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Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents Against OXA-48 β-lactamase–Producing *Enterobacterales* Collected in International Medical Centers, Including in the United States, in 2017–2019

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CONCLUSION

This in vitro susceptibility study demonstrated that CAZ-AVI was the most effective agent when compared with other antibiotics, including β-lactams, β-lactam–β-lactamase inhibitor combinations, and aminoglycosides against OXA-48–producing *Enterobacterales* carrying multiple β-lactamases

RESULTS

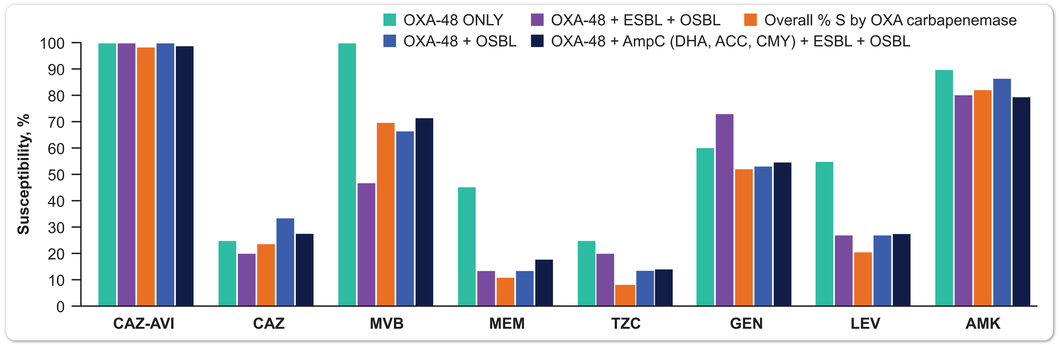
Antimicrobial activity of CAZ-AVI and comparators against 113 *Enterobacterales* producing OXA-48 alone or co-harboring with other β-lactamases (Table 1, Figures 1 and 2)

- Of 113 OXA-48 carbapenemase-producing clinical isolates, 20 isolates carried OXA-48 alone
- The remaining 93 isolates carried additional β-lactamases, including 61 with ESBL (CTX-M, SHV) + OSBL (SHV, TEM), 17 with AmpC (DHA, ACC, CMY) + ESBL (CTX-M), and 15 with OSBL (SHV, TEM)
- All isolates tested except one were susceptible to CAZ-AVI (99.1%), whereas 71.7%, 17.7%, and 14.2% were susceptible to MVB, MEM, and TZC, respectively
- Among isolates (n=61) harboring multiple resistant mechanisms (OXA-48 + ESBL + OSBL), 98.4%, 68.9%, 8.2%, and 4.9% were susceptible to CAZ-AVI, MVB, MEM, and TZC, respectively
- Among isolates (n=15) carrying OXA-48 + AmpC + ESBL + OSBL, 100% were susceptible to CAZ-AVI, 46.7% to MVB, 13.3% to MEM, and 20.0% to TZC
- Aminoglycosides (AMK and GEN) and other β-lactams (eg, CAZ) were 20%–90% active against these isolates

CAZ-AVI activity against OXA-48–produced *Enterobacterales* stratified by species (Table 2)

- CAZ-AVI was highly active against all OXA-48–producing *Enterobacterales*, including *Enterobacter* spp (n=19; 50%/90% minimum inhibitory concentration [$MIC_{50/90}$], 0.5/4 mg/L), *Escherichia coli* (n=11; $MIC_{50/90}$, 0.5/1 mg/L), and *Klebsiella* spp (n=79; $MIC_{50/90}$, 0.5/2 mg/L)
- CAZ-AVI was the only antibiotic with >90% susceptibility rate against OXA-48–producing *E coli* and *Klebsiella* spp

Figure 1. In Vitro Susceptibility of CAZ-AVI and Comparator Agents Tested Against *Enterobacterales* Producing OXA-48 Alone or in Combination With Other Resistance Mechanisms



