into Kp 23, a wild-type clinical isolate, and KPM 20, a clinical isolate deficient in OmpK35/36 and PhoE. MICs to ceftolozane/tazobactam, cefotaxime, ceftazidime, cefepime, and meropenem were determined by E-test. Kp 23 and KPM 20 were characterized by Western blot and whole genome sequencing.

Results. Production of CMY-2 alone led to a resistant phenotype for ceftolozane/tazobactam, cefotaxime, and ceftazidime regardless of porin production (Figure 1). CMY-2 production in KPM 20 resulted in non-susceptibility to meropenem. Both clones were susceptible to cefepime. Production of CTX-M-14 and CTX-M-15 in Kp 23 resulted in only cefotaxime resistance. Production of CTX-M-14 and CTX-M-15 in KPM 20 resulted in isolates non-susceptible to all antibiotics tested.

	Isolate	Ceftolozane/tazobactam	Cefotaxime	Ceftazidime	Cefepime	Meropenem
With porins	Kp 23	0.064 (S)	0.032 (S)	0.064 (S)	0.047 (S)	0.047 (S)
	Kp 23 - CMY-2	16 (R)	>32 (R)	>256 (R)	1.5 (S)	0.125 (S)
	Kp 23 - CTX-M-14	0.19 (S)	>32 (R)	1.5 (S)	12 (SDD)	0.064 (S)
	Kp 23 - CTX-M-15	0.25 (S)	>32 (R)	12 (I)	24 (R)	0.064 (S)
Without porins	KPM 20	1 (S)	1 (S)	1.5 (S)	1.5 (S)	0.5 (S)
	KPM 20 - CMY-2	16 (R)	>32 (R)	>256 (R)	4 (SDD)	2 (I)
	KPM 20 - CTX-M-14	128 (R)	>32 (R)	24 (R)	>256 (R)	4 (R)
	KPM 20 - CTX-M-15	>256 (R)	>32 (R)	>256 (R)	>256 (R)	2 (I)

Figure 1. MICs of K. pneumoniae clones against panel of β-lactam antibiotics.

Conclusion. When evaluating clinical isolates, it is impossible to determine the contribution of individual resistance mechanisms in the susceptibility pattern. This study demonstrated that resistance is not solely dependent on the β-lactamase produced and that the impact of porin deficiency varies with the antibiotic being evaluated. These data suggest that antibiotic selection may be more nuanced and that a broader range of therapeutics may be available given the appropriate diagnostic tools. Understanding the contributions of all resistance mechanisms is necessary to inform selection of the most appropriate antibiotic therapy.

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1231. *In Vitro* Activity of Aztreonam-Avibactam and Comparator Agents Against Enterobacterales from Patients with Lower Respiratory Tract Infections Collected During the ATLAS Global Surveillance Program, 2017-2019

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Session: P-72. Resistance Mechanisms

Background. β-lactamase-producing Enterobacterales (Ebact) frequently co-carry resistance to antimicrobials from other classes, limiting treatment options. Avibactam (AVI) inhibits class A, class C, and some class D serine β-lactamases, while aztreonam (ATM) is refractory to hydrolysis by class B metallo-β-lactamases (MBLs). ATM-AVI is being developed for use against drug-resistant isolates of Ebact, especially those co-producing MBLs and serine β-lactamases. This study evaluated the *in vitro* activity of ATM-AVI and comparators against Ebact collected in 2017-2019 from patients with lower respiratory tract infections (LRTI) as part of the Antimicrobial Testing Leadership and Surveillance (ATLAS) program.

Methods. Non-duplicate clinical isolates were collected in 52 countries in Europe, Latin America, Asia/Pacific (excluding mainland China and India), and Middle East/Africa. Susceptibility testing was performed by CLSI broth microdilution and interpreted using CLSI 2021 and FDA (tigecycline) breakpoints. ATM-AVI was tested at a fixed concentration of 4 μg/mL AVI. MDR was defined as resistant (R) to ≥3 of 7 sentinel drugs: amikacin, aztreonam, cefepime, colistin, levofloxacin, meropenem, and piperacillin-tazobactam. PCR and sequencing were used to determine the β-lactamase genes present in all isolates with meropenem MIC >1 μg/mL, and *Escherichia coli*, *Klebsiella* spp. and *Proteus mirabilis* with ATM or ceftazidime MIC >1 μg/mL.

