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ORIGINAL ARTICLE

Antimicrobial activities of aztreonam-avibactam and comparator agents tested against *Enterobacterales* from European hospitals analysed by geographic region and infection type (2019–2020)

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Abstract
The purpose of this study is to evaluate the activities of aztreonam-avibactam and comparator agents against *Enterobacterales* isolates from European medical centres as well as the occurrence of carbapenemases (CPEs). A total of 11,655 *Enterobacterales* isolates were collected consecutively in 2019–2020 from 38 medical centres located in Western Europe (W-EU; $n = 8{,}784$; 25 centres in 10 countries) and the Eastern European and Mediterranean region (E-EU; $n = 2{,}871$; 13 centres in 10 countries). Isolates were susceptibility tested by broth microdilution methods in a monitoring laboratory. The antimicrobial susceptibility and frequency of key resistance phenotypes were assessed and stratified by geographic region and infection type. Isolates that showed resistance to carbapenems (CRE) and/or elevated MICs (> 8 mg/L) for aztreonam-avibactam were screened for β-lactamase-encoding genes by whole-genome sequencing. Aztreonam-avibactam inhibited 99.9% of *Enterobacterales* at ≤ 8 mg/L ($MIC_{50/90}$, ≤ 0.03/0.12 mg/L) and retained potent activity against CRE ($MIC_{50/90}$, 0.25/0.5 mg/L), multidrug-resistant isolates (MDR; $MIC_{50/90}$, 0.12/0.5 mg/L), and extensively drug-resistant (XDR) isolates ($MIC_{50/90}$, 0.25/0.5 mg/L). Susceptibility to comparator agents was consistently lower among isolates from E-EU compared to W-EU for all infection types evaluated. CRE rates varied from 0.6% (urinary tract infection [UTI]) to 2.3% (bloodstream infection) in W-EU, and from 6.1% (UTI) to 17.0% (pneumonia) in E-EU. A CPE-encoding gene was identified in 360 of 424 (84.9%) CRE isolates, and the most common CPEs were bla_{KPC} (36.3% of CRE), bla_{OXA-48} type (27.1% of CRE), and the MBLs (25.7% of CRE). All CPE producers were inhibited at an aztreonam-avibactam concentration of ≤ 8 mg/L. Aztreonam-avibactam demonstrated potent activity across the evaluated geographic regions and infection types.

Keywords Beta-lactamase inhibitor · Carbapenemase · Metallo-beta-lactamase · NDM-1

Introduction

Aztreonam-avibactam is currently under clinical investigation for treatment of Gram-negative infections, including those caused by *Enterobacterales* producing MBLs and/or serine carbapenemases (CPEs) [1]. Aztreonam was approved by the FDA in 1986, and it still is the only clinically available member of the monobactam class [2]. Aztreonam is stable to hydrolysis by MBLs; however, it is hydrolysed by most clinically relevant serine β-lactamases, such as ESBLs, AmpC, and KPC. Because *Enterobacterales* isolates that produce an MBL usually coproduce a serine β-lactamase, aztreonam was combined with avibactam. Avibactam is a non-β-lactam β-lactamase inhibitor that inhibits the activities of Ambler class A (including extended-spectrum β-lactamases), class C, and some class D β-lactamases [1].

Enterobacterales can express a broad range of mechanisms of antimicrobial resistance, and the treatment of infections caused by multidrug-resistant (MDR) *Enterobacterales*, especially carbapenem-resistant *Enterobacterales* (CRE), remains an important challenge for physicians. Resistance to carbapenems in *Enterobacterales* is usually due to the acquisition of CPEs or overexpressed cephalosporinases combined with decreased permeability. Although globally distributed in many *Enterobacterales* species, certain CPEs are associated with specific regions or countries [3–5]. KPC-producing *Enterobacterales*, mainly *K. pneumoniae*, have been extensively reported in the USA and some

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European countries, such as Greece and Italy [6]. OXA-48 and its derivatives (e.g., OXA-181 and OXA-232) hydrolyse narrow-spectrum β-lactams and weakly hydrolyse carbapenems, but spare broad-spectrum cephalosporins, such as ceftazidime and cefepime. OXA-48-producing *Enterobacterales* are endemic in Turkey and are frequently reported in several European countries, such as France and Belgium [7]. Class B, or MBLs, are commonly identified in *Enterobacterales* and *Pseudomonas aeruginosa* in some geographic regions. NDM, VIM, and IMP are the most frequent MBLs identified in *Enterobacterales* worldwide. NDM-producing *Enterobacterales* have been identified globally, with the highest prevalence in the Indian subcontinent, the Middle East, and southeast Europe. VIM-producing *Enterobacterales* are common in Italy and Greece, whereas IMP is mainly found in *Acinetobacter baumannii* from China, Japan, or Australia [8, 9].

In the present study, we assessed the in vitro activity of aztreonam-avibactam against a large collection of contemporary (2019–2020) clinical *Enterobacterales* isolates recovered from patients hospitalised in European medical centres. We also evaluated variations of susceptibility rates by geographic region and infection type and assessed the prevalence of CPE-encoding genes among CREs.

Materials and methods

Bacterial isolates were collected via the SENTRY Antimicrobial Surveillance Program and sent to JMI Laboratories (North Liberty, IA, USA) for susceptibility testing [10]. Each participating centre was asked to collect a designated number of consecutive bacterial isolates per infection type, including bloodstream infection (BSI), pneumonia, skin and soft tissue infection (SSTI), urinary tract infection (UTI), and intra-abdominal infection (IAI). The number of isolates to be collected from each infection type was established by the study protocol, and the isolates were consecutively collected during a predetermined period of time, which was also specified by the study protocol and varied according to the type of infection. If a patient had more than one isolate, only the first isolate collected during the time period specified by the protocol was included in the study.