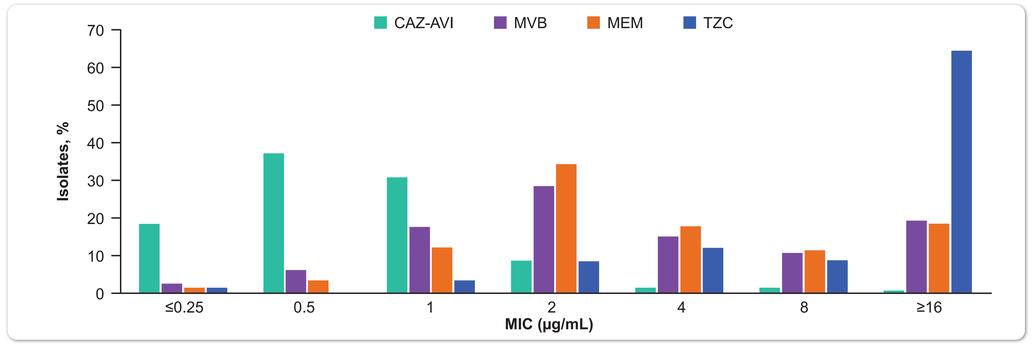
% S, percentage susceptibility; AMK, amikacin; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; ESBL, extended spectrum β-lactamase; GEN, gentamicin; LEV, levofloxacin; MEM, meropenem; MVB, meropenem-vaborbactam; OSBL, original spectrum β-lactamases; TZC, ceftolozane-tazobactam

Table 1. Antimicrobial Activity (% Susceptibility) of CAZ-AVI and Comparator Agents Tested Against 113 *Enterobacterales* Producing OXA-48 Alone or Co-harboring With Other β-lactamases

Resistance Mechanisms (Number of Isolates)	CAZ-AVI	CAZ	MVB	MEM	TZC	GEN	LEV	AMK
OXA-48 only (n=20)	100	25.0	100	45.0	25.0	60.0	55.0	90.0
OXA-48 + OSBL (n=15)	100	20.0	46.7	13.3	20.0	73.3	26.7	80.0
OXA-48 + SHV-OSBL (n=10)								
OXA-48; SHV or TEM-OSBL(n=5)								
OXA-48 + ESBL + OSBL (n=61)	98.4	18.0	68.9	8.2	4.9	50.8	18.0	82.0
OXA-48; CTX-M-15; SHV or TEM-OSBL (n=44)								
OXA-48; CTX-M-9; SHV-12 (n=11)								
OXA-48; CTX-M-9,14,15,55 (n=6)								
OXA-48 + AmpC (DHA, ACC, CMY) + ESBL + OSBL (n=17)	100	41.2	64.7	11.8	11.8	52.9	52.9	88.2
OXA-48, CTX-M-15; CMY-6 or DHA-1; TEM or SHV-OSBL; (n=9)								
OXA-48; DHA-1,21 or CMY-16,42 (n=6)								
OXA-48; ACC; TEM or SHV-OSBL (n=2)								
Overall % S by OXA carbapenemase (n=113)	99.1	27.4	71.7	17.7	14.2	54.9	27.4	79.6

% S, percentage susceptibility; AMK, amikacin; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; ESBL, extended spectrum β-lactamase; GEN, gentamicin; LEV, levofloxacin; MEM, meropenem, MVB, meropenem-vaborbactam; OSBL, original spectrum β-lactamases; TZC, ceftolozane-tazobactam.

Figure 2. MIC Distribution of CAZ-AVI and Comparator Agents Against *Enterobacterales* Producing OXA-48 Alone, or in Combination With Other Resistance Mechanisms



CAZ-AVI, ceftazidime-avibactam; MEM=meropenem; MIC, minimum inhibitory concentration; MVB, meropenem-vaborbactam; TZC, ceftolozane-tazobactam.

