Infection and Drug Resistance

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ORIGINAL RESEARCH

Ceftazidime/Avibactam and Other Commonly Used Antibiotics Activity Against Enterobacterales and *Pseudomonas aeruginosa* Isolated in Poland in 2015–2019

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Purpose: Infections caused by resistant Gram-negative bacteria are becoming increasingly common and now pose a serious public health threat worldwide, because they are difficult to treat due to few treatment options and they are associated with high morbidity and mortality. The combination of ceftazidime with the beta-lactamase inhibitor avibactam – seems to be the right choice in this situation. The aim of the study was to evaluate the activity of ceftazidime/avibactam and other commonly used antibiotics against Enterobacterales and *Pseudomonas aeruginosa* strains isolated within last years in Poland.

Patients and Methods: This study analyzed the antibiotic susceptibility of 1607 Enterobacterales isolates and 543 nonfermenting *P. aeruginosa* strains collected between 2015 and 2019 in 4 medical laboratories participating in the ATLAS (Antimicrobial Testing Leadership And Surveillance) program in Poland. Unduplicated clinically significant Enterobacterales and *P. aeruginosa* strains were collected from patients with respiratory, skin and musculoskeletal, genitourinary, abdominal, bloodstream or other infections (ear, eye).

Results: The ceftazidime/avibactam combination demonstrates the highest activity against Enterobacterales (98.9%), in both adults and children, including strains presenting MDR (multidrug-resistant) (97.5%) and ESBL (extended spectrum β-lactamase) (96.3%) phenotypes. The activity of ceftazidime/avibactam increased to 100% when only MBL (metallo-β-lactamase)-negative subset of Enterobacterales was considered. This combination also achieved the second highest activity result (89.3%) after colistin in *P. aeruginosa*, including isolates of MDR (65.9%) and carbapenem-resistant (CR) phenotypes (54.8%). When MBL-positive isolates were excluded, susceptibility rate of *P. aeruginosa* increased to 94.7%. It is worth to note that susceptibility of the examined *P. aeruginosa* strains to ceftazidime/avibactam was very high in children (93.3%), especially in a pediatric intensive care unit (94.2%).

Conclusion: Enterobacterales and *P. aeruginosa* included in this analysis presented high susceptibility rates to ceftazidime/avibactam. Ceftazidime/avibactam showed the highest activity against Enterobacterales strains among all antibiotics studied, both for the total population as well as for MDR phenotype and ESBL phenotype. Ceftazidime/avibactam also achieved the second highest activity result against *P. aeruginosa* strains (including MDR and CR phenotypes). These results are much higher when excluding MBL-positive isolates that exhibit intrinsic resistance to ceftazidime/avibactam.

Keywords: ceftazidime/avibactam, drug resistance, Gram-negative rods, MDR, ESBL, carbapenem resistance

Introduction

Gram-negative multidrug-resistant (MDR) organisms, defined as resistant to at least one agent in three or more drug classes, cause significant morbidity and mortality, prolonged hospitalization, and increased costs compared with

Received: 4 December 2021
Accepted: 19 February 2022
Published: 25 March 2022

infections caused by susceptible organisms. Infections caused by this group of bacteria require the immediate introduction of effective antimicrobial therapy.[1,2] Antimicrobial resistance of Gram-negative rods can result from a variety of mechanisms, however, production of beta-lactamases is one of the most common mechanisms of resistance observed in this group of bacteria.

Bacteria, such as: *Escherichia coli, Klebsiella pneumoniae* or *Pseudomonas aeruginosa* have varying pathogenic potential. However, any of these bacteria can be responsible for a severe infection, that is refractory to treatment with previously known therapeutic options.[3] The World Health Organization (WHO) has listed the main priorities for the pharmaceutical industry in the search for antibiotics against the currently most resistant pathogens, in particular carbapenem-resistant Enterobacterales (CRE) and *Pseudomonas* spp.[4] CRE has been also described as an "urgent threat", a term formally used to describe the Centers for Disease Control and Prevention's (CDC) highest level of concern to human health. MDR *P. aeruginosa* is classified as a "serious threat" to human health with resistance rates on the rise.[1] The diversity of resistance mechanisms in *P. aeruginosa* make them difficult to eliminate from the hospital environment.[5]

In Poland, a high prevalence of β-lactamase-producing and carbapenem-resistant Gram-negative bacteria is observed. Moreover, Poland, together with Portugal and Slovakia, is one of the countries where a statistically significant increase in carbapenem resistance has been recorded in recent years.[6] In 2015, Gram-negative Enterobacterales and non-fermentative rods were the etiological factor of 35.7% of nosocomial infections in Poland. The main species causing these infections were *E. coli* (37.0% of isolates) and *K. pneumoniae* (36.4% of isolates). Of particular concern, is the high ratio of MDR strains. Gram-negative, non-fermentative strains were the cause of 14.9% of nosocomial infections in Poland, and *P. aeruginosa* had the highest proportion among them (47.7%).[7]

One of the antibiotics available in Poland with the most extensive registered indications and activity against MDR Gram-negative strains is ceftazidime/avibactam. This antibiotic is a combination of a well-known third-generation, broad-spectrum cephalosporin (used for years for numerous indications) with a new beta-lactamase inhibitor. Avibactam effectively inactivates class A (ESBLs [Extended-spectrum beta-lactamases] and KPCs - *K. pneumoniae* carbapenemases), class C (cephalosporinases; AmpCs), and some class D (such as OXA-48 - oxacillinases) β-lactamases.[8,9] Ceftazidime/avibactam is indicated in adults and pediatric patients aged 3 months and older for the treatment of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and is used for the treatment of adult patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above. This antibiotic is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and pediatric patients aged 3 months and older with limited treatment options.[4,10]

The aim of the study was to compare the in vitro activity of the ceftazidime/avibactam and the most commonly used antibiotics in Poland against Enterobacterales and *P. aeruginosa*, using isolates collected by Polish centers participating in the ATLAS (Antimicrobial Testing Leadership and Surveillance) program between 2015 and 2019.

Materials and Methods

Bacterial Isolates

The data presented in this paper has been obtained as part of the ATLAS program, strictly with the project's recommendations. The isolated strains were identified locally and a predefined number of selected bacterial species were collected by each participating center. Isolates were accepted into the study regardless of antimicrobial susceptibility. They were shipped to the central reference laboratory of International Health Management Associates (IHMA) for the further analysis. Non-duplicate, clinically significant Enterobacterales and *P. aeruginosa* strains were collected from patients with respiratory tract, skin and musculoskeletal tissue, genitourinary tract, intra-abdominal, bloodstream or other (ear, eye) infections by 4 centers located in Poland. A total of 1607 isolates of Enterobacterales (*Citrobacter* spp. n=94, *Enterobacter* spp. n=216, *E. coli* n=482, *Klebsiella* spp. n=572, *Morganella* spp. n=43, *Proteus* spp. n=103, *Providencia* spp. n=34, *Raoultella* spp. n=4, *Serratia* spp. n=59) and 543 *P. aeruginosa* strains were collected between 2015 and 2019. A large proportion of isolates (66.3% of Enterobacterales and 63.9% of *P. aeruginosa*) was collected from adults and

approximately 40% were from elderly (>60 years) patients. Most isolates (70.9% of Enterobacterales and 67.4% of *P. aeruginosa*) were from patients located in wards that were not classified as intensive care units (ICU).