A total of 11,655 *Enterobacterales* isolates were collected consecutively in 2019 and 2020 from 38 medical centres located in Western Europe (W-EU; $n = 8{,}784$; 25 centres in 10 countries; Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, Switzerland, and the UK) and the Eastern European and Mediterranean region (E-EU; $n = 2{,}871$; 13 centres in 10 countries; Belarus, Czech Republic, Greece, Hungary, Israel, Poland, Romania, Russia, Slovenia, and Turkey). Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in this investigation. Species identification was confirmed by using standard biochemical tests and/or a MALDI Biotyper (Bruker Daltonics, Billerica, MA, USA), when necessary.

Carbapenem-resistant *Enterobacterales* (CRE) isolates were defined as displaying imipenem or meropenem MIC values at ≥ 4 mg/L. Imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to their intrinsically elevated MIC values. Isolates were categorised as MDR or XDR according to criteria defined in 2012 by the joint European and US Centers for Disease Control, which state MDR as nonsusceptible to ≥ 1 agent in ≥ 3 antimicrobial classes and XDR as susceptible to ≤ 2 classes [11]. The antimicrobial classes and drug representatives in this analysis included cephalosporins (ceftazidime, cefepime, and ceftriaxone), carbapenems (imipenem, meropenem, and doripenem), a broad-spectrum penicillin combined with a β-lactamase-inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), and a polymyxin (colistin).

Isolates were tested against aztreonam-avibactam and 12 comparator agents by the reference broth microdilution method specified by CLSI standards [12]. All tests were conducted in a central monitoring laboratory (JMI Laboratories). Aztreonam-avibactam was tested with avibactam at a fixed concentration of 4 mg/L. A tentative aztreonam-avibactam pharmacokinetic/pharmacodynamic (PK/PD) susceptible breakpoint of ≤ 8 mg/L was applied for comparison [1, 13]. EUCAST breakpoints were applied for the comparator agents where available [14]. The tigecycline susceptible breakpoint published by EUCAST for *E. coli* and *C. koseri* (≤ 0.5 mg/L) was applied to all *Enterobacterales* species for comparison. Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures. The QC strains tested included *Escherichia coli* ATCC 25,922 and ATCC 35,218; *Klebsiella pneumoniae* ATCC 700,603, ATCC BAA-1705, and ATCC BAA-2814; *Pseudomonas aeruginosa* ATCC 27,853; and *Staphylococcus aureus* ATCC 29,213.

All CRE isolates ($n = 424$) and the isolates with elevated aztreonam-avibactam MICs (> 8 mg/L; $n = 6$) were assessed for β-lactamase-encoding genes using next-generation sequencing (NGS), as previously described. [15] Furthermore, relative quantification of AmpC expression, the gene sequences encoding for OmpC and OmpF porins, and the penicillin-binding protein 3 (PBP3) were investigated in isolates with an elevated (> 8 mg/L) aztreonam-avibactam MIC [16].

Results

Aztreonam-avibactam activity was very consistent across the evaluated geographic regions and infection types. Aztreonam-avibactam inhibited 99.9% of *Enterobacterales* at ≤ 8 mg/L ($n = 8{,}786$; $MIC_{50/90}$, ≤ 0.03/0.12 mg/L) and retained potent activity against CRE ($n = 424$; $MIC_{50/90}$, 0.25/0.5 mg/L; 99.5% inhibited at ≤ 8 mg/L), MDR ($n = 1{,}875$; $MIC_{50/90}$, 0.12/0.5 mg/L; 99.6% inhibited at ≤ 8 mg/L), and XDR isolates ($n = 335$; $MIC_{50/90}$, 0.25/0.5 mg/L; 99.7% inhibited at ≤ 8 mg/L; Table 1).

A CPE encoding gene was identified in 360 of 424 (84.9%) CRE isolates (Table 1). The most common CPEs were bla_{KPC} (154 isolates [36.3% of CRE], including bla_{KPC-2} [42] and bla_{KPC-3} [112]), followed by bla_{OXA-48} type (115 isolates [27.1% of CRE], including bla_{OXA-48} [92], $bla_{OXA-48-like}$ [1], $bla_{OXA-232}$ [18], and $bla_{OXA-181}$ [5]) and the MBLs (109 isolates [25.7% of CRE], including bla_{NDM-1} [81], bla_{NDM-5} [3], bla_{VIM-1} [22], bla_{VIM-19} [3], and bla_{IMP-1} [1]). Notably, 2 CPE-encoding genes were identified in 20 isolates, including one isolate with 2 bla_{OXA-48} type (bla_{OXA-48} and $bla_{OXA-181}$) and one isolate with 2 MBL genes (bla_{NDM-1} and bla_{VIM-1}; Table 1). Among MBL producers, 94 (86.2%) isolates were from E-EU and 15 (13.8%) isolates were from W-EU. All CPE-producer CRE isolates were inhibited at an aztreonam-avibactam ≤ 8 mg/L ($MIC_{50/90}$, 0.25/0.5 mg/L; Table 1). Importantly, the highest aztreonam-avibactam MIC value among MBL-producing strains and among isolates producing 2 CPEs was only 0.5 mg/L (Table 1).

