1590. Activity of Meropenem-Vaborbactam and Single-Agent Comparators against *Enterobacterales* Isolates Including KPC-Producing Isolates, from European Patients Hospitalized with Pneumonia Including Ventilator-Associated Pneumonia (2014-2019)

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Meropenem-vaborbactam (MVB) was recently approved in Europe for the treatment of complicated UTIs, including acute pyelonephritis, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia, ventilator-associated pneumonia (VAP), and bacteremia. KPC-producing *Enterobacterales* (ENT) isolates have disseminated worldwide. We analysed the activity of MVB and single-agent comparators against 6,846 ENT isolates from patients hospitalised with pneumonia (PHP) including VAP in European hospitals (2014–2019).

Methods. Among 6,846 ENT clinical isolates from PHP collected in 40 European hospitals located in 20 countries that were susceptibility (S) tested using reference broth microdilution methods. Of the carbapenem-resistant isolates submitted to whole genome sequencing, 75 carried bla_{KPC}. ENT isolates were also characterized for an extended spectrum beta-lactamase (ESBL) phenotype as described (CLSI, 2020). EUCAST (2020) interpretive criteria were used. %S from patients in the intensive care unit (ICU), ICU patients with VAP, and non-ICU isolates were also analysed.

Results. The most common ENT pathogens isolated from PHP were *Klebsiella pneumoniae* (KPN; n=1,877) and *Escherichia coli* (EC; n=1,646). The %S of MVB and comparators to ENT, ICU, ICU/VAP, and non-ICU are shown in the table. Overall, 98.2% of ENT were S to MVB. For 3,218 ENT isolates from ICU patients, MVB %S was 96.6% and for 2,627 non-ICU isolates MVB %S was 98.5%. The %S of comparators for ICU vs non-ICU isolates were similar, except for levofloxacin. 29 KPC-producing isolates were from ICU (11 from VAP), 46 were from non-ICU. Most KPC-producing isolates were KPN (n=71; 54 bla_{KPC-3}, 16 bla_{KPC-2} and 1 bla_{KPC-12}). 4 EC contained bla_{KPC-3}. KPC were from 7 countries, Italy had the highest number of KPC-producing isolates at 42 (56%). MVB inhibited 100% of KPC-producing isolates. Amikacin was the most active comparator against all ENT (94.2%S); colistin was the most active comparator against KPC-producing isolates (79.7%S).

Conclusion. These results demonstrate MVB has potent activity against ENT isolates from PHP including those producing KPC enzymes and suggest MVB is a useful treatment option for ICU and non-ICU PHP including VAP.

Table 1

Organisms and organism groups (n)	% susceptible using EUCAST breakpoints					
	Meropenem-vaborbactam	Meropenem	Amikacin	Gentamicin	Levofloxacin	Colistin
Enterobacterales (6,846)	98.0	95.1	94.2	85.3	75.0	76.8
ESBL-phenotype (1,368)	90.6	77.4	75.1	48.8	22.6	88.3
KPC-producing (75)	100.0	0.0	48.0	60.0	6.7	81.3
ICU isolates (3,218)	96.6	94.2	93.0	84.6	76.0	76.4
ESBL-phenotype (706)	87.5	75.3	71.2	45.7	22.8	86.1
KPC-producing (29)	100.0	0.0	37.9	75.9	6.9	62.1
ICU-VAP isolates (1,890)	96.7	93.2	91.5	82.6	74.3	76.8
ESBL-phenotype (455)	86.8	73.8	67.3	44.6	20.7	86.5
KPC-producing (11)	100.0	0.0	18.2	81.8	0.0	72.7
non-ICU isolates (2,627)	98.5	94.5	94.0	83.7	70.3	78.2
ESBL phenotype (530)	92.8	75.1	76.6	48.9	19.2	89.4
KPC-producing (46)	100.0	0.0	54.3	50.0	6.5	93.5

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1591. Antibiotic Utilization Trends in Veterans Affairs (VA) Patients with Carbapenem Resistant Enterobacteriaceae (CRE) Infections

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Carbapenem-resistant Enterobacteriaceae (CRE) are classified as an "urgent threat" to public health. Historically, colistin and tigecycline had been considered the drugs of choice for CRE infections, while other agents such as aminoglycosides and carbapenems had been used as adjunctive therapy. However, the FDA approval of ceftazidime-avibactam in 2015, meropenem-vaborbactam in 2017, and plazomicin in 2018 has expanded treatment options. Our purpose was to assess trends in CRE treatment for "new" antibiotics (ceftazidime-avibactam, meropenem-vaborbactam, plazomicin) as compared with other antibiotics with CRE activity.