The predominant Enterobacterales and *P. aeruginosa* isolates sources were respiratory (24.8% vs 40.3%), genitourinary (27.6% vs 22.7%) and skin or musculoskeletal (23.4% vs 26.3%). Demographic information recorded for each isolate included specimen source, patient age and type of hospital setting.

Antimicrobial Susceptibility Testing and Screening for β-Lactamase Genes

Identification of the isolated strains to the species level were confirmed by the central reference laboratory (IHMA) by mass spectrometry, using MALDI-TOF technique (matrix-assisted laser desorption/ionization time-of-flight) (Bruker Biotyper MALDI-TOF, Bruker Daltonics, Billerica, MA, USA). MIC (minimum inhibitory concentration) assessments were performed by IHMA using broth microdilution method, in accordance with CLSI (Clinical Laboratory Standards Institute) guidelines (CLSI 2018).[11] MIC values were interpreted using breakpoints according to European Committee on Antimicrobial Susceptibility Testing (EUCAST Clinical Breakpoint Tables v. 11.0), where available.

The percent susceptibility (% S) and, if applicable, susceptible with increased exposure (% I) strains, if any, and the minimum and maximum MIC values were analyzed. MIC_{90} values were determined for the antibiotics and chemotherapeutics tested, ie, the lowest concentration of the substances that inhibits the growth of 90% of the strains tested.

Avibactam was tested at a fixed concentration of 4 mg/L in combination with doubling dilutions of ceftazidime. According to EUCAST clinical breakpoints for carbapenems, imipenem MICs were interpreted using different values for *Morganellaceae* only and for Enterobacterales except *Morganellaceae*. Isolates naturally resistant to this antibiotic were excluded from the analysis for colistin. For tigecycline, EUCAST 11.0 recommendations have been applied. MDR was defined as resistance to at least one agent in three or more drug classes: aminoglycosides (amikacin, gentamicin), β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam), monobactams (aztreonam), cephalosporins (cefepime, ceftazidime, ceftazidime/avibactam, ceftolozane/tazobactam), carbapenems (doripenem, imipenem, meropenem), glycylcyclines (tigecycline), fluoroquinolones (levofloxacin) and polymyxins (colistin).[12]

Isolates classified as DTR were defined as those with MICs above the susceptibility breakpoint for cefepime, ceftazidime, imipenem, meropenem, levofloxacin and ciprofloxacin.

Isolates were screened for the presence of genes encoding clinically relevant β-lactamases: carbapenemases (KPC, GES [Guiana extended-spectrum], NDM - New Delhi metallo-β-lactamase, IMP [Imipenemase], VIM - Verona integron-encoded metallo-β-lactamase, OXA-48-like), ESBLs (SHV, CTX-M, VEB), OSBLs [original-spectrum β-lactamase] (TEM and SHV) and plasmid-mediated AmpC β-lactamases (AmpC, CMY, DHA). MBL-positive isolates were identified as those with genes encoding NDM, IMP and VIM enzyme.

The presence of β-lactamase genes was determined using multiplex polymerase chain reaction (PCR) assays and sequencing according to Lob et al[13] and Nichols et al.[14] All detected β-lactamase genes were amplified using flanking primers and sequenced, and sequences were compared against publicly available databases.

Rates of isolates susceptible to ceftazidime/avibactam of subsets with genes encoding MBLs (MBL-positive) and when MBL-positive isolates were excluded (MBL-negative) were also determined.

Results

Enterobacterales

Susceptibility to ceftazidime/avibactam was assessed for 1523 strains including:

- 674 (44.3%) MDR isolates,
- 434 (28.5%) producing ESBL, and
- 23 (1.5%) CRE (carbapenem resistant Enterobacterales) isolates.

MIC values for ceftazidime/avibactam are shown in Figure 1 and Supplementary Table S1.

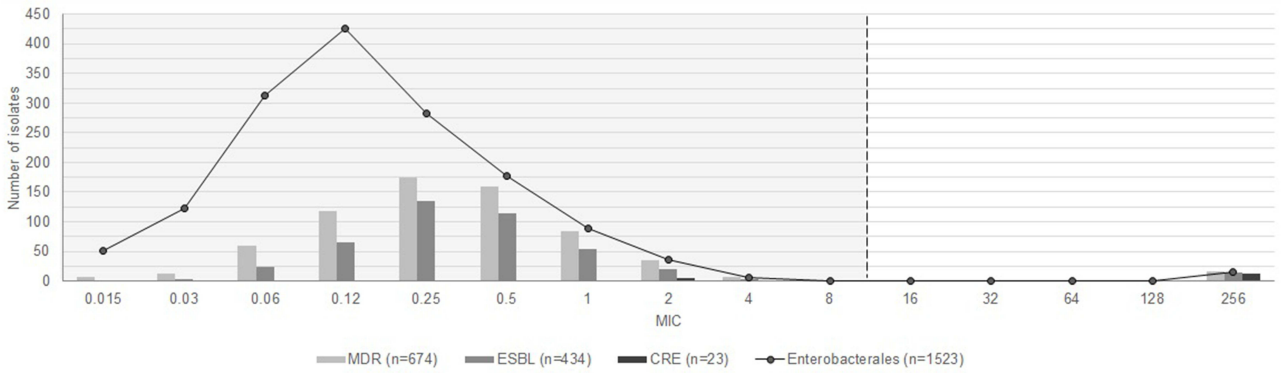

Figure 1 Ceftazidime/avibactam MIC distribution for Enterobacterales (n=1523) by phenotype. The dashed line shows the breakpoint for ceftazidime/avibactam according to EUCAST (EUCAST Clinical Breakpoint Tables v. 11.0). 17 isolates with MIC above the breakpoint was observed, including 1 strain with MIC_{90} = 64 µg/mL and 16 strains with MIC_{90} = 256 µg/mL; all of them were MDR strains, including 16 ESBL producers and 12 CRE.

Almost all Enterobacterales strains tested (98.9%) were susceptible to ceftazidime/avibactam (MIC_{90} = 0.5 µg/mL). A similar high percentage (98.2%) of susceptible strains was found for tigecycline (MIC_{90} = 2 µg/mL). The high activity was observed also for doripenem (MIC_{90} = 0.25 µg/mL), imipenem (MIC_{90} = 1 µg/mL) and meropenem (MIC_{90} = 0.12 µg/mL). Most isolates (97.0%) were also susceptible to colistin (MIC_{90} = 1 µg/mL). The lowest susceptibility of this group of strains was found for aztreonam and levofloxacin. Detailed data on antibiotic susceptibility of Enterobacterales strains are presented in Table 1. When only MBL-negative isolates of Enterobacterales were considered the activity of ceftazidime/avibactam increased substantially up to 100% (MIC_{90} = 0.5 µg/mL) (Table 2).