Results. ATM-AVI was active *in vitro* against Ebact isolates from LRTI (MIC_{90}, 0.25 μg/mL), with 99.97% of isolates inhibited by ≤8 μg/mL of ATM-AVI, including 100% of isolates that produced MBLs. ATM-AVI tested with MIC_{90} values of 0.5 μg/mL against subsets of cefepime-nonsusceptible (NS), meropenem-NS, amikacin-NS, colistin-resistant, and MBL-positive Ebact (Table). The tested β-lactam comparators showed susceptibility of < 78% against these subsets of resistant isolates.

Results Table

	MIC₉₀ [μg/mL] / % Susceptible											
	ATM-AVI		ATM		FEP		MEM		AMK		TGC	
Phenotype (n)	MIC₉₀	%S	MIC₉₀	%S	MIC₉₀	%S	MIC₉₀	%S	MIC₉₀	%S	MIC₉₀	%S
All (10242)	0.25	NA	128	73.1	>16	76.8	0.12	94.4	8	96.5	1	97.2
FEP-NS (2373)	0.5	NA	>128	6.0	>16	0.0	>8	77.4	>32	86.4	2	94.4
MEM-NS (570)	0.5	NA	>128	10.7	>16	5.8	>8	0.0	>32	64.7	2	91.9
AMK-NS (354)	0.5	NA	>128	16.4	>16	8.5	>8	43.2	>32	0.0	2	92.1
CST-R (319)[a]	0.5	NA	>128	42.6	>16	53.3	>8	66.5	32	87.2	2	95.3
MDR (1579)	0.5	NA	>128	4.6	>16	3.4	>8	65.3	>32	79.5	2	92.4
MBL-positive (196)	0.5	NA	>128	11.7	>16	0.0	>8	8.2	>32	52.6	4	88.8

ATM-AVI, aztreonam-avibactam; ATM, aztreonam, FEP, cefepime; MEM, meropenem; AMK, amikacin; TGC, tigecycline; CST, colistin; S, susceptible; NS, susceptible; NA, no breakpoint available; MBL, metallo-β-lactamase.
[a]Excluded *Morganellaceae* and *Serratia* spp. with intrinsic resistance to colistin.

Conclusion. Based on MIC_{90} values, ATM-AVI was the most potent agent tested against drug-resistant and MBL-positive subsets of Ebact collected from LRTI. The promising *in vitro* activity of ATM-AVI warrants further development of this combination for treatment of LRTI caused by drug-resistant Ebact.

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1232. *In Vitro* Activity of Cefiderocol and Comparator Agents against Molecularly characterized Carbapenem-resistant *Enterobacterales* Clinical Isolates Causing Infection in United States Hospitals (2020)

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Session: P-72. Resistance Mechanisms

Background. Cefiderocol (CFDC) represents a new addition to the antimicrobial armamentarium with broad activity against Gram-negative bacteria (GNB). CFDC remains stable to hydrolysis in the presence of serine β-lactamases (ESBLs, KPC and OXA-type carbapenemases) and metallo-β-lactamases. The CFDC and comparator activities were analyzed against *Enterobacterales* (ENT), including molecularly characterized carbapenem-resistant isolates (CRE), as a part of the SENTRY Antimicrobial Surveillance Program in the USA.

Methods. 4,053 ENT were collected from 31 sites in 2020. Susceptibility testing was performed by broth microdilution and CFDC testing used iron-depleted media. CLSI/FDA breakpoints were used. Isolates displaying MIC values ≥4 μg/mL for imipenem (excluded for *P. mirabilis, P. penneri* and indole-positive *Proteus*) or meropenem (MER) were subjected to genome sequencing and screening of β-lactamase genes.