Aztreonam-avibactam was highly active against *Enterobacterales* isolates from W-EU ($MIC_{50/90}$, ≤ 0.03/0.12 mg/L). Only 1 of 8784 isolates (0.01%) showed an aztreonam-avibactam MIC > 8 mg/L (MIC of 16 mg/L), an *E. coli* from Italy isolated from a patient with UTI (Table 2). The most active comparator agents against W-EU *Enterobacterales* isolates were meropenem (98.7% susceptible [S]), amikacin (97.7%S), and gentamicin (90.4%S; Table 2). Susceptibility varied slightly by infection type. The frequency of CRE, MDR, and XDR was the highest among BSI isolates while the CRE and MDR rates were lowest among UTI isolates and the XDR rate was lowest among SSTI isolates (Fig. 1).

Aztreonam-avibactam inhibited 99.9% of MDR isolates from W-EU at ≤ 8 mg/L; none of the comparator agents were active against > 90% of isolates (Table 2). The most active comparator agents against MDR isolates were meropenem, with susceptibility rates varying from 84.5% (BSI) to 93.8% (UTI; 88.5% overall), followed by amikacin (74.7–85.9%S; 80.7% overall) and colistin (69.5–80.8%S; 76.0% overall; Table 2). All CRE isolates from W-EU were inhibited at ≤ 8 mg/L of aztreonam-avibactam, and only colistin (90.6%S overall), amikacin (65.4%S), and tigecycline (52.8%S) were active against > 50% of W-EU CRE isolates (Table 2).

Aztreonam-avibactam was slightly (twofold) less active against isolates from E-EU ($MIC_{50/90}$, 0.06/0.25 mg/L) compared to W-EU ($MIC_{50/90}$, ≤ 0.03/0.12 mg/L). Only 5 of 2871 isolates (0.2%) from E-EU showed an aztreonam-avibactam MIC > 8 mg/L, 3 isolates from Poland (2 *E. cloacae* and 1 *E. coli*) and 2 from Turkey (2 *E. coli*; data not shown). The activities of the comparator agents were markedly lower against isolates from E-EU than W-EU (Tables 2 and 3). The most active comparator agents against E-EU isolates were meropenem (90.6%S), amikacin (88.2%S), and colistin (83.1%S; Table 3). Overall, CRE, MDR, and XDR rates were 10.3%, 32.0%, and 8.9% in E-EU and 1.4%, 10.9%, and 1.1% in W-EU, respectively (Figs. 1 and 2). The frequencies of CRE, MDR, and XDR in E-EU were highest among isolates from pneumonia and lowest among isolates from UTI (Fig. 2).

Percentages of E-EU MDR isolates inhibited at ≤ 8 mg/L of aztreonam-avibactam were 99.3% overall, and ranged from 99.1% (BSI and pneumonia) to 100.0% (IAI; Table 3). The most active comparator agents were colistin (69.0–83.2%S; 74.8% overall), meropenem (61.2–79.6%S; 70.8% overall), and amikacin (58.9–71.4%S; 64.3% overall; Table 3). Overall, 99.7% of CRE isolates from E-EU were inhibited at ≤ 8 mg/L of aztreonam-avibactam, including all isolates from SSTI, UTI, and IAI (Table 3). The most active comparator agents against E-EU CRE were colistin (74.0%S overall), gentamicin (40.1%S), and amikacin (38.7%S; Table 3).

Overall, only 6 of 11,655 (< 0.1%) *Enterobacterales* isolates tested showed an aztreonam-avibactam MIC > 8 mg/L: 4 *E. coli* and 2 *E. cloacae*. Results of the characterisation of these organisms are summarised in Table 4. Five organisms were from E-EU (Poland and Turkey) and 1 was from W-EU (Italy). A CPE-encoding gene was not detected in any of these isolates, except for a $bla_{OXA-244}$ in *E. coli* 1,177,727. Four organisms were susceptible to meropenem (MIC, 0.06–0.5 mg/L) and ceftazidime-avibactam (MIC, 2–8 mg/L). Amino acid insertions and substitutions within PBP3 (YRIK) and a CMY-encoding gene were detected in all *E. coli* strains. In addition, these *E. coli* isolates carried multiple β-lactamase genes. Both *E. cloacae* overproduced AmpC (*act-17* and *act-24*), carried ESBL genes, and had alterations in the porin sequence.

Discussion

Aztreonam-avibactam showed potent activity against a large collection of *Enterobacterales* isolates from W-EU and E-EU medical centres independent of infection type.

Table 1 Antimicrobial activity of aztreonam-avibactam against the main organisms and organism groups