In general, ceftazidime/avibactam demonstrated the highest antibacterial activity compared to all other antibiotics tested against Enterobacterales strains. Susceptibility rates were similar in each age groups (Supplementary Table S2 and Figure S1). The percentage of susceptibility to ceftazidime/avibactam was superior for children (99.2%), as well as for adults (98.7%), especially elderly patients - 61+ (99.0%). In the elderly patients the highest susceptibility of CRE strains (61.5%) was observed. Very high susceptibility rates for ceftazidime/avibactam were observed also for patients admitted to the intensive care units: 99.2% for adults and 100% for pediatric patients.

Approximately two-thirds of the MDR (65.3%), ESBL-positive Enterobacterales (65.2%) and CRE (66.7%) were isolated from non-ICU patients.

The most common sources of resistant isolates were genital/urinary (MDR 29.8%, ESBL 32.2%, CRE 41.7%) and respiratory (MDR 26.8%, ESBL 29.5%, CRE 25.0%) tract. *K. pneumoniae* isolates were found to be the most prevalent species of those classified as MDR (46.0%), ESBL (67.2%) and CRE (62.5%). Other frequently occurring species were: *E. coli* (20.7% of MDR, 18.3% of ESBL and 8.3% of CRE isolates) and *Enterobacter cloacae* (12.7% of MDR and 5.1% of ESBL).

With respect to the antibiotics included in the analysis, most multidrug-resistant (MDR) Enterobacterales strains were susceptible to ceftazidime/avibactam (observed susceptibility was 97.5% (MIC_{90} = 1 µg/mL)). Relatively high susceptibility rates were also observed for tigecycline, doripenem, colistin, imipenem and meropenem. Susceptibility ratio was the lowest for aztreonam and ceftazidime (Table 1).

The susceptibility rate among the subset of ESBL-positive Enterobacterales strains was the highest for ceftazidime/avibactam (96.3% susceptible, MIC_{90} = 1 µg/mL). Most of these strains were susceptible to tigecycline, colistin, doripenem and imipenem. Less than tenth of strains were susceptible to aztreonam and ceftazidime (Table 1).

Ceftazidime/avibactam showed reduced activity (47.8% susceptible) against 23 CRE isolates. This result is explained by the observation that 52.2% of the meropenem resistant isolates were MBL-positive. CRE strains had the highest susceptibility for colistin (90.9% susceptibility, MIC_{90} = 2 µg/mL).

Table 3 shows the in vitro activity of ceftazidime/avibactam and other commonly used antibiotics against subsets of Enterobacterales isolates, that were molecularly characterized for β-lactamase genes. Ceftazidime/avibactam inhibited 100%

Table 1 In vitro Activity of Ceftazidime/Avibactam and Other Commonly Used Antibiotics Tested Against 1607 Enterobacterales Isolates Collected from 2015 to 2019

Antibacterial	n	% S	% I	MIC_{90}	MIN (μg/mL)	MAX (μg/mL)
Enterobacterales (n=1607)						
Amikacin	1607	94.2	n/a	8	0.25	128
Aztreonam	1523	62.4	2.5	128	0.015	256
Cefepime	1607	65.7	4.3	32	0.12	64
Ceftazidime	1607	62.5	3.7	128	0.015	256
Ceftazidime/avibactam	1523	98.9	n/a	0.5	0.015	256
Ceftolozane/tazobactam[a]	401	87.5	n/a	4	0.06	64
Colistin[b]	1294	97.0	n/a	1	0.06	16
Doripenem[c]	853	97.5	1.1	0.25	0.008	16
Gentamicin[d]	670	76.1	n/a	32	0.12	32
Imipenem[e]	180	n/a	95.0	4	0.12	16
Imipenem[f]	1343	96.7	1.2	1	0.06	16
Levofloxacin	1607	62.5	4.9	16	0.008	16
Meropenem	1607	96.5	2.0	0.12	0.008	32
Piperacillin/tazobactam	1607	70.9	n/a	128	0.12	256
Tigecycline[g]	499	98.2	n/a	2	0.015	8
Enterobacterales MDR (n=691)						
Amikacin	691	87.3	n/a	16	0.25	128
Aztreonam	674	16.6	4.0	256	0.015	256
Cefepime	691	23.9	8.7	64	0.12	64
Ceftazidime	691	17.2	5.6	256	0.015	256
Ceftazidime/avibactam	674	97.5	n/a	1	0.015	256
Ceftolozane/tazobactam[a]	164	69.5	n/a	32	0.06	64
Colistin[b]	626	94.1	n/a	1	0.06	16
Doripenem[c]	340	94.7	2.1	0.5	0.008	16
Gentamicin[d]	334	53.6	n/a	32	0.12	32
Imipenem[e]	42	n/a	85.7	8	0.25	16
Imipenem[f]	632	93.4	2.2	2	0.06	16
Levofloxacin	691	29.7	8.0	16	0.03	16
Meropenem	691	91.9	4.6	2	0.008	32
Piperacillin/tazobactam	691	34.4	n/a	256	0.12	256
Tigecycline[g]	144	95.1	n/a	2	0.06	8

(*Continued*)

Table 1 (Continued).

Antibacterial	n	% S	% I	MIC_{90}	MIN (μg/mL)	MAX (μg/mL)
Enterobacterales ESBL (n=454)						
Amikacin	454	86.8	n/a	16	0.25	128
Aztreonam	434	1.4	4.8	256	0.25	256
Cefepime	454	6.6	4.2	64	0.12	64
Ceftazidime	454	4.0	6.8	256	0.5	256
Ceftazidime/avibactam	434	96.3	n/a	1	0.03	256
Ceftolozane/tazobactam[a]	99	66.7	n/a	64	0.12	64
Colistin[b]	426	93.9	n/a	1	0.06	16
Doripenem[c]	262	93.5	2.7	0.5	0.008	16
Gentamicin[d]	172	45.4	n/a	32	0.12	32
Imipenem[e]	7	n/a	85.7	16	1	16
Imipenem[f]	427	91.1	3.0	2	0.06	16
Levofloxacin	454	17.8	9.9	16	0.03	16
Meropenem	454	89.7	6.0	4	0.015	32
Piperacillin/tazobactam	454	29.3	n/a	256	0.25	256
Tigecycline[g]	83	95.2	n/a	64	1	64
Enterobacterales CRE (n=24)						
Amikacin	24	62.5	n/a	128	0.5	128
Aztreonam	23	8.7	0	256	0.015	256
Cefepime	24	4.2	4.2	64	0.5	64
Ceftazidime	24	4.2	0	256	0.25	256
Ceftazidime/avibactam	23	47.8	n/a	256	0.12	256
Ceftolozane/tazobactam[a]	2	0	n/a	64	64	64
Colistin[b]	22	90.9	n/a	2	0.25	16
Doripenem[c]	6	0	0	16	4	16
Gentamicin[d]	17	47.1	n/a	32	0.25	32
Imipenem[e]	1	n/a	0.0	16	16	16
Imipenem[f]	22	13.6	9.1	16	0.25	16
Levofloxacin	24	4.2	8.3	16	0.25	16
Meropenem	24	0	0	32	16	32
Piperacillin/tazobactam	24	0	n/a	256	64	256
Tigecycline[g]	2	50.0	n/a	2	0.25	8

