN), which is conducted by the US Center for Disease Control and Prevention, monitors central line-associated BSI in US medical centres and reports results of pathogen occurrence and antimicrobial susceptibility to selected agents [16]. The last report from NHSN included data collected in 2015–2017 showing high frequencies of antimicrobial resistance among Enterobacterales, with CRE frequencies among *Klebsiella* spp. ranging from 4.9% in oncology units to 24.7% in long-term acute-care hospitals. CRE frequencies were also high among *Enterobacter* spp. (4.7–9.4%) and *E. coli* (1.2–2.4%) [16]. Comparison of the NHSN data with the data reported here by the INFORM Program suggests that resistance rates are much higher among Enterobacterales causing central line-associated BSI compared to other types of BSI.

When comparing results of this investigation with previous data from the INFORM program (2015–2016) on BSI, Enterobacterales susceptibility to meropenem was identical (89.8%) and susceptibility to ceftazidime and cefepime were slightly higher in 2015–2016 (87.1% and 90.0%, respectively) compared to 2020–2022 (84.7% and 86.9%, respectively) [9]. Notably, susceptibility to ceftazidime-avibactam against CRE decreased from 97.5% in 2015–2016 (n=238 and included all infection types) to 81.6% in 2020–2022. This decrease in the activity of ceftazidime-avibactam can be explained by changes in the epidemiology of carbapenemases. During the same period, the frequency of KPC producers among CRE decreased from 82.3% in 2015–2016 to 57.1% in 2020–2022 and the frequency of MBL producers increased from 2.5 to 14.3% [9].

Our results on the in vitro activity of aztreonam-avibactam corroborate other investigations. The ATLAS Global Surveillance Program evaluated the activity of aztreonam-avibactam against a large collection of Enterobacterales from various geographic regions.

Rossoline et al. reported data on 18,713 Enterobacterales collected worldwide in 2019 through the ATLAS Program, including 2,420 from North America, and aztreonam-avibactam inhibited 99.8% of Enterobacterales from North America at ≤8 mg/L, including 99.4% of CRE isolates [17]. In another investigation, Rossoline et al. assessed 106,686 Enterobacterales collected from 2016 to 2020; this collection included 1,707 MBL producers. Aztreonam-avibactam inhibited 99.9% of Enterobacterales and 99.4% of MBL producers at ≤8 mg/L [18].

Susceptibility results for MBL producers (n=8), OXA-48 producers (n=7), and carbapenemase-negative CRE (n=6) should be analysed with caution since only a small number of isolates were tested (Table 1; Fig. 3). In a previous study, we evaluated the activity of aztreonam-avibactam against 103 carbapenemase-negative CRE isolates collected outside the US; of these isolates, 98.1% were inhibited at ≤8 mg/L of aztreonam-avibactam [19]. Mushtaq et al. evaluated 51 carbapenemase-negative CRE isolates from the United Kingdom and found that 80.4% (41/51) were inhibited at ≤8 mg/L of aztreonam-avibactam [20].

Only 2 isolates showed decreased susceptibility (MIC, >8 mg/L) to aztreonam-avibactam: a carbapenem-susceptible *E. coli* and a *K. aerogenes* with a meropenem MIC of 2 mg/L and an imipenem MIC of 4 mg/L (CRE). The mechanism of resistance to aztreonam-avibactam in the *E. coli* isolate was identified as alterations in the PBP3 protein combined with the production of CMY-42, which has been described before by various investigators [19, 21, 22]. The *K. aerogenes* showed hyperproduction of AmpC and porin alterations, similar to what has been previously described in *Enterobacter cloacae* species complex [19].

The limitations of the study should be considered when interpreting the results. The lack of differentiation between central line associated BSI and non-central line associated BSI is a limitation since organisms from central line associated BSI tend to have higher frequencies of antimicrobial resistance [16]. Another limitation is the lack of clinical information such as demographic data of patients, their clinical diagnosis and treatment outcome.

In summary, aztreonam-avibactam demonstrated almost complete coverage against Enterobacterales causing BSI in US medical centres and exhibited potent activity against CRE independent of carbapenemase type. The results of this investigation also emphasize the increasing resistance among Enterobacterales to recently approved BLICs. Continued monitoring of antimicrobial resistance via comprehensive and well-designed surveillance programs remains a valuable tool for planning empirical therapy recommendations and infection control measures.

Abbreviations

CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem-resistant Enterobacterales
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
INFORM	International Network for Optimal Resistance Monitoring
KPC	*Klebsiella pneumoniae* carbapenemase
MBL	Metallo-β-lactamase
NHSN	National Healthcare Safety Network
NGS	Next-Generation Sequencing
US	United States

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
HSS: Conceptualization, Formal Analysis, Data Curation, Writing – Original Draft, Visualization, Funding Acquisition JHK: Methodology, Formal Analysis, Investigation, Data Curation, Review & Edit, Software, Validation, Supervision REM: Conceptualization, Validation, Resources, Writing – Review & Edit, Supervision, Funding AcquisitionMC: Conceptualization, Validation, Resources, Writing – Review & Edit, Supervision, Funding AcquisitionAll authors reviewed and approved the manuscript.

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Data availability
The datasets generated and/or analysed during the current study are available in the Sequence Read Archive (SRA) repository under accession number PRJNA1171316. Also, DNA sequencing results are provided in supplemental material.