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at aztreonam-avibactam MIC (mg/L) of:											MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16		
Enterobacterales (8786)	6328 54.3%	3042 80.4%	1320 91.7%	587 96.7%	232 98.7%	97 99.6%	30 99.8%	7 99.9%	6 99.9%	4 >99.9%	2 100.0%	≤0.03	0.12
MDR (1875)	467 24.9%	462 49.5%	406 71.2%	319 88.2%	133 95.3%	50 98.0%	18 98.9%	7 99.3%	6 99.6%	4 99.8%	3 100.0%	0.12	0.5
XDR (335)	18 5.1%	32 14.1%	85 38.0%	141 77.7%	62 95.2%	11 98.3%	5 99.7%	0 99.7%	0 99.7%	0 99.7%	1 100.0%	0.25	0.5
CRE (424)	15 3.5%	42 13.4%	89 34.4%	174 75.5%	83 95.0%	11 97.6%	6 99.1%	1 99.3%	1 99.5%	0 99.5%	2 100.0	0.25	0.5
CPE producers (360)	15 4.2%	41 15.6%	80 37.8%	153 80.3%	60 96.9%	8 99.2%	2 99.7%	0 99.7%	1 100.0%			0.25	0.5
KPC-like producers (154)[a]	3 1.9%	18 13.6%	31 33.8%	70 79.2%	27 96.8%	4 99.4%	1 100.0%					0.25	0.5
OXA-48-like producers (115)[b]	2 1.7%	9 9.6%	26 32.2%	49 74.8%	23 94.8%	4 98.3%	1 99.1%	0 99.1%	1 100.0%			0.25	0.5
MBL producers (109)[c]	11 10.1%	16 24.8%	29 51.4%	38 86.2%	15 100.0%							0.12	0.5
Isolates producing 2 CPEs (20)[d]	1 5.0%	2 15.0%	6 45.0%	6 75.0%	5 100.0%							0.25	0.5
Non-CPE producers (64)	0 0.0%	1 1.6%	9 15.6%	21 48.4%	23 84.4%	3 89.1%	4 95.3%	1 96.9%	0 96.9%	0 96.9%	2 100.0%	0.5	2

[a]Include isolates producing KPC-2 (42) and KPC-3 (112)

[b]Includes isolates producing OXA-48 (92), OXA-48-like (1), OXA-232 (18), and OXA-181 (5). One isolate had an OXA-48 and an OXA-181

[c]Include isolates producing NDM-1 (81), NDM-5 (3), VIM-1 (22), VIM-19 (3), and IMP-1 (1). One isolate had NDM-1 and VIM-1

[d]Includes isolates producing NDM-1 and OXA-48 (9), KPC-3 and VIM-1 (6), KPC-2 and NDM-1 (2), NDM-1 and VIM-1 (1), NDM-5 and OXA-181 (1), and OXA-181 and OXA-48

Table 2 Antimicrobial activity of aztreonam-avibactam and comparator agents tested against *Enterobacterales* isolates from Western Europe (W-EU) and stratified by infection type

Antimicrobial agent	% Susceptible per EUCAST by infection type (no. of isolates)[a]					
	BSI	Pneumonia	SSTI	UTI	IAI	All
Enterobacterales	(2825)	(1810)	(1289)	(2077)	(783)	(8784)
Aztreonam-avibactam[b]	[100.0][b]	[100.0][b]	[100.0][b]	[99.9][b]	[100.0][b]	[> 99.9][b]
Ceftriaxone	77.9	77.4	80.5	84.3	80.2	79.9
Ceftazidime	78.2	82.6	81.0	84.4	80.3	80.2
Cefepime	81.0	87.3	86.1	87.3	87.0	84.6
Ampicillin/sulbactam[c]	45.4	38.6	41.1	51.6	42.7	44.6
Piperacillin/tazobactam	84.8	84.4	84.9	90.5	84.7	85.2
Meropenem	98.0	98.1	99.3	99.5	99.0	98.7
Ciprofloxacin	74.7	79.9	79.8	78.8	80.3	78.0
Levofloxacin	77.8	82.7	81.6	81.1	82.7	80.6
Gentamicin[d]	88.0	92.9	91.4	90.9	91.7	90.4
Amikacin[d]	96.4	99.2	98.4	98.3	98.5	97.7
Tigecycline[e]	70.1	54.1	53.2	72.7	70.1	65.0
Colistin	88.3	76.9	73.4	85.5	86.0	82.9
MDR *Enterobacterales*[f]	(368)	(203)	(130)	(178)	(78)	(957)
Aztreonam-avibactam	[100.0][b]	[100.0][b]	[100.0][b]	[99.4][b]	[100.0][b]	[99.9]
Ceftriaxone	9.0	16.7	20.8	21.3	19.2	15.4
Piperacillin/tazobactam	36.7	25.1	37.7	39.9	24.4	34.0
Meropenem	84.5	87.7	93.1	93.8	89.7	88.5
Levofloxacin	12.5	22.2	18.5	14.0	20.8	16.3
Gentamicin[d]	29.6	48.8	40.0	37.6	47.4	38.0
Amikacin[d]	74.7	86.2	84.6	81.5	85.9	80.7
Tigecycline[e]	67.9	63.1	64.6	66.9	73.1	66.7
Colistin	80.4	69.5	71.5	75.7	80.8	76.0
CRE[g]	(64)	(31)	(9)	(13)	(10)	(127)
Aztreonam-avibactam	[100.0][b]	[100.0][b]	[100.0][b]	[100.0][b]	[100.0][b]	[100.0][b]
Levofloxacin	6.2	22.6	0.0	23.1	30.0	13.4
Gentamicin[d]	50.0	54.8	33.3	38.5	40.0	48.0
Amikacin[d]	59.4	67.7	88.9	53.8	90.0	65.4
Tigecycline[e]	56.2	48.4	44.4	46.2	60.0	52.8
Colistin	90.6	83.9	100.0	92.3	100.0	90.6

[a]Criteria as published by EUCAST (2020)[14]

[b]Values in brackets indicate % inhibited at ≤ 8 mg/L for comparison purposes[1]

[c]Breakpoints for oral administration are relevant for uncomplicated urinary tract infections only[14]

[d]Infections originating from the urinary tract; for systemic infections, aminoglycosides must be used in combination with other active therapy[14]

[e]The EUCAST susceptible breakpoint published for *E. coli* and *C. koseri* (≤ 0.5 mg/L) was applied for all *Enterobacterales* species for comparison purposes[14]