Notes: [a]Years contributing data: 2017; [b]Enterobacterales species without intrinsic colistin resistance (Enterobacterales without *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Serratia* spp.); [c]Years contributing data: 2015, 2016, 2017; [d]Years contributing data: 2018, 2019; [e]Data only for *Morganellaceae*; [f]Enterobacterales species without *Morganellaceae* (*Morganella* spp., *Proteus* spp. and *Providencia* spp.); [g]Organisms contributing data were: *E. coli, Citrobacter koseri*; S - susceptible (standard dosing regimen); I – susceptible with increased exposure.
Abbreviation: n/a, not applicable.

Table 2 Susceptibility to Ceftazidime/Avibactam for MBL-Positive and MBL-Negative Subsets of Enterobacterales

Organism	Susceptible n (%)	Resistant n (%)
Enterobacterales (n=1523)	1506 (98.9)	17 (1.1)
Enterobacterales MBL-positive (n=18)	1 (5.6)	17 (94.4)
Enterobacterales MBL-negative (n=1505)	1505 (100)	0 (0)

of KPC-2, VEB, OXA-48 and plasmid-mediated AmpC-positive isolates, approximately 98% of SHV-OSBL, TEM-OSBL and CTX-M strains. In children, 100% of SHV-OSBL, TEM-OSBL and CTX-M strains were susceptible to ceftazidime/avibactam. Ceftazidime/avibactam was poorly active (5.6%) against isolates carrying metallo-β-lactamases (VIM, NDM); only tigecycline, colistin and amikacin retained activity against majority of MBL-positive isolates (Tables 2 and 3).

Among 23 isolates of non-susceptible to meropenem Enterobacterales (CRE), most presented more than one resistance mechanism. 14 of isolates were identified as carbapenemase-producing, while in 21 of 23 strains enzymes other than carbapenemases were found: CTX-M (n=17), SHV (n=15) and TEM (n=8). Ceftazidime/avibactam displayed activity against CRE isolates which meropenem-non-susceptibility was conferred primarily by serine carbapenemases: KPC-2 (n=1) and OXA-48 (n=1). A total of 12 CRE isolates identified as MBL were resistant to ceftazidime/avibactam and including NDM (n=8) and VIM (n=4). Among analyzed strains the most frequent producers of MBLs were *K. pneumoniae* (n=6) and *E. cloacae* (n=3).

In this study, a total number of 17 isolates of Enterobacterales resistant to ceftazidime/avibactam were observed (Table 2). All of them were MBL, including NDM-1 (n=7), NDM-5 (n=1), VIM-1 (n=7), VIM-4 (n=1) and VIM-44 (n=1). They were simultaneously resistant to patterns including 6–10 different antibiotics. Among them, 15 isolates showed the coexistence of MBL and other resistance mechanism (ESBL or OSBL).

The most frequent resistant bacteria were *Klebsiella* spp. and *Enterobacter* spp. strains. The antibiotic with the highest susceptibility outcome among ceftazidime/avibactam-resistant Enterobacterales isolates was colistin (82.4% susceptibility).

Pseudomonas aeruginosa

Susceptibility to ceftazidime/avibactam was assessed for 523 strains including:

- 164 (31.4%) MDR isolates,
- 96 (18.4%) DTR (difficult-to-treat) isolates, and
- 93 (17.8%) CR (carbapenem-resistant) isolates.

A detailed summary of MIC values is shown in Figure 2 and Supplementary Table S3.

High proportion of *P. aeruginosa* strains tested (89.3%) were susceptible to ceftazidime with avibactam (MIC_{90} = 16 µg/mL). It was the second highest antibiotic activity among all analyzed in this study (Table 4). When MBL-positive isolates were removed from this latter set, the activity of ceftazidime/avibactam increased spectacularly to 94.7% (MIC_{90} = 8 µg/mL) (Table 5).

The highest percentage of susceptible strains (99.4%) was found for colistin (MIC_{90} = 2 µg/mL). 87.8% of the isolates (MIC_{90} = 64 µg/mL) were susceptible to ceftolozane/tazobactam (data limited to one year), 87.5% were susceptible to amikacin (MIC_{90} = 64 µg/mL) and 82.0% (including 12.2% susceptible with increased exposure) to meropenem (MIC_{90} = 16 µg/mL). *P. aeruginosa* strains were classified as susceptible only with increased exposure to the following antibiotics: aztreonam, cefepime, ceftazidime, doripenem, imipenem, levofloxacin and piperacillin/tazobactam (susceptibility range: 60.4–74.6%). Detailed data on antibiotic susceptibility of *P. aeruginosa* strains are presented in Table 4.

https://doi.org/10.2147/IDR.S344165 DovePress

Table 3 In vitro Activity of Ceftazidime/Avibactam and Other Commonly Used Antibiotics Tested Against Enterobacterales Isolates (n=1607) Collected from 2015 to 2019, Stratified by Genome (Ambler Classification of β-Lactamases)