Methods. This was a retrospective cohort study describing treatment of CRE blood stream infections (BSI) across 134 VA facilities from 2012-2018. Patients were censored at their first positive blood culture with CRE. Categorical data was assessed with a Fisher's exact test or chi-square test. Trends test and logistic regression were used to describe changes in CRE treatment over time.

Results. 724 patients with positive blood cultures for CRE were identified during the study period. Most patients were male (94%), white (32%) or Hispanic (38%), and the mean age was 71.5+11.9. Of those patients that received antibiotics (N=697), 53.4% carbapenems, 40.3% received aminoglycosides, 39.3% received polymyxins, 32.9% penicillins, 32.6% extended spectrum cephalosporins, 26.1% fluoroquinolones, 11.6% ceftazidime/avibactam, and 0.4% ceftolazone/tazobactam. Over the study period, there was decreased utilization of aminoglycosides ($P < 0.0026$) and colistin ($P< 0.002$) and increases in extended spectrum cephalosporins ($P < 0.001$) and ceftazidime/avibactam ($P < 0.001$).

Conclusion. Utilization of "older" agents such as aminoglycosides and polymyxins for the treatment of CRE blood stream infections is decreasing in the VA. Treating CRE with ceftazidime/avibactam, a newly approved antibiotic, and extended spectrum cephalosporins are increasing.

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1592. Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents Against *Enterobacterales* and *Pseudomonas aeruginosa* With Overexpression of AmpC β-Lactamase From Phase 3 Clinical Trials

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. AmpC overproduction is a main mechanism of carbapenem resistance, in the absence of acquired carbapenemases. Ceftazidime-avibactam (CAZ-AVI) has potent in vitro activity against AmpC-producing *P. aeruginosa and Enterobacterales* that are resistant to carbapenems and other β-lactams.

Methods. Activity of CAZ-AVI and comparators was evaluated against AmpC-overproducing *Enterobacterales* (n=77) and *P. aeruginosa* (n=53) collected from 4 CAZ-AVI clinical trials: RECLAIM (complicated intra-abdominal infection [cIAI]), REPRISE (cIAI/complicated urinary tract infection [cUTI]), RECAPTURE (cUTI) and REPROVE (hospital-acquired pneumonia/ventilator associated pneumonia). In vitro susceptibility of CAZ-AVI and comparators was performed by broth microdilution using ThermoFisher custom panels. CLSI breakpoints were used to determine susceptibility. Quantitative PCR and microarray data were used to characterize presence and expression of AmpC. Clinical response at test of cure was assessed.

Results. Against 77 AmpC-overproducing *Enterobacterales* isolates, meropenem-vaborbactam (MVB) (98.7% susceptible [S]), CAZ-AVI (96.1% S), and meropenem (MEM) (96.1% S) had similar in vitro activity **(Table)**, with greater in vitro activity than amikacin (AMK) (84.4% S), gentamicin (61.0% S), and ceftolozane-tazobactam (TZC) (35.1% S). Clinical cures in patients with baseline AmpC-overproducing *Enterobacterales* were 21/26 (81%) in CAZ-AVI group vs 17/20 (85%) in control groups. Against 53 AmpC-overproducing *P. aeruginosa* isolates, CAZ-AVI (73.6% S) showed greater in vitro activity than AMK (69.8% S), TZC (58.5% S), and MEM (37.7% S). Clinical cures in patients with baseline AmpC-overproducing *P. aeruginosa* were 12/14 (86%) in CAZ-AVI group vs 9/12 (75%) in control groups. MIC distributions against the same *P aeruginosa* isolates were CAZ-AVI ($MIC_{50/90}$, 4/ >64 µg/mL), MVB ($MIC_{50/90}$, 8/32 µg/mL), and MEM ($MIC_{50/90}$, 8/32 µg/mL).