[f]Organisms include *Citrobacter amalonaticus/farmeri* (1), *C. freundii* species complex (23), *C. koseri* (2), *Enterobacter asburiae* (3), *E. cloacae* (27), *E. cloacae* species complex (72), *E. hormaechei* (1), *E. kobei* (1), *Escherichia coli* (523), *Hafnia alvei* (16), *Klebsiella aerogenes* (21), *K. oxytoca* (20), *K. pneumoniae* (802), *Morganella morganii* (41), *Proteus mirabilis* (95), *P. vulgaris* group (1), *Providencia rettgeri* (2), *P. stuartii* (13), *Serratia liquefaciens* (1), and *S. marcescens* (41)

[g]Organisms include *Citrobacter freundii* species complex (2), *Enterobacter cloacae* species complex (18), *Escherichia coli* (15), *Klebsiella aerogenes* (5), *K. oxytoca* (8), *K. pneumoniae* (336), *Proteus mirabilis* (3), *Providencia rettgeri* (1), *P. stuartii* (1), and *Serratia marcescens* (7)

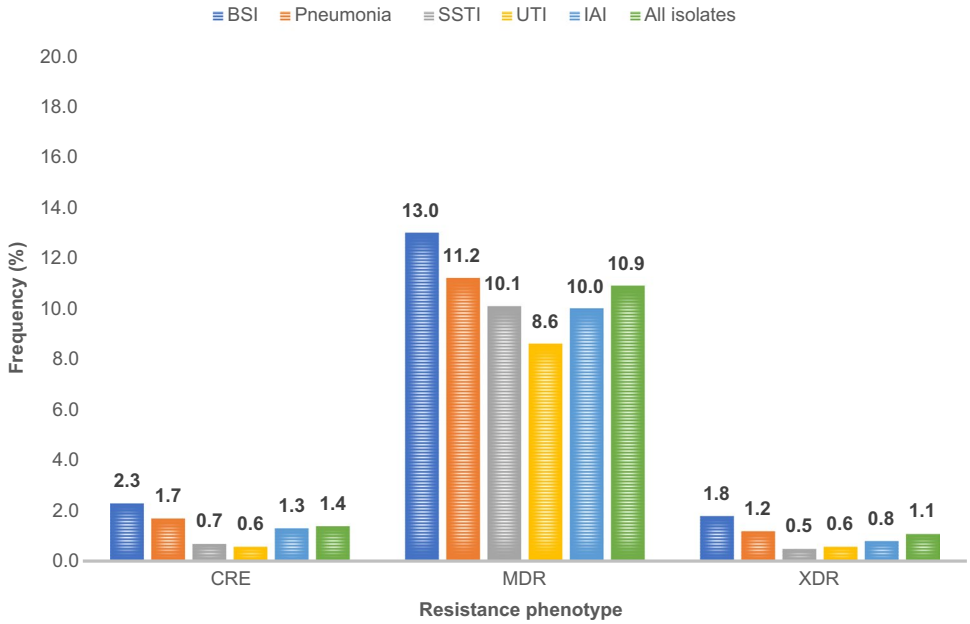

Fig. 1 Frequency of carbapenem-resistant *Enterobacterales* (CRE), multidrug-resistant (MDR), and extensively drug-resistant (XDR) isolates in Western Europe (W-EU) stratified by infection type

Moreover, aztreonam-avibactam retained strong activity against CRE, including MBL producers, MDR, and XDR isolates. Our results corroborate those published by other investigators. Sonnevend et al. evaluated the activity of aztreonam-avibactam against 1192 CREs from 33 hospitals in 5 countries from the Arabian Peninsula. [17] Almost half (46.3%) of the isolates produced an MBL and 52.9% produced an OXA-48-like. Aztreonam-avibactam inhibited 95.5% of isolates at ≤ 4 mg/L and 46.7% of isolates were resistant to ceftazidime-avibactam. Notably, aztreonam-avibactam was active against 94.4% of ceftazidime-avibactam-resistant strains [17].

Resistance to aztreonam-avibactam (MIC, > 8 mg/L) was observed in only 6 isolates, 4 *E. coli* and 2 *E. cloacae* (Table 4). Decreased susceptibility to aztreonam-avibactam in *E. coli* has been reported by other investigators and seems to be caused by the association of PBP3 alterations and production of a CMY β-lactamase [16, 18–20]. Sadek et al. elegantly showed that the amino acid insertions YRIK and YRIN in the PBP3 protein are not sufficient to raise the aztreonam-avibactam MIC value to resistant levels (greater than 4 or 8 mg/L) and the presence of a bla_{CMY} β-lactamase gene was associated with higher aztreonam-avibactam MIC values on isolates with those PBP3 alterations [20, 21]. All 4 aztreonam-avibactam-resistant *E. coli* isolates evaluated in this investigation showed an insertion of 4 amino acids (YRIK) in the PBP3 protein associated with a bla_{CMY} gene. Plus, 2 isolates had a bla_{CMY-42}, as reported by Sadek et al. [20, 21], whereas the other 2 isolates had bla_{CMY} genes that differed from bla_{CMY-42} by only 1 amino acid, $bla_{CMY-145}$ (N90T) and $bla_{CMY-141}$ (I141L).

We did not identify β-lactamases known to be refractory to the avibactam inhibition, such PER or VEB, on the 2 aztreonam-avibactam-resistant *E. cloacae* isolates [19]. Moreover, the AmpC gene of one of the isolates (*act-17*) was cloned into an *E. coli* background and did not alter the aztreonam-avibactam MIC value of the recipient strain without this gene, which remained 0.12 mg/L [22]. Thus, we hypothesise that resistance to aztreonam-avibactam on these 2 *E. cloacae* strains was due to the association of AmpC hyperproduction and porin alterations.