Antibacterial	Class A												Class B				Class C						Class D	
	CTX-M (n=376)		SHV-12* (n=9)		KPC-2 (n=2)		VEB (n=2)		SHV-OSBL (n=303)		TEM-OSBL (n=287)		VIM (n=10)		NDM (n=8)		AmpC (n=6)		CMY (n=7)		DHA (n=24)		OXA-48 (n=8)	
	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I	% S	% I
Amikacin	86.4	n/a	77.8	n/a	50	n/a	0	n/a	88.5	n/a	84.7	n/a	90	n/a	62.5	n/a	66.7	n/a	100	n/a	75	n/a	37.5	n/a
Aztreonam	0	2.9	0	0	0	0	0	0	2.3	2	0.4	1.7	0	0	12.5	0	33.3	0	14.3	0	4.2	8.3	0	0
Cefepime	0.5	2.7	11.1	0	0	0	0	0	4.3	1	1.1	1.7	10	0	0	0	33.3	0	71.4	0	12.5	4.2	0	0
Ceftazidime	2.9	5.6	0	0	0	0	0	0	0.7	2.6	1.7	3.5	0	0	0	0	0	0	0	0	0	0	0	0
Ceftazidime/avibactam	97.6	n/a	33.3	n/a	100	n/a	100	n/a	98.4	n/a	98.6	n/a	10	n/a	0	n/a	100	n/a	100	n/a	100	n/a	100	n/a
Ceftolozane/tazobactam[a]	67.4	n/a	0	n/a	0	n/a	–	–	61.3	n/a	59.7	n/a	0	n/a	–	–	–	–	50	n/a	40	n/a	0	n/a
Colistin[b]	93.6	n/a	100	n/a	50	n/a	–	–	91.4	n/a	92.6	n/a	88.9	n/a	87.5	n/a	80	n/a	100	n/a	87.5	n/a	87.5	n/a
Doripenem[c]	94.7	2.4	33.3	16.7	0	0	–	–	93.5	3	94	3	14.3	14.3	–	–	–	–	100	0	93.3	0	0	75
Gentamicin[d]	45.8	n/a	33.3	n/a	100	n/a	0	n/a	48.2	n/a	38.8	n/a	33.3	n/a	50	n/a	33.3	n/a	66.7	n/a	22.2	n/a	25	n/a
Imipenem[e]	n/a	100	n/a	0	–	–	n/a	100	–	–	n/a	100	n/a	0	–	–	n/a	100	n/a	100	–	–	–	–
Imipenem[f]	91.7	2.9	37.5	12.5	0	0	–	–	91.8	3	93.7	2.8	11.1	11.1	0	0	40	0	66.7	16.7	75	0	37.5	50
Levofloxacin	15.2	9	22.2	22.2	0	0	0	0	13.2	9.6	13.9	10.5	10	40	0	0	0	0	28.6	0	0	0	0	0
Meropenem	88.8	6.7	55.6	11.1	0	50	100	0	87.8	8.3	90.9	6.3	30	30	0	0	50	50	71.4	28.6	75	25	50	37.5
Piperacillin/tazobactam	27.7	n/a	22.2	n/a	0	n/a	100	n/a	17.8	n/a	23	n/a	0	n/a	0	n/a	50	n/a	42.9	n/a	16.7	n/a	0	n/a
Tigecycline[g]	97.1	n/a	100	n/a	–	–	–	–	100	n/a	96.3	n/a	–	–	100	n/a	–	–	100	n/a	–	–	–	–

Notes: *Coexistence of other resistance mechanisms is highly probable; [a]Years contributing data: 2017; [b]Enterobacterales species without intrinsic colistin resistance (Enterobacterales without *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Serratia* spp.); [c]Years contributing data: 2015, 2016, 2017; [d]Years contributing data: 2018, 2019; [e]Data only for Morganellaceae; [f]Enterobacterales species without Morganellaceae (*Morganella* spp., *Proteus* spp. and *Providencia* spp.); [g]Organisms contributing data were: *E. coli, Citrobacter koseri*; S - susceptible (standard dosing regimen); I – susceptible with increased exposure.

Abbreviation: n/a, not applicable.

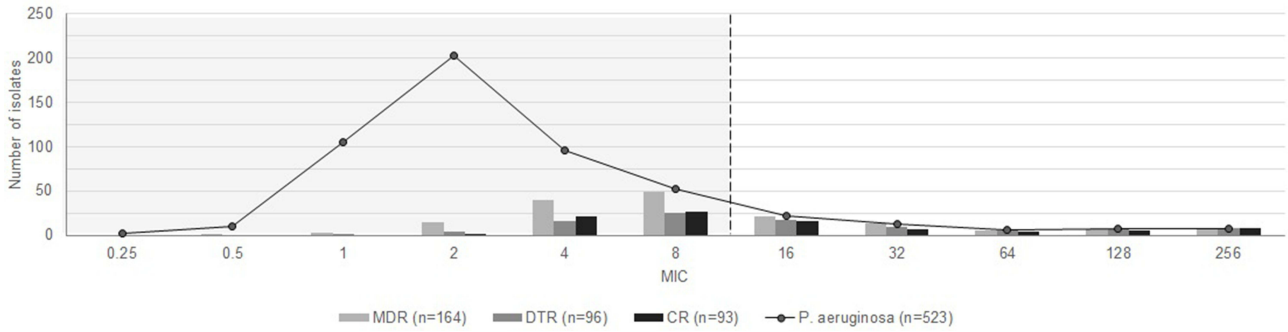

Figure 2 Ceftazidime/avibactam MIC distribution for *P. aeruginosa* (n=523) by phenotype. The dashed line shows the breakpoint for ceftazidime/avibactam according to EUCAST (EUCAST Clinical Breakpoint Tables v. 11.0). 56 isolates with MIC above the breakpoint was observed, among them 56 were MDR, 48 - DTR and 42 - CR.

Some differences in *P. aeruginosa* susceptibility to ceftazidime/avibactam was observed between age groups (Figure 3 and Supplementary Table S4). The percent susceptibility was highest for children (93.3%), specifically in a pediatric intensive care unit (94.2%). For adults this value was 86.9% (and 86.7% in adult intensive care unit).

More than a half of the MDR (53.8%), DTR (56.4%), and CR (52.0%) isolates of *P. aeruginosa* were obtained from patients who were treated in non-intensive care units. The most common sources of isolates were the respiratory tract (52.5% of MDR, 56.4% of DTR, 60.2% of CR), genitourinary tract (15.4% of MDR, 12.9% of DTR, 12.2% of CR) and skin and musculoskeletal tissue (17.8% of MDR, 11.9% of DTR, 8.2% of CR).

Overall, 65.9% of MDR *P. aeruginosa* strains were susceptible to ceftazidime/avibactam (MIC_{90} = 64 µg/mL). Ceftazidime/avibactam remained the second most effective agent, after colistin (98.8% susceptibility, MIC_{90} = 2 µg/mL), regarding MDR *P. aeruginosa*. The percentages of isolates susceptible to ceftolozane/tazobactam (60.5% susceptibility, MIC_{90} = 64 µg/mL; data limited) and amikacin (60.4% susceptibility, MIC_{90} = 128 µg/mL) were slightly lower than the percentage of susceptibility to ceftazidime/avibactam observed for these strains. Only 46.2% of strains were susceptible to meropenem (in this 17.8% susceptible with increased exposure).

One-half of DTR *P. aeruginosa* strains were susceptible to ceftazidime/avibactam (MIC_{90} = 128 µg/mL). Analyzed DTR strains had the highest susceptibility for colistin (100% susceptibility, MIC_{90} = 2 µg/mL). Only 5.9% of DTR strains were susceptible to meropenem in standard dosing regimen, and 22.8% - with increased exposure.

Out of the CR *P. aeruginosa* strains, 54.8% (69.2% for children and 49.3% for adults) were susceptible to ceftazidime/avibactam. CR strains had the highest susceptibility for colistin (100% susceptibility, MIC_{90} = 2 µg/mL). 57.1% of isolates were susceptible to ceftolozane/tazobactam (data limited) and 52.0% of isolates were susceptible to amikacin.