Table 2. Antimicrobial Activity of CAZ-AVI and Comparator Agents Tested Against *Enterobacterales* Stratified by Species

Pathogen (Number of Isolates)	CAZ-AVI	CAZ	MVB	MEM	TZC	GEN	LEV	AMK
Enterobacter spp (*E cloacea, E kobei;* n=19)								
MIC_{50}, mg/L	0.5	32	2	2	16	8	16	2
MIC_{90}, mg/mL	2	>64	4	4	>64	>32	>16	8
MIC, range	0.06–8	0.06–>64	1–16	1–16	0.5–>64	0.25–>32	0.5–>16	0.5–16
Escherichia coli (n=11)								
MIC_{50}, mg/L	0.5	64	2	2	16	8	8	8
MIC_{90}, mg/mL	1	>64	32	32	>64	>32	>16	>128
MIC, range	0.25–2	2–>64	0.5–64	1–64	4–>64	0.5–>32	0.5–>16	1–>128
Klebsiella spp (*K aerogenes, K oxytoca, K pneumonia;* n=79)								
MIC_{50}, mg/L	0.5	>64	4	4	64	1	>16	4
MIC_{90}, mg/mL	2	>64	64	64	>64	>32	>16	>128
MIC, range	0.06–>64	0.12–>64	≥0.03–>64	0.06–>64	1–>64	0.25–>32	≥0.06–>16	≥0.5–>128
Other *Enterobacterales* (*Citrobacter freundii, Citrobacter koseri, Morganella morganii, Proteus mirabilis*; n=4)								
MIC_{50}, mg/L	0.12	1	1	1	1	1	0.06	4
MIC_{90}, mg/mL	–	–	–	–	–	–	–	–
MIC, range	0.06–0.25	0.06–4	0.5–1	0.5–1	0.5–1	0.5–2	0.06–8	1–4

AMK, amikacin; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; GEN, gentamicin; LEV, levofloxacin; MEM, meropenem, $MIC_{50/90}$=50%/90% minimum inhibitory concentration; MVB, meropenem-vaborbactam; TZC, ceftolozane-tazobactam.

INTRODUCTION

- OXA-48 is a unique carbapenemase with low-level hydrolytic activity toward cephalosporins
- Isolates harboring bla OXA-48 usually carry other β-lactamases showing high rates of extended spectrum β-lactamase (ESBL) coproduction that frequently result in resistance to cephalosporins and other β-lactam agents[1,2]
- Surveillance studies have shown that OXA-48–like carbapenemases are the most common carbapenemases in *Enterobacterales* in certain regions of the world
- The increasing number of OXA-48–producing *Enterobacterales* is becoming a serious threat because the treatment options are limited[1,2]
- Ceftazidime-avibactam (CAZ-AVI) has demonstrated strong in vitro susceptibility and efficacy in clinical treatments against OXA-48 *Enterobacterales* coproducing ESBL, KPC, AmpC, and OMP/porin alternations[3-5]
- This study evaluated in vitro activities of CAZ-AVI, meropenem (MEM), meropenem-vaborbactam (MVB), ceftolozane-tazobactam (TZC), and other antimicrobial agents against 113 OXA-48–producing *Enterobacterales* with multiple resistance mechanisms collected from international medical centers in a 3-year period of global surveillance

METHODS

Bacterial isolates

- Non-duplicate clinical isolates of 113 *Enterobacterales* were collected from medical centers in 25 countries in 2017–2019 as part of the ATLAS surveillance program conducted by Pfizer/International Health Management Associates
- The organisms tested included *Klebsiella pneumoniae* (n=65), *K oxytoca* (n=6), *K aerogenes* (n=5), *Enterobacter cloacae* (n=17), *E kobei* (n=2), *E coli* (n=11), and others (n=4)

Resistant subsets

- The data of whole genome sequencing or quantitative PCR were used to determine resistance mechanisms in β-lactamases, including OXA-48, ESBL (CTX-M, TEM, SHV), original spectrum β-lactamases (OSBL; SHV, TEM), and AmpC (DHA, CMY)

Susceptibility testing

- In vitro susceptibility testing was performed by broth microdilution method using a custom-made panel (ThermoFisher Scientific, Waltham, MA) consisting of CAZ-AVI, ceftazidime (CAZ), MEM, MVB, TZC, gentamicin (GEN), levofloxacin, and amikacin (AMK)
- Clinical and Laboratory Standards Institute (CLSI) test methods were followed, and CLSI breakpoints were applied for susceptibility interpretations

DISCLOSURES

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