Our results also showed that susceptibility to comparator agents varied between W-EU and E-EU and among infection types in each region. Resistance rates were generally higher in E-EU than W-EU. Notably, rates of CRE, MDR, and XDR were markedly higher among isolates from E-EU than W-EU (Figs. 1 and 2). These results clearly indicate a higher dissemination of ESBLs, CPEs, and other resistance mechanisms in E-EU compared to W-EU, corroborating the results from other large surveillance programmes. Results from previous SENTRY Program investigations as well as from those from other European surveillance programmes, such as the EARS-Net, have also shown a marked regional variation of antimicrobial resistance within Europe. Important antimicrobial resistance problems have been identified in many E-EU countries, such as Belarus, Greece, Poland, Russia, and Turkey [23–28].

Resistance rates also varied by infection type. In W-EU, resistance rates tended to be higher among isolates from BSI (13.0% MDR rate) and pneumonia (11.2% MDR rate) than other infection types, whereas in E-EU, resistance rates tended to be higher among isolates from pneumonia (39.2%

Table 3 Antimicrobial activity of aztreonam-avibactam and comparator agents tested against *Enterobacterales* isolates from Eastern Europe (E-EU) and stratified by infection type

Antimicrobial agent	% Susceptible (EUCAST) by geographic region (no. of isolates)[a]					
	BSI	Pneumonia	SSTI	UTI	IAI	All
Enterobacterales	(761)	(545)	(577)	(820)	(166)	(2871)
Aztreonam-avibactam[b]	[99.7][b]	[99.6][b]	[100.0][b]	[99.9][b]	[100.0][b]	[99.8][b]
Ceftriaxone	58.1	52.4	71.5	62.0	53.9	57.4
Ceftazidime	59.0	53.1	55.9	62.3	52.7	57.8
Cefepime	60.1	57.0	60.2	65.2	58.7	60.9
Ampicillin/sulbactam[c]	31.6	32.1	32.2	36.8	31.7	33.3
Piperacillin/tazobactam	70.4	59.3	65.6	74.1	62.9	67.9
Meropenem	91.7	84.8	90.0	94.3	89.2	90.6
Ciprofloxacin	54.0	54.6	54.8	54.1	58.1	54.5
Levofloxacin	58.4	57.4	58.8	57.0	59.9	58.0
Gentamicin[d]	78.2	74.7	78.2	79.4	80.2	78.0
Amikacin[d]	88.6	83.7	87.2	91.0	91.0	88.2
Tigecycline[e]	59.7	44.9	51.7	63.0	64.7	56.5
Colistin	85.5	77.0	82.4	83.8	90.9	83.1
MDR *Enterobacterales*[f]	(232)	(214)	(193)	(230)	(49)	(918)
Aztreonam-avibactam	[99.1][b]	[99.1][b]	[99.5][b]	[99.6][b]	[100.0][b]	[99.3][b]
Ceftriaxone	8.6	3.7	8.8	9.6	4.1	7.5
Piperacillin/tazobactam	21.1	12.1	16.1	28.3	14.3	19.4
Meropenem	73.3	61.2	69.9	79.6	63.3	70.8
Levofloxacin	14.7	9.4	11.9	5.7	6.1	10.1
Gentamicin[d]	39.7	36.9	42.0	36.1	40.8	38.7
Amikacin[d]	65.1	58.9	61.7	69.1	71.4	64.3
Tigecycline[e]	59.1	51.4	66.3	52.2	55.1	56.9
Colistin	75.8	69.0	83.2	70.7	80.9	74.8
CRE[g]	(72)	(93)	(64)	(50)	(18)	(297)
Aztreonam-avibactam	[98.6][b]	[98.9][b]	[100.0][b]	[100.0][b]	[100.0][b]	[99.7][b]
Levofloxacin	13.9	8.7	4.7	2.0	0.0	7.4
Gentamicin[d]	51.4	40.9	40.6	22.0	38.9	40.1
Amikacin[d]	38.9	37.6	40.6	34.0	50.0	38.7
Tigecycline[e]	16.7	14.0	17.2	20.0	5.6	15.8
Colistin	77.8	67.7	82.8	72.0	64.7	74.0

[a]Criteria as published by EUCAST (2020)[14]

[b]Values in brackets indicate % inhibited at ≤ 8 mg/L for comparison purposes[1]

[c]Breakpoints for oral administration are relevant for uncomplicated urinary tract infections only[14]

[d]Infections originating from the urinary tract; for systemic infections, aminoglycosides must be used in combination with other active therapy[14]

[e]The EUCAST susceptible breakpoint published for *E. coli* and *C. koseri* (≤ 0.5 mg/L) was applied for all *Enterobacterales* species for comparison purposes[14]

[f]Organisms included *Citrobacter amalonaticus/farmeri* (1), *C. freundii* species complex (23), *C. koseri* (2), *Enterobacter asburiae* (3), *E. cloacae* (27), *E. cloacae* species complex (72), *E. hormaechei* (1), *E. kobei* (1), *Escherichia coli* (523), *Hafnia alvei* (16), *Klebsiella aerogenes* (21), *K. oxytoca* (20), *K. pneumoniae* (802), *Morganella morganii* (41), *Proteus mirabilis* (95), *P. vulgaris* group (1), *Providencia rettgeri* (2), *P. stuartii* (13), *Serratia liquefaciens* (1), and *S. marcescens* (41)