In most cases, *P. aeruginosa* resistance was probably caused by non-enzymatic mechanisms or coexisting several resistance mechanisms. There were 35 isolates of *P. aeruginosa* that were screened for β-lactamase genes. Of these, 32 isolates were identified as MBLs (VIM-1, VIM-2, VIM-16, IMP-1). MBLs of the VIM type were the most frequently identified carbapenemases (84.4%). Ceftazidime/avibactam showed reduced activity against isolates carrying MBLs (6.3% susceptibility). These subsets of *P. aeruginosa* strains were susceptible for colistin (100% susceptibility).

Among 93 of non-susceptible to carbapenems/meropenem *P. aeruginosa* (CR *P. aeruginosa*), 30 isolates were identified as carbapenemase-producing (MBL-positive: VIM-1 (n=1), VIM-16 (n=1), VIM-2 (n=23), IMP-1 (n=5)), while 3 of 93 were found to be ESBLs belonging to the Ambler class A (GES-1 (n=1), VEB-9 (n=2)). 64.5% of isolates (n=60) contained non-enzymatic resistance mechanisms.

A total of 56 ceftazidime/avibactam-resistant *P. aeruginosa* isolates (10.7% of all isolates) were identified in this study (Table 5). All of them were simultaneously resistant to patterns including 5–11 different antibiotics. Among ceftazidime/avibactam-non-susceptible *P. aeruginosa*, 41.1% of isolates (n=23) contained non-enzymatic resistance mechanisms; 30 isolates were identified as carbapenemase-producing (VIM-2 was the most common carbapenemases, n=23) and 3 as non-carbapenemase-producing.

Table 4 In vitro Activity of Ceftazidime/Avibactam and Other Commonly Used Antibiotics Tested Against 543 *Pseudomonas aeruginosa* Isolates Collected from 2015 to 2019

Antibacterial	n	% S	% I	MIC_{90}	MIN (μg/mL)	MAX (μg/mL)
***P. aeruginosa* (n=543)**						
Amikacin	543	87.5	n/a	64	0.25	128
Aztreonam	523	n/a	74.6	32	0.25	256
Cefepime	543	n/a	74.6	32	0.12	64
Ceftazidime	543	n/a	71.5	64	0.5	256
Ceftazidime/avibactam	523	89.3	n/a	16	0.25	256
Ceftolozane/tazobactam[a]	123	87.8	n/a	64	0.25	64
Colistin	523	99.4	n/a	2	0.25	16
Doripenem[b]	262	n/a	73.3	16	0.06	16
Gentamicin[c]	261	n/a	n/a	32	0.12	32
Imipenem	523	n/a	68.1	16	0.25	16
Levofloxacin	543	n/a	60.4	16	0.12	16
Meropenem	543	69.8	12.2	16	0.06	32
Piperacillin/tazobactam	543	n/a	69.4	128	0.12	256
Tigecycline[d]	543	n/a	n/a	16	0.25	16
***P. aeruginosa* MDR (n=169)**						
Amikacin	169	60.4	n/a	128	1	128
Aztreonam	164	n/a	29.3	64	4	256
Cefepime	169	n/a	24.3	64	4	64
Ceftazidime	169	n/a	18.3	128	2	256
Ceftazidime/avibactam	164	65.9	n/a	64	0.5	256
Ceftolozane/tazobactam[a]	38	60.5	n/a	64	0.5	64
Colistin	164	98.8	n/a	2	0.25	16
Doripenem[b]	74	n/a	31.1	16	0.25	16
Gentamicin[c]	90	n/a	n/a	32	0.25	32
Imipenem	164	n/a	31.1	16	0.5	16
Levofloxacin	169	n/a	18.9	16	0.25	16
Meropenem	169	28.4	17.8	32	0.25	32
Piperacillin/tazobactam	169	n/a	11.8	256	8	256
Tigecycline[d]	169	n/a	n/a	16	0.5	16
***P. aeruginosa* DTR (n=101)**						
Amikacin	101	47.5	n/a	128	1	128
Aztreonam	96	n/a	36.5	64	4	256

(*Continued*)

Table 4 (Continued).

Antibacterial	n	% S	% I	MIC_{90}	MIN (μg/mL)	MAX (μg/mL)
Cefepime	101	n/a	12.9	64	8	64
Ceftazidime	101	n/a	6.9	256	4	256
Ceftazidime/avibactam	96	50.0	n/a	128	1	256
Ceftolozane/tazobactam[a]	23	43.5	n/a	64	1	64
Colistin	96	100	n/a	2	0.25	2
Doripenem[b]	39	n/a	5.1	16	0.5	16
Gentamicin[c]	57	n/a	n/a	32	0.25	32
Imipenem	96	n/a	9.4	16	1	16
Levofloxacin	101	n/a	0	16	2	16
Meropenem	101	5.9	22.8	32	0.5	32
Piperacillin/tazobactam	101	n/a	6.9	256	8	256
Tigecycline[d]	101	n/a	n/a	16	0.5	16
***P. aeruginosa* CR (n=98)**						
Amikacin	98	52.0	n/a	128	1	128
Aztreonam	93	n/a	34.4	64	4	256
Cefepime	98	n/a	27.6	64	4	64
Ceftazidime	98	n/a	26.5	256	4	256
Ceftazidime/avibactam	93	54.8	n/a	128	2	256
Ceftolozane/tazobactam[a]	28	57.1	n/a	64	0.5	64
Colistin	93	100	n/a	2	0.5	2
Doripenem[b]	48	n/a	0	16	4	16
Gentamicin[c]	45	n/a	n/a	32	0.25	32
Imipenem	93	n/a	1.1	16	4	16
Levofloxacin	98	n/a	13.3	16	0.25	16
Meropenem	98	0	0	32	16	32
Piperacillin/tazobactam	98	n/a	19.4	256	8	256
Tigecycline[d]	98	n/a	n/a	16	0.5	16

Notes: [a]Years contributing data: 2017; [b]Years contributing data: 2015, 2016, 2017; [c]Years contributing data: 2018, 2019, no breakpoint has been established; [d]no breakpoint has been established; S - susceptible (standard dosing regimen); I – susceptible with increased exposure.
Abbreviation: n/a, not applicable.

Discussion

According to recent estimates based on data from EARS-Net, more than 670,000 infections due to antibiotic-resistant bacteria occur annually in the EU/EEA and about 33,000 people die directly as a result of these infections. The associated costs to the healthcare systems of EU/EEA countries amount to approximately €1.1 billion.[15] Infections caused by resistant Gram-negative bacteria are becoming increasingly common and are now a serious public health threat worldwide, as they are difficult to treat and are associated with high morbidity and mortality rates.[16] According to the EARS-

Table 5 Susceptibility to Ceftazidime/Avibactam for MBL-Positive and MBL-Negative Subsets of *P. aeruginosa*

Organism	Susceptible n (%)	Resistant n (%)
P. aeruginosa (n=523)	467 (89.3)	56 (10.7)
P. aeruginosa MBL-positive (n=32)	2 (6.3)	30 (93.8)
P. aeruginosa MBL-negative (n=491)	465 (94.7)	26 (5.3)

Net data for 2019, the most commonly reported bacterial species was *E. coli* (44%), followed by *K. pneumoniae* (11%) and *P. aeruginosa* (6%). In EU/EEA countries carbapenem resistance was prevalent in *P. aeruginosa*, at a higher ratio than in *K. pneumoniae*. The widespread of beta-lactamases conferring resistance to carbapenem has left physicians and patients with very few treatment options. The combination of ceftazidime with the beta-lactamase inhibitor - avibactam appears to be a promising therapeutic option.