Table

Table. Antimicrobial activity of CAZ-AVI and comparators tested against AmpC-overproducing *Enterobacterales* and *Pseudomonas aeruginosa* isolates

	CLSI	
Organism and antimicrobial agent (no. of isolates)	**Susceptible, n (%)**	**Nonsusceptible, n (%)***
Enterobacterales, AmpC overproducing (n=77)		
Ceftazidime-avibactam	74 (96.1)	3 (3.9)
Ceftazidime	5 (6.5)	72 (93.5)
Meropenem-vaborbactam	76 (98.7)	1 (1.3)
Meropenem	74 (96.1)	3 (3.9)
Ceftolozane-tazobactam	20 (35.1)	57 (64.9)
Gentamicin	47 (61.0)	30 (39.0)
Levofloxacin	37 (48.1)	40 (51.9)
Amikacin	65 (84.4)	12 (15.6)
P. aeruginosa, AmpC overproducing (n=53)		
Ceftazidime-avibactam	39 (73.6)	14 (26.4)
Ceftazidime	1 (1.9)	52 (98.1)
Meropenem-vaborbactam	No CLSI breakpoints	
Meropenem	20 (37.7)	33 (62.3)
Ceftolozane-tazobactam	31 (58.5)	22 (41.5)
Gentamicin	25 (47.2)	28 (52.8)
Levofloxacin	9 (17.0)	44 (83.0)
Amikacin	37 (69.8)	16 (30.2)

*Nonsusceptible includes intermediate or resistant isolates. CLSI=Clinical & Laboratory Standards Institute

Conclusion. CAZ-AVI was the most active agent against AmpC-overproducing *P. aeruginosa* with higher proportion of clinical cure than controls. CAZ-AVI was also among the most active agents against AmpC-overproducing *Enterobacterales*, with >96% isolates susceptible.

Disclosures. Lynn-Yao Lin, MS, AbbVie (Employee) Dmitri Debabov, PhD, AbbVie (Employee) William Chang, BS, AbbVie (Employee) Urania Rappo, MD, MS, PharmD, Allergan (before its acquisition by AbbVie) (Employee)

1593. Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents Against OXA-48 β-lactamase–Producing *Enterobacterales* Collected in International Medical Centers, Including the United States, in 2017–2018

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. OXA-48 is a carbapenemase with low-level hydrolytic activity toward cephalosporins. This study evaluated in vitro activities of ceftazidime-avibactam (CAZ-AVI), meropenem (MEM), meropenem-vaborbactam (MVB), ceftolozane-tazobactam (C/T), and other antimicrobial agents against 113 OXA-48-producing *Enterobacterales* with multiple resistance mechanisms collected in a 2017–2018 global surveillance program.

Methods. Nonduplicate clinical isolates of 113 *Enterobacterales* were collected from medical centers in 25 countries in 2017–2018. In vitro susceptibility tests were performed by broth microdilution with a custom-made panel consisting of CAZ-AVI, ceftazidime (CAZ), MEM, MVB, C/T, colistin (COL), gentamicin (GEN), levofloxacin (LEV), and amikacin (AMK). Whole genome sequencing or quantitative PCR data were used to analyze resistance mechanisms, such as OXA-48, extended-spectrum β-lactamase (ESBL), original-spectrum β-lactamase (OSBL), and AmpC β-lactamase. Clinical and Laboratory Standards Institute breakpoints were applied for susceptibility interpretations.