[g]Organisms included *Citrobacter freundii* species complex (2), *Enterobacter cloacae* species complex (18), *Escherichia coli* (15), *Klebsiella aerogenes* (5), *K. oxytoca* (8), *K. pneumoniae* (336), *Proteus mirabilis* (3), *Providencia rettgeri* (1), *P. stuartii* (1), and *Serratia marcescens* (7)

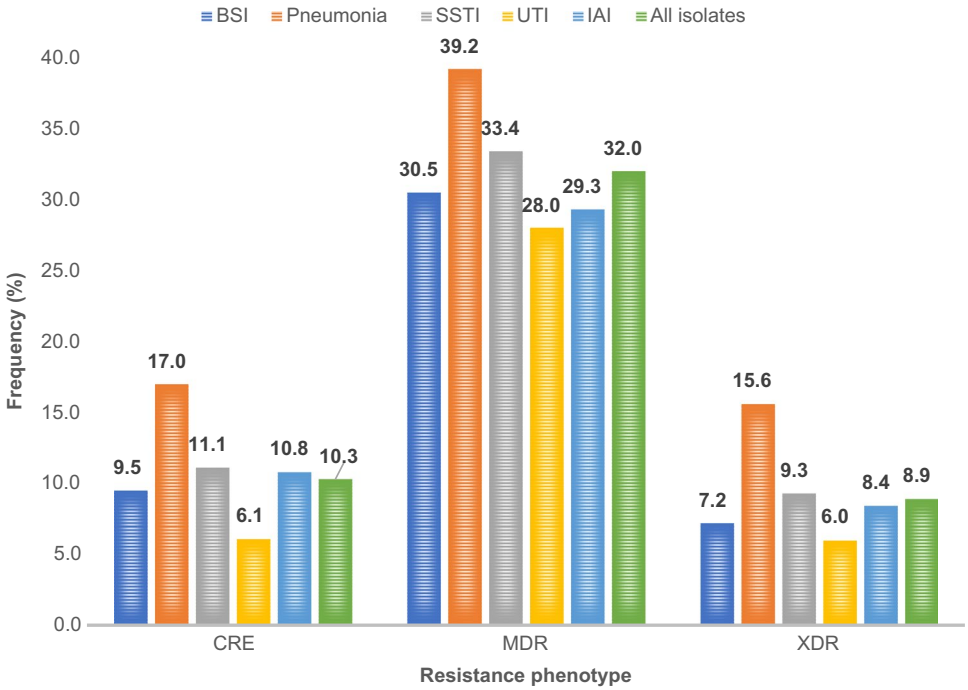

Fig. 2 Frequency of carbapenem-resistant *Enterobacterales* (CRE), multidrug-resistant (MDR), and extensively drug-resistant (XDR) isolates in Eastern Europe (E-EU) stratified by infection type

MDR rate) and SSTI (33.4% MDR rates). Varying resistance rates by infection type have been reported by other investigators and could be related to several factors, including but not limited to underlying illness, duration of hospitalisation before acquiring the infection, or previous antibiotic exposure [29].

A few antimicrobial agents that are active against CRE have been licensed in the last few years, including ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol. Although the approval of these agents represented a remarkable progress in the treatment of infections caused by CRE, except for cefiderocol, these agents are not active against MBL-producing *Enterobacterales* [9, 30].

The results of this investigation revealed that 84.9% (360/424) of CRE isolates from this large European collection produced a CPE. Moreover, 30.3% (109/360) of CPE producers and 25.7% of CRE isolates (109/424) produced an MBL and are probably resistant to the β-lactam-β-lactamase inhibitors currently available, including ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam.

Our results have some limitations. The fact that the criteria used to categorise a bacterial isolate as clinically significant were not defined in the study protocol and were based on local algorithms is a limitation since these criteria can vary among participating medical centres. Also, we could not differentiate between subsets of infection types that may present different susceptibility patterns, such as catheter-related versus non-catheter-related BSI or surgical versus non-surgical SSTI. Finally, this study had a restricted number of medical centres in some countries. These limitations should be considered when interpreting the results and conclusions.

In conclusion, resistance to aztreonam-avibactam was extremely rare among a large collection of *Enterobacterales* from European medical centres. The results of this large, international investigation support the clinical development of aztreonam-avibactam for treatment of *Enterobacterales* infections, including those infections caused by MBL-producing strains.

Table 4 Summary of the results on the characterisation of isolates exhibiting aztreonam-avibactam MIC results > 8 mg/L

Collection number	Organism	Country	MIC[a] (mg/L)				MLST	β-lactamase genes	mRNA Expression[b]		Amino acid alterations		
			ATM-AVI[a]	**CAZ-AVI**	**MEM**	**ATM**			**AcrA**	**AmpC**	**OmpF**	**OmpC**	**PBP3**
1,114,251	*E. coli*	Turkey	16	8	0.06	16	410	CMY-42, CTX-M-15, OXA-1, TEM-1	3.5	< 1	WT	WT	R333insYRIK
1,118,254	*E. cloacae*	Poland	16	2	0.12	16	78	SHV-12, TEM-1	< 1	570	WT	P177A, D188E	E258_S259insE
1,155,924	*E. coli*	Italy	16	4	0.06	16	6870	CMY-145, OXA-1/OXA-30	4.8	1.3	G48D, E51V, M60K, T99K, Y112F, V115A, F118I, D186A, D186_T187insG, T187I, A188P, R189E, Y204F, N220D, L221A, E224A, S225E, S226F, L227R, K229Q, T263E, N264G, K265_S270del	G48D, E51V, M60K, T99K, Y112F, V115A, F118I, D186A, D186_T187insG, T187I, A188P, R189E, Y204F, N220D, L221A, E224A, S225E, S226F, L227R, K229Q, T263E, N264G, K265_S270del	R333insYRIK
1,177,727	*E. coli*	Turkey	16	4	0.5	16	4450	CMY-42, CTX-M-15, TEM-1, OXA-244	2.5	1.1	E224A, S225Q, S226P, K229N	A85S, P86A, S88N, I106V, Q173K, V177A, S178R, N181_H188del, I190M, K196D, V218I, W229D, D230A, N233T, T234A, G235A, L236Y, T239N, V312T, V313I, A314G, G315T, A358D, D365N	R333insYRIK
1,183,154	*E. coli*	Poland	> 16	> 32	32	> 16	410	CMY-141, TEM-190	2.6	1.1	Y316X	N147X	R333insYRIK
1,183,311	*E. cloacae*	Poland	> 16	> 32	32	> 16	89	CTX-M-88, CTX-M-15, OXA-1, TEM-1	NA	85.6	D226X	E188D, L211I, Y229F, L360P	R2K, I20V, R152K, H162R, S268A, N277S, T287A, A298S, E378D, V440I, I458V, V563I

[a]Abbreviations: *ATM-AVI*, aztreonam-avibactam; *CAZ-AVI*, ceftazidime-avibactam; *MLST*, multilocus sequence typing; *PBP*, penicillin-binding protein; *WT*, wildtype; *NA*, not available

[b]Expression results were reported relative to a control isolate

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Data availability Not required.

Code availability Not required.

Declarations

JMI Laboratories contracted to perform services in 2018–2021 for Achaogen, Inc., Affinity Biosensors, Albany College of Pharmacy and Health Sciences, Allecra Therapeutics, Allergan, Amicrobe Advanced Biomaterials, Inc., American Proficiency Institute, AmpliPhi Biosciences Corp., Amplyx Pharma, Antabio, Arietis Corp., Arixa Pharmaceuticals, Inc., Artugen Therapeutics USA, Inc., Astellas Pharma Inc., Athelas, Becton, Basilea Pharmaceutica Ltd., Bayer AG, Becton, Beth Israel Deaconess Medical Center, BIDMC, bioMerieux, Inc., bioMerieux SA, BioVersys Ag, Boston Pharmaceuticals, Bugworks Research Inc., CEM-102 Pharmaceuticals, Cepheid, Cidara Therapeutics, Inc., Cipla, Contrafect, Cormedix Inc., Crestone, Inc., Curza, CXC7, DePuy Synthes, Destiny Pharma, Dickinson and Company, Discuva Ltd., Dr. Falk Pharma GmbH, Emery Pharma, Entasis Therapeutics, Eurofarma Laboratorios SA, Fedora Pharmaceutical, F. Hoffmann-La Roche Ltd., Fimbrion Therapeutics, US Food and Drug Administration, Fox Chase Chemical Diversity Center, Inc., Gateway Pharmaceutical LLC, GenePOC Inc., Geom Therapeutics, Inc., GlaxoSmithKline plc, Guardian Therapeutics, Hardy Diagnostics, Harvard University, Helperby, HiMedia Laboratories, ICON plc, Idorsia Pharmaceuticals Ltd., IHMA, Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences, KBP Biosciences, Laboratory Specialists, Inc., Luminex, Matrivax, Mayo Clinic, Medpace, Meiji Seika Pharma Co., Ltd., Melinta Therapeutics, Inc., Menarini, Merck & Co., Inc., Meridian Bioscience Inc., Micromyx, Microchem Laboratory, MicuRx Pharmaceutics, Inc., Mutabilis Co., N8 Medical, Nabriva Therapeutics plc, National Institutes of Health, NAEJA-RGM, National University of Singapore, North Bristol NHS Trust, Novartis AG, Novome Biotechnologies, Oxoid Ltd., Paratek Pharmaceuticals, Inc., Pfizer, Inc., Pharmaceutical Product Development, LLC, Polyphor Ltd., Prokaryotics Inc., QPEX Biopharma, Inc., Ra Pharmaceuticals, Inc., Rhode Island Hospital, RIHML, Roche, Roivant Sciences, Ltd., Safeguard Biosystems, Salvat, Scynexis, Inc., SeLux Diagnostics, Inc., Shionogi and Co., Ltd., SinSa Labs, Specific Diagnostics, Spero Therapeutics, Summit Pharmaceuticals International Corp., Super-Trans Medical LT, Synlogic, T2 Biosystems, Taisho Pharmaceutical Co., Ltd., TenNor Therapeutics Ltd., Tetraphase Pharmaceuticals, The Medicines Company, The University of Queensland, Theravance Biopharma, Thermo Fisher Scientific, Tufts Medical Center, Universite de Sherbrooke, University of Colorado, University of Southern California-San Diego, University of Iowa, University of Iowa Hospitals and Clinics, University of North Texas Health Science Center, University of Wisconsin, UNT System College of Pharmacy, URMC, UT Southwestern, VenatoRx, Viosera Therapeutics, Vyome Therapeutics Inc., Wayne State University, Wockhardt, Yukon Pharmaceuticals, Inc., Zai Lab, and Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

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Conflict of interest The authors declare no competing interests.

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