In this study, we report in vitro antimicrobial susceptibility rates for ceftazidime/avibactam and other commonly used antibiotics to a collection of clinical isolates of Enterobacterales and *P. aeruginosa* from Poland. Susceptibility to ceftazidime/avibactam was highest for all Enterobacterales isolates, and similar susceptibility rates were observed for MDR and ESBL phenotypes. Nearly 99% of the strains tested were sensitive to this combination. This high activity was also observed regardless of age group and in patients admitted to the ICU. The results reported in our study are similar to the susceptibility rates observed for ceftazidime/avibactam in Enterobacterales isolates collected across Europe between 2012 and 2016 in the INFORM study. In this study also ceftazidime/avibactam was most effective against all Enterobacterales (98% susceptibility).[17] This trend continued in Kaye et al[16] another multinational study that evaluated the in vitro activity of ceftazidime/avibactam and comparators against Enterobacterales isolates from Central Europe and Israel in 2014–2017 and 2018. The susceptibility rates of Enterobacterales to ceftazidime/avibactam were highest in Central Europe (≥99%) and in Poland (almost 100%). Our study, with a susceptibility rate of almost 99% to ceftazidime/avibactam, is consistent with the sustained trend of high activity of this antibiotic combination observed over the years in Central Europe and Poland. Moreover, ceftazidime/avibactam achieved similar high activity in an American 4-year study by Sader et al[1] where it inhibited 99.9% of all Enterobacterales.[1]

In our analysis, 28% of Enterobacterales isolates were identified as ESBL producers and 44% as MDR isolates. Ceftazidime/avibactam achieved the highest activity against them with susceptibility of 96.3% and almost 97.5%, respectively. *K. pneumoniae* isolates were among the most abundant organisms (46% of MDR and 67% of ESBL isolates) in these phenotypes. The same trend of high ceftazidime/avibactam susceptibility is maintained in the study by Kristof et al[18] based on Central Europe, where MDR Enterobacterales had a susceptibility of almost 99% in Poland and 98% in all included countries. Similar results were obtained in the USA according to Hirsch et al, where ceftazidime/

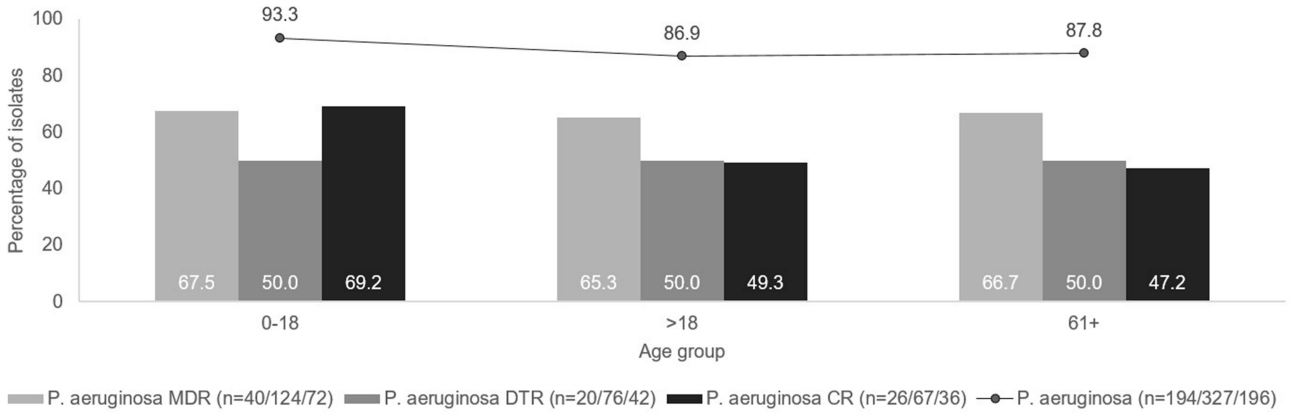

Figure 3 Antimicrobial susceptibility (*P. aeruginosa*) to ceftazidime/avibactam stratified by age.

avibactam showed the highest activity against ESBL Enterobacterales with 92% susceptibility.[19] The above confirms the consistently high activity of ceftazidime/avibactam against this group of bacteria.

According to our analysis, 47.8% of meropenem-resistant isolates (CRE) were susceptible to ceftazidime/avibactam, which was the third highest susceptibility result. This result is explained by the observation that 52% of the meropenem-resistant isolates were MBL-positive, which have innate resistance to this antibiotic combination. Among CRE isolates, most had more than one resistance mechanism: 61% of isolates were identified as carbapenemase-producing (14.3% susceptible) and 91% as non-carbapenemase-producing (47.6% susceptible). In the study by Spiliopoulou et al[18] that examined Enterobacterales collected worldwide from 2015 to 2017 as part of the surveillance program INFORM, a total of 1460 meropenem non-susceptible isolates were collected and 73% of them were susceptible to ceftazidime/avibactam. This is due to the fact that only 27% of the isolates were MBL-positive, whereas this rate was almost double in our study. Among the isolates identified as carbapenemase-positive and MBL-negative or carbapenemase-negative and MBL-negative, susceptibility to ceftazidime/avibactam was highest (almost 100% and 96%, respectively).[20] In our study, MBL-negative and carbapenemase-positive MBL-negative Enterobacterales isolates had similar susceptibility (100%), which consisted of 100% susceptibility of KPC−2, VEB, OXA-48, and plasmid-mediated AmpC-positive isolates and about 98% susceptibility of SHV-OSBL, TEM-OSBL, and CTX-M strains.