Results. Of 113 OXA-48–producing clinical isolates, 20 carried OXA-48 alone. The remaining 93 isolates carried additional β-lactamases, including 63 with ESBL (CTX-M-15) + OSBL (SHV, TEM), 15 with AmpC (DHA, AAC, CMY) + ESBL (CTX-M-15), and 15 with OSBL (SHV, TEM). 99.1% (all but 1) of all isolates tested were susceptible to CAZ-AVI, whereas 71.7%, 17.7%, and 14.2% were susceptible to MVB, MEM, and C/T, respectively. Among isolates harboring multiple resistance mechanisms (OXA-48 + ESBL + OSBL; n=63), 98.4%, 69.8%, 11.1%, and 7.9% were susceptible to CAZ-AVI, MVB, MEM, and C/T, respectively. Among isolates carrying OXA-48 + AmpC + ESBL + OSBL (n=15), 100%, 66.7%, 13.3%, and 13.3% were susceptible to CAZ-AVI, MVB, MEM, and C/T, respectively (Table). Aminoglycosides (AMK and GEN) and other β-lactams (eg, CAZ) were 20%–90% active against these isolates. COL was the second most effective comparator, inhibiting 83.2% of these isolates.

Table

Table. In vitro susceptibility of ceftazidime-avibactam and comparators against isolates with OXA-48–producing *Enterobacterales* with multiple resistance mechanisms.

Antimicrobial agent	% Susceptible				
	All OXA-48 (n=113)	OXA-48 alone (n=20)	OXA-48 + OSBL (n=15)	OXA-48 + ESBL + OSBL (n=63)	OXA-48 + AmpC (DHA, AAC, CMY) + ESBL +OSBL (n=15)
CAZ-AVI	99.1	100	100	98.4	100
CAZ	27.4	25	20	23.8	33.3
MVB	71.7	100	46.7	69.8	66.7
MEM	17.7	45	13.3	11.1	13.3
C/T	14.2	25	20	7.9	13.3
GEN	54.9	60	73.3	52.3	53.3
LEV	27.4	55	26.7	20.6	26.7
AMK	79.6	90	80	82.5	86.7
COL	83.2	85	80	79.4	100

AmpC, AmpC β-lactamase; AMK, amikacin; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; COL, colistin; C/T, ceftolozane-tazobactam; ESBL, extended-spectrum β-lactamase; GEN, gentamicin; LEV, levofloxacin; MEM, meropenem; MVB, meropenem vaborbactam; OSBL, original-spectrum β-lactamase.

Conclusion. CAZ-AVI was the most effective agent in this study compared with other antibiotics, including β-lactams, β-lactam–β-lactamase inhibitor combinations, aminoglycosides, and COL, against OXA-48-producing *Enterobacterales* carrying multiple β-lactamases.

Disclosures. Lynn-Yao Lin, MS, AbbVie (Employee) Dmitri Debabov, PhD, AbbVie (Employee) William Chang, BS, AbbVie (Employee)

1594. Antimicrobial Resistance Monitoring through the ATLAS Global Surveillance Program 2012-2018

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Antimicrobial resistance is an increasingly serious threat to global public health. The Antimicrobial Testing Leadership and Surveillance (ATLAS) program has provided reliable, global, regional and local *in vitro* susceptibility data, including mechanisms of resistance, since 2004. In this analysis, data from the ATLAS program are used to measure the *in vitro* activity of several key gram-negative/gram-positive agents against major global pathogens.

Methods. A total of 251,837 gram-negative and 132,363 gram-positive non-duplicate, clinical isolates were collected from multiple infection sources from 743 unique sites in 74 countries during 2012-2018 in the ATLAS program. Identification was confirmed to the species level using MALDI-TOF spectrometry. Only one clinically relevant causative isolate per patient was accepted into the study. MICs were determined by broth microdilution following CLSI guidelines and interpreted using 2020 CLSI breakpoints. Phenotypic ESBL screening and confirmatory testing were performed using the CLSI M100 method.

Results. The *in vitro* activities of selected antimicrobial agents are provided in the table below. Based on percent susceptibility, ceftazidime-avibactam, amikacin, tigecycline, meropenem, and ceftolozane-tazobactam were the most active agents against most gram-negative isolates. The CRE rate among Enterobacterales isolates was 3.2%, with tigecycline and ceftazidime-avibactam the most active among this resistant subgroup. Ceftazidime-avibactam, ceftolozane-tazobactam, and amikacin were the most active agents against *Pseudomonas aeruginosa*. Ceftaroline, linezolid, tigecycline and vancomycin all showed good activity against gram-positive isolates.