Results. Susceptibility data are shown in the Table. Percentages of susceptibility (% S) to the tested agents were 0.3-2.9% lower among *Eba* and *Pae* from bloodstream infections compared to isolates from combined sources in most cases. CAZ-AVI showed potent *in vitro* activity against all *Eba* bloodstream isolates and the CAZ-NS subset (MIC_{90}, 0.5-2 μg/ml, 93.4-98.1% S). Reduced activity against MEM-NS *Eba* was attributable to carriage of class B metallo-β-lactamases (MBLs) because 99% of MEM-NS MBL-negative isolates were susceptible to CAZ-AVI. None of the tested comparators exceeded the activity of CAZ-AVI. CAZ-AVI also showed good *in vitro* activity against the majority of *Pae* bloodstream isolates (MIC_{90}, 16 μg/ml, 89.4% S). Activity was reduced against CAZ-NS and MEM-NS subsets (54.2-63.8% S), which included isolates carrying MBLs, but exceeded the activity of CAZ and MEM against these subsets by 26-31 percentage points. Amikacin was the only tested comparator that demonstrated comparable activity against *Pae* bloodstream isolates.

Table

Source	Organism/Phenotype (n)	CAZ-AVI MIC_{90}	%S	CAZ MIC_{90}	%S	MEM MIC_{90}	%S	TZP MIC_{90}	%S	AMK MIC_{90}	%S
All Blood	Enterobacterales, All (57048)	0.5	98.6	64	74.5	0.12	95.6	> 64	84.0	8	97.0
	All (7720)	0.5	98.1	64	71.6	0.12	94.2	> 64	83.7	8	96.6
	CAZ-NS (2192)	2	93.4	> 128	0.0	> 8	81.0	> 128	52.8	32	89.7
	MEM-NS (445)	> 128	69.4	> 128	6.5	> 16	0.0	> 128	1.1	> 64	62.9
	MEM-NS, MBL-negative (312)	4	99.0	> 128	9.3	> 16	0.0	> 128	1.0	> 64	69.6
All Blood	*P. aeruginosa*, All (15813)	8	90.9	64	76.5	> 8	73.2	128	72.2	32	89.9
	All (1286)	16	89.4	64	76.9	> 8	71.6	> 64	73.9	> 32	87.0
	CAZ-NS (297)	128	54.2	> 128	0.0	> 16	23.6	> 128	7.7	> 64	53.5
	MEM-NS (365)	128	63.8	> 128	37.8	> 16	0.0	> 128	31.5	> 64	58.1
	MEM-NS, MBL-negative (288)	32	80.2	> 128	47.2	16	0.0	> 128	38.2	64	69.8

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; NS, non-susceptible; MBL, metallo-β-lactamase. % Susceptible was determined using CLSI 2020 breakpoints.

Conclusion. CAZ-AVI provides a valuable therapeutic option for treating bloodstream infections caused by MBL-negative *Eba* and *Pae* isolates.

1570. *In Vitro* Activity of Ceftazidime-Avibactam and Comparator Agents Against Enterobacterales from ICU and Non-ICU Wards Collected in Latin America and Globally as part of the ATLAS Surveillance Program 2017-2018

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Ceftazidime-avibactam (CAZ-AVI) is a β-lactam/non-β-lactam β-lactamase inhibitor combination with activity against Enterobacterales producing class A, C and some class D β-lactamases. Resistance caused by these β-lactamases is especially high in ICUs. This study evaluated the *in vitro* activity of CAZ-AVI and comparators against Enterobacterales isolates from patients in ICU and non-ICU wards.

Methods. Non-duplicate clinical isolates were collected in 2017-2018 from patients in Asia/Pacific, Europe, Latin America, and Middle East/Africa. Susceptibility testing was performed using CLSI broth microdilution and interpreted using CLSI 2020 and FDA (tigecycline) breakpoints. PCR and sequencing were used to determine the β-lactamase genes present in all isolates with meropenem (MEM) MIC >1 μg/ml, and *Escherichia coli*, *Klebsiella* spp. and *Proteus mirabilis* with aztreonam or ceftazidime MIC >1 μg/ml.