According to our analysis, ceftazidime/avibactam was the antibiotic with the second highest susceptibility outcome against *P. aeruginosa* among all antibiotics analyzed (89.3% susceptible), just after colistin. The susceptibility rate for ceftazidime/avibactam increased to 94.7% when only MBL-negative isolates of *P. aeruginosa* were considered. Ceftazidime/avibactam also retained the second highest activity among all antibiotics, just after colistin, in the MDR phenotype and third in CR phenotype. However, colistin due to its potential nephrotoxicity and neurotoxicity has limited use in its intravenous form. This antibiotic is mainly used as a rescue therapy in the treatment of life-threatening infections[21] but according to the IDSA guidance colistin should be considered only as an alternate for treating DTR-*P. aeruginosa* cystitis.[22]

A similar trend of activity to *P. aeruginosa* was confirmed by Kristof et al[16] (Central Europe and Israel, 2014–2018). The susceptibility rates of *P. aeruginosa* to ceftazidime/avibactam were second highest in Central Europe (≥92%) and Poland (92%).[18] Our study with a susceptibility rate of almost 90% to ceftazidime/avibactam is consistent with the sustained trend of high activity of this antibiotic combination observed over years in Central Europe and Poland. In the study by Sader et al[1] an American 4-year study, ceftazidime/avibactam also achieved the second highest activity against *P. aeruginosa* isolates among all agents. Ceftazidime/avibactam showed potent activity (97% susceptible), including MDR isolates (87% susceptible), which was higher than in our study. However, the study does not report the percentage of MBL-positive isolates which might affect the susceptibility to ceftazidime/avibactam. In the study INFORM, based on data from 2012 to 2016, ceftazidime/avibactam (92% susceptibility) was the second most effective agent against isolates of *P. aeruginosa*. The susceptibility of MDR isolates was ≤54% to all agents except colistin (95% susceptible) and ceftazidime/avibactam (68%). A subset of *P. aeruginosa* isolates was identified as ESBL-positive, and less than 10% of them were susceptible to all agents except ceftazidime/avibactam or colistin.[23]

In our study, the susceptibility of *P. aeruginosa* strains to ceftazidime/avibactam was high in children (93.3%), especially in a pediatric intensive care unit (94%). This was lower in adults (>18) with susceptibility of 86.9% and in patients over 61 years of age with susceptibility of 87.8%. Susceptibility rates decreased significantly with age for all agents except colistin. In the study by Sader et al[24] based on data from INFORM from 2011 to 2015, ceftazidime/avibactam achieved very high activity against isolates from pediatric patients with susceptibility of 99%. Ceftazidime/avibactam activity against 6209 *P. aeruginosa* isolates from adult patients (≥18 years old) was lower, with susceptibility of 97%.

Among meropenem-resistant *P. aeruginosa* strains identified in our study, 54.8% of isolates were susceptible to ceftazidime/avibactam. The analysis showed that 65% of CR *P. aeruginosa* likely had a non-enzymatic resistance mechanism.

In the study by Sader et al[1], ceftazidime/avibactam retained the second highest activity against *P. aeruginosa* isolates that were not susceptible to meropenem with 55% susceptibility, which is a similar result to our study. In the study INFORM, based on data from 2012 to 2016, 2975 isolates were non-susceptible to meropenem, in which no β-lactamase was detected by PCR screening. The susceptibility rate for ceftazidime/avibactam for this subgroup was 88%.[23]

According to the study by Nichols et al,[14] based on data from INFORM from 2012 to 2014, the percentage of susceptibility to ceftazidime/avibactam among meropenem-non-susceptible isolates was 72%, of which 15.6% MBL-positive. This susceptibility increased to 85% when isolates with MBL genes were excluded. This result is much higher than in our study, where 55% of isolates were susceptible to ceftazidime/avibactam. The likely cause of this difference is the high proportion of MBL-positive isolates in our analysis (32%) showing innate resistance to this antibiotic combination.

Importantly, from the prevalence point of view, most of the strains analyzed in our study, including resistant ones, were isolated outside the ICU (Enterobacterales - 70.9%/CRE - 66.7%; *P. aeruginosa* - 67.4%/CR - 52.0%). A similar observation was made by Gill et al, in the study based on ERACE-PA Global Surveillance Program (2019–2021), stating that it might have an impact on appropriate empiric therapy for the non-ICU patient population, where early treatment active against carbapenem-resistant strains should be considered.[25] Due to the involvement of the Central Laboratory in the study, the data obtained are of high quality, but there are some limitations to the current analysis. These limitations include: no information on prior antibiotic therapy, hospitalizations, and nursing home stays in patients from whom material was acquired. In addition, the specified number of isolates was collected from each center, so our observations of susceptibility rates cannot be interpreted as epidemiologic reports and the data for some antibiotics cover only a few years of the period studied. The material for the study also came from only four Polish centers, so the data may not be representative of the whole country. These factors may influence the results obtained.

This publication is consistent with the concept of antibiotic stewardship, which aims to optimize antimicrobial therapy in hospitalized patients to ensure cost-effective therapy and improve patient outcomes while curbing bacterial resistance. Relatively high rates of MDR and carbapenem-resistant strains demonstrate the need for continued surveillance to identify regional and local trends in antimicrobial resistance.

Conclusion

In conclusion, susceptibility rates to ceftazidime/avibactam in Poland appear to be high among the isolates of Enterobacterales and *P. aeruginosa* collected in this analysis. Ceftazidime/avibactam showed the highest activity against Enterobacterales strains among all antibiotics studied, equally for the total population, MDR phenotype and ESBL phenotype. Ceftazidime/avibactam also achieved the second highest activity result against *P. aeruginosa* strains, including MDR and CR phenotypes. These results are much higher after exclusion of MBL-positive isolates showing intrinsic resistance to ceftazidime/avibactam.

Our observations support the persistence of high ceftazidime/avibactam activity against pathogenic strains of Enterobacterales and *P. aeruginosa*, including those carrying different types of antibiotic resistance.

Abbreviations

AmpC, ampicillinase C; ATLAS, Antimicrobial Testing Leadership and Surveillance; CDC, Center for Disease Control and Prevention; cIAI, complicated intra-abdominal infections; CLSI, Clinical Laboratory Standards Institute; CR, carbapenem resistant; CRE, carbapenem resistant Enterobacterales; cUTI, complicated urinary tract infections; DBO, diazabicyclooctanes; DTR, difficult-to-treat; ESBL, extended spectrum β-lactamase; EUCAST, European Committee at Antimicrobial Susceptibility Testing; GES, Guiana extended-spectrum; HAP, hospital-acquired pneumonia; HGT, horizontal gene transfer; IHMA, International Health Management Associates;, IMP, Imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MDR, multidrug resistant; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; PBP, Penicillin-binding proteins; SHV-OSBL, Original-spectrum β-lactamase, VAP, respiratory pneumonia; VIM, Verona integron-encoded metallo-β-lactamase.

Ethical Approval

The study was exempt from Institutional Review Boards approval as it is a non-patient-based antimicrobial surveillance study, and it follows the policies and guidelines from the ATLAS database managed by International Health Management Associates (IHMA). Informed Consent is not a requirement of surveillance initiatives due to the lack of direct involvement or monitoring of specific patients in the program.

Disclosure

P. Zalas-Więcek, M. Prażyńska, D. Żabicka, M. Orczykowska-Kotyna, and A. Polak report grants from International Health Management Associates, Inc (IHMA), during the conduct of the study and outside the submitted work. M. Prażyńska, Ł. Pojnar report personal fees from Pfizer Polska Sp. z o.o., outside the submitted work. B. Możejko-Pastewka, M. Bogiel, and EA. Głowacka are employees of Pfizer Polska Sp. z o.o. I. Pieniążek, M. Pawlik, and M. Grys are affiliated with Arcana Institute, a Certara company that provided medical writing support funded by Pfizer Polska Sp. z o.o. The authors report no other conflicts of interest in this work.

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