Results. A total of 36 (0.9%) CRE were detected, and represented mostly by isolates carrying bla_{KPC} (75.0%; 27/36; Table). A small number of ENT (11.1%; 4/36) carried other carbapenemase genes (1 each of bla_{NDM-1}, bla_{NDM-5}, $bla_{OXA-232}$, and bla_{SME-2}), whereas 13.9% (5/36) of isolates did not carry any known carbapenemases. CFDC (99.8% susceptible [S]), imipenem-relebactam (IMR; 99.7-99.9%S), meropenem-vaborbactam (MEV; 99.9-100%S), ceftazidime-avibactam (CZA; 99.9-100%S), and MER (99.1-99.9%S) were active against all ENT and the non-CRE subset. CFDC ($MIC_{50/90}$, 0.5/4 μg/mL; 97.2%S) and CZA ($MIC_{50/90}$, 1/8 μg/mL; 94.4%S) were the most active agents against CRE, whereas CFDC, IMR, MEV and CZA were active (100%S) against the KPC subset. Finally, CFDC (MIC, 0.5-4 μg/mL; 100%S) was the most active agent against ENT carrying genes other than bla_{KPC}, whereas CZA (1-8 μg/mL; 100%S) was most active against CRE with no known carbapenemases, followed by CFDC (0.5-8 μg/mL; 80.0%S).

Conclusion. The CFDC activity was consistent, regardless of phenotypes or genotypes, including against isolates carrying genes other than bla_{KPC}, where approved β-lactam/β-lactamase inhibitor combinations showed limited activity. These data confirm CFDC as an important option for the treatment of infections caused by ENT and resistant subsets.

Table

Phenotype/genotype (No. isolates)	MIC₅₀/MIC₉₀ in μg/mL (% susceptible by CLSI M100 criteria)[a]				
	CFDC	IMR	MEV	CZA	MER
Enterobacterales (4,053)	0.06/0.5 (99.8)	0.12/0.5 (99.7)	0.03/0.06 (99.9)	0.12/0.25 (99.9)	0.03/0.06 (99.1)
Non-CRE[b] (4,017)	0.06/0.5 (99.8)	0.12/0.5 (99.9)	0.03/0.06 (100.0)	0.12/0.25 (100.0)	0.03/0.06 (99.9)
CRE[b] (36)	0.5/4 (97.2)	0.12/4 (80.6)	0.03/8 (83.3)	1/8 (94.4)	8/>32 (2.8)
KPC[c] (27)	0.5/2 (100)	0.12/0.25 (100)	0.03/1 (100.0)	0.5/2 (100)	8/>32 (3.7)
Other[d] (4)	0.5/- (100)	8/- (0.0)	8/- (25.0)	2/- (50.0)	>32/- (0.0)
No-carbapenemases[e] (5)	2/- (80.0)	2/- (40.0)	8/- (40.0)	2/- (100)	16/- (0.0)

[a] MIC interpreted according to the CLSI M100 interpretive criteria (2021); CFDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; CZA, ceftazidime-avibactam; MER, meropenem
[b] Non-CRE, includes isolates with imipenem and/or meropenem MIC ≤2 μg/mL; CRE, defined as isolates with imipenem (excluded for *P. mirabilis, P. penneri* and indole-positive *Proteus*) and/or meropenem MIC ≥4 μg/mL and includes *Citrobacter freundii* (3), *Enterobacter cloacae* (3), *Escherichia coli* (2), *Klebsiella aerogenes* (2), *K. oxytoca* (4), *K. pneumoniae* (18), *Serratia marcescens* (2), *Raoultella ornithinolytica* (2)
[c] Includes 12 isolates carrying bla_{KPC-2} and 15 bla_{KPC-3}
[d] Includes 1 isolate each of bla_{NDM-1}, bla_{NDM-5}, $bla_{OXA-232}$, and bla_{SME-2}
[e] Includes 5 CRE with no known carbapenemase genes detected

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