Results. The activity of CAZ-AVI and comparators is shown in the table. Susceptibility rates among global Enterobacterales were generally lower for isolates from patients in ICU than non-ICU wards, but this difference was small for CAZ-AVI, which inhibited ≥97% of isolates from both ward types. Among MEM-nonsusceptible (NS) isolates, CAZ-AVI was active against 66.5% and 68.1% of ICU and non-ICU isolates, respectively (of which 31.8% and 30.8%, respectively, carried metallo-β-lactamases [MBLs]). CAZ-AVI inhibited >97% of MEM-NS MBL-negative isolates collected globally. Antimicrobial activity against all Enterobacterales from both ICU and non-ICU wards in Latin America (LA) was generally similar to the global average. Among MEM-NS isolates, antimicrobial activity of CAZ-AVI and TGC was higher in LA than the global average among isolates from both ward types, at least partly because of a lower proportion of MBL-positive isolates in this subset (15.8% and 17.9% in ICU and non-ICUs, respectively). CAZ-AVI inhibited 100% of MEM-NS MBL-negative isolates from LA.

Table

Region/phenotype	Ward type (n)	Drug (% Susceptible)					
		CAZ-AVI	CAZ	MEM	TZP	AMK	TGC
Global[a]							
All Enterobacterales	ICU (6896)	97.0	66.6	91.5	77.7	94.5	97.0
	Non-ICU (19259)	98.6	75.0	96.1	85.8	97.6	96.7
MEM-NS	ICU (585)	66.5	6.8	0.0	1.9	58.0	93.0
	Non-ICU (759)	68.1	8.0	0.0	4.5	68.8	90.5
MEM-NS MBL-negative	ICU (399)	97.5	10.0	0.0	2.3	66.4	93.5
	Non-ICU (525)	97.9	11.6	0.0	5.5	74.7	93.9
Latin America							
All Enterobacterales	ICU (1166)	98.2	61.7	89.7	78.0	94.5	97.0
	Non-ICU (3101)	99.1	70.0	95.7	84.9	97.0	97.2
MEM-NS	ICU (120)	84.2	2.5	0.0	0.8	70.0	97.5
	Non-ICU (134)	82.8	9.0	0.0	3.7	67.9	95.5
MEM-NS MBL-negative	ICU (101)	100	3.0	0.0	1.0	75.3	97.0
	Non-ICU (110)	100	10.9	0.0	2.7	72.7	98.2

[a]Includes isolates from Asia/Pacific (excluding mainland China), Europe, Latin America, and Middle East/Africa
CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; TGC, tigecycline; NS, non-susceptible; MBL, metallo-β-lactamase

Conclusion. CAZ-AVI provides a valuable treatment option for infections caused by Enterobacterales that do not carry MBLs, including those among patients in ICU wards, where antimicrobial resistance is typically higher.

1571. *In Vitro* Activity of Ceftazidime-Avibactam and Comparator Agents Against MDR Enterobacterales and *Pseudomonas aeruginosa* Collected in Latin America During the ATLAS Global Surveillance Program 2017-2018

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Ceftazidime-avibactam (CAZ-AVI) is a β-lactam/non-β-lactam β-lactamase inhibitor combination that can inhibit class A, C and some class D β-lactamases. Resistance caused by these β-lactamases often results in multidrug-resistance (MDR). This study evaluated the *in vitro* activity of CAZ-AVI and comparators against MDR Enterobacterales and *Pseudomonas aeruginosa* isolates collected from patients in Latin America.

Methods. Non-duplicate clinical isolates were collected in 2017-2018 in 10 countries in Latin America. Susceptibility testing was performed using CLSI broth microdilution and interpreted using CLSI 2020 and FDA (tigecycline) breakpoints. MDR was defined as resistant (R) to ≥3 of 7 sentinel drugs: amikacin (AMK), aztreonam (ATM), cefepime (FEP), colistin (CST), levofloxacin (LVX), meropenem (MEM), and piperacillin-tazobactam (TZP).

Results. The activity of CAZ-AVI and comparators against all isolates and MDR subsets is shown in the table. MDR rates for the studied species ranged from 17.6% among *E. cloacae* to 31.0% among *K. pneumoniae*. CAZ-AVI was active against 99% of Enterobacterales isolates and maintained activity against 85-99% of MDR isolates of the examined species. Only tigecycline showed comparable or higher activity. Among *P. aeruginosa*, CAZ-AVI was active against 86% of all isolates and 45% of MDR isolates; no other studied drug was more active. The three most common MDR phenotypes among Enterobacterales were 1) R to ATM, FEP, and LVX (n=538, 50% of all MDR Enterobacterales; 100% susceptible (S) to CAZ-AVI), 2) R to all sentinel drugs except AMK and CST (n=112, 10% of all MDR isolates; 88% S to CAZ-AVI), and 3) R to ATM, FEP, LVX, and TZP (n=111, 10% of all MDR Enterobacterales; 100% S to CAZ-AVI). The three most common MDR phenotypes among *P. aeruginosa* were 1) R to all sentinel drugs except CST (n=70, 22% of all MDR isolates; 20% S to CAZ-AVI), 2) R to AMK, LVX, and MEM (n=33, 10% of all MDR isolates; 33% S to CAZ-AVI), and 3) R to all sentinel drugs except AMK and CST (n=30, 9% of all MDR isolates; 70% S to CAZ-AVI).

Table

Species/phenotype (n)	Drug (% susceptible)					
	CAZ-AVI	CAZ	MEM	TZP	AMK	TGC
All Enterobacterales (5532)	98.9	70.1	94.6	84.4	96.7	97.3
MDR (1070)	95.0	5.6	73.6	47.5	85.4	96.2
E. coli (1860)	99.8	71.9	99.3	93.4	93.4	99.9
MDR (401)	99.3	3.0	97.0	83.0	94.8	100
K. pneumoniae (1523)	98.4	53.1	85.8	69.1	94.0	97.9
MDR (472)	95.1	1.9	55.3	22.7	82.0	95.6
E. cloacae (482)	96.9	60.8	94.6	75.1	95.0	97.7
MDR (85)	84.7	0.0	71.8	18.8	75.3	92.9
P. aeruginosa (1403)	85.7	71.4	67.6	70.7	82.2	NA
MDR (322)	44.7	9.6	8.4	7.5	35.7	NA

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; TGC, tigecycline; NA, not applicable

Conclusion. These *in vitro* data suggest that CAZ-AVI can be an effective treatment option for infections caused by MDR Enterobacterales and *P. aeruginosa* collected in Latin America.

Disclosures. Krystyna Kazmierczak, PhD, IHMA (Employee)Pfizer, Inc. (Consultant) Sibylle Lob, PhD, IHMA (Employee)Pfizer, Inc. (Consultant) Greg Stone, PhD, AztraZeneca (Shareholder, Former Employee)Pfizer, Inc. (Employee) Daniel F. Sahm, PhD, IHMA (Employee)Pfizer, Inc. (Consultant)Shionogi & Co., Ltd. (Independent Contractor)

1572. Combination Cefuroxime and Sulopenem is active *in vitro* against Mycobacterium abscessus

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. *Mycobacterium abscessus* (Mab) is a highly drug-resistant nontuberculous mycobacteria (NTM). Efforts to discover new treatments for *Mab* infections are accelerating with a focus on cell wall synthesis proteins (L, D-transpeptidases, Ldt$_{Mab1-5}$, and D, D-carboxypeptidase) that are targeted by combination β-lactam antibiotics. The US Food and Drug Administration (FDA) has granted Qualified Infectious Disease Product (QIDP) to the oral and intravenous (IV) formulations of Sulopenem (SUL). Data on SUL *in vitro* activity against *Mab* is currently unavailable. Here, we evaluated activity of SUL alone and in combination with Cefuroxime salt (CEF) against representative clinical isolates belonging to the *Mab* complex. Both CEF and SUL are available in oral formulation and can be considered as oral step-down therapy.

Methods. Minimum inhibitory concentrations (MICs) of SUL and CEF alone and in combination were determined using microdilution. Approximately 5 x 105 colony-forming units (CFU) per milliliter were inoculated into Middlebrook 7H9 Broth supplemented with 10% (vol/vol) oleic albumin dextrose catalase and 0.05% (vol/vol) Tween 80. CEF was added at fixed concentration of 4 μg/ml to serial dilutions of SUL. Mab isolates were incubated with test agents at 30 °C for 48 h, and MIC was defined as lowest antibiotic concentration that prevented visible bacterial growth.

Results. Fifty-five clinically derived and previously characterized isolates were tested in these assays. MIC$_{50}$ and MIC$_{90}$ of CEF is 16 and 32 ug/ml; MIC50 and MIC90 of SUL is 2 and 4 ug/ml, the range of MICs are as follows: CEF (8 → 64 ug/ml); SUL (1→8 ug/ml); and SUL and CEF at fixed 4 ug/ml (< 0.25 → 4 ug/ml). Combination SUL and CEF lowered MIC to < 0.25 ug/ml in 52 clinical isolate (Figure).

Fig. MIC distributions of cefuroxime salt, sulopenem, sulopenem with 4 μg/ml cefuroxime monohydrate against 55 Mab clinical strains
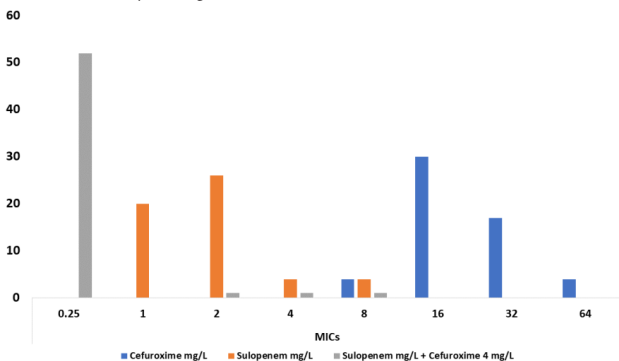
Conclusion: Our results support the emerging hypothesis that dual β-lactam therapy is a promising strategy in the treatment of serious Mab infections.

Investigating the biochemical rationale for this combination will support the application to clinical trials.

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1573. Daptomycin Resistant *Enterococcus faecium*: Combination Therapy Screening

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. *Enterococcus faecium* infections are difficult to treat and there is a growing concern regarding the rising occurrence of daptomycin resistance. We have previously demonstrated that only daptomycin plus ampicillin combination was effective against DAP-R *E. faecium* R497. The efficacy and systematic screening DAP plus β-lactams and DAP plus other combinations against daptomycin-resistant strains of *E. faecium* has not been investigated. Here, we evaluated 40 selected single, dual and triple combinations of antibacterial regimens against two clinical isolates of DAP-R *E. faecium* (R497 and R496 (with daptomycin MIC of 16 and 32 μg/L, respectively).

Methods. *E.faecium* R497 and R496 were tested against an array of antibacterial agents including daptomycin, tigecycline, linezolid, ertapenem, ceftaroline and ceftriaxone using MIC susceptibility tests and 24h time-kill curves (TKC). All susceptibility tests and TKCs were performed in MHB broth containing 50 mg/L calcium. TKCs were performed at half MIC or free peak concentration of each antibacterial (whichever was lower). Synergy was defined as >2 log$_{10}$ CFU/ml decrease compared to the most potent antibacterial agent.

Results. Susceptibility tests demonstrated resistance to all listed β-lactams for both organisms. TKCs demonstrated that combination of daptomycin-ertapenem, daptomycin-ceftriaxone and daptomycin-ceftaroline was not effective against R497. However, addition of ceftriaxone