Declarations

Ethics approval and consent to participate
This study does not include factors necessitating patient consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Timsit JF, Ruppe E, Barbier F, Tabah A, Bassetti M. Bloodstream infections in critically ill patients: an expert statement. Intensive Care Med. 2020;46(2):266–84.
2. Adrie C, Garrouste-Orgeas M, Ibn Essaied W, Schwebel C, Darmon M, Mourvillier B, et al. Attributable mortality of ICU-acquired bloodstream infections: impact of the source, causative micro-organism, resistance profile and antimicrobial therapy. J Infect. 2017;74(2):131–41.
3. Barbier F, Hraiech S, Kerneis S, Veluppillai N, Pajot O, Poissy J, et al. Rationale and evidence for the use of new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol in critically ill patients. Ann Intensive Care. 2023;13(1):65.
4. Boyd SE, Livermore DM, Hooper DC, Hope WW. Metallo-beta-lactamases: structure, function, epidemiology, treatment options, and the development pipeline. Antimicrob Agents Chemother. 2020;64(10):e00397–20.
5. Sader HS, Mendes RE, Carvalhaes CG, Kimbrough JH, Castanheira M. Changing epidemiology of carbapenemases among carbapenem-resistant enterobacterales from United States hospitals and the activity of aztreonam-avibactam against contemporary Enterobacterales (2019–2021). Open Forum Infect Dis. 2023;10(2):ofad046.
6. Zhanel GG, Golden AR, Zelenitsky S, Wiebe K, Lawrence CK, Adam HJ, et al. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant Gram-negative bacilli. Drugs. 2019;79(3):271–89.
7. Karakonstantis S, Rousaki M, Kritsotakis EI, Cefiderocol. Systematic review of mechanisms of resistance, heteroresistance and in vivo emergence of resistance. Antibiot (Basel). 2022;11(6):723.
8. Lasarte-Monterrubio C, Guijarro-Sanchez P, Vazquez-Ucha JC, Alonso-Garcia I, Alvarez-Fraga L, Outeda M, et al. Antimicrobial activity of cefiderocol against the carbapenemase-producing *Enterobacter cloacae* complex and characterization of reduced susceptibility associated with metallo-beta-lactamase VIM-1. Antimicrob Agents Chemother. 2023;67(5):e0150522.
9. Sader HS, Castanheira M, Duncan LR, Flamm RK. Antimicrobial susceptibility of Enterobacteriaceae and *Pseudomonas aeruginosa* isolates from United States medical centers stratified by infection type: results from the International Network for Optimal Resistance Monitoring (INFORM) Surveillance Program, 2015–2016. Diagn Microbiol Infect Dis. 2018;92(1):69–74.
10. CLSI. M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Wayne, PA, 2018.
11. Cornely OA, Cisneros JM, Torre-Cisneros J, Rodriguez-Hernandez MJ, Tallon-Aguilar L, Calbo E, et al. Pharmacokinetics and safety of aztreonam/avibactam for the treatment of complicated intra-abdominal infections in hospitalized adults: results from the REJUVENATE study. J Antimicrob Chemother. 2020;75(3):618–27.
12. CLSI. M100Ed33. Performance standards for antimicrobial susceptibility testing: 33nd informational supplement. Wayne, PA, 2023.
13. FDA. US FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria. https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria
14. Breakpoint tables for interpretation of MICs and zone diameters [Internet]. European Committee on Antimicrobial Susceptibility Testing. 2023. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0_Breakpoint_Tables.pdf
15. Bankevich A, Nurk S, Antipov D, Gurevich AA, Dvorkin M, Kulikov AS, et al. SPAdes: a new genome assembly algorithm and its applications to single-cell sequencing. J Comput Biol. 2012;19(5):455–77.
16. Weiner-Lastinger LM, Abner S, Edwards JR, Kallen AJ, Karlsson M, Magill SS, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015–2017. Infect Control Hosp Epidemiol. 2020;41(1):1–18.
17. Rossolini GM, Stone G, Kantecki M, Arhin FF. In vitro activity of aztreonam/avibactam against isolates of Enterobacterales collected globally from ATLAS in 2019. J Glob Antimicrob Resist. 2022;30:214–21.
18. Rossolini GM, Arhin FF, Kantecki M. In vitro activity of aztreonam-avibactam and comparators against metallo-beta-lactamase-producing enterobacterales from ATLAS Global Surveillance Program, 2016–2020. J Glob Antimicrob Resist. 2023;36:123–31.
19. Sader HS, Carvalhaes CG, Kimbrough JH, Mendes RE, Castanheira M. Activity of aztreonam-avibactam against Enterobacterales resistant to recently approved beta-lactamase inhibitor combinations collected in Europe, Latin America, and the Asia-Pacific Region (2020–2022). Int J Antimicrob Agents. 2024:107113.
20. Mushtaq S, Vickers A, Woodford N, Livermore DM. Activity of aztreonam/avibactam and ceftazidime/avibactam against Enterobacterales with carbapenemase-independent carbapenem resistance. Int J Antimicrob Agents. 2024;63(3):107081.
21. Mendes RE, Doyle TB, Streit JM, Arhin FF, Sader HS, Castanheira M. Investigation of mechanisms responsible for decreased susceptibility of aztreonam/avibactam activity in clinical isolates of Enterobacterales collected in Europe, Asia and Latin America in 2019. J Antimicrob Chemother. 2021;76(11):2833–8.
22. Sadek M, Juhas M, Poirel L, Nordmann P. Genetic features leading to reduced susceptibility to aztreonam-avibactam among metallo-beta-lactamase-producing *Escherichia coli* isolates. Antimicrob Agents Chemother. 2020;64(12):e01659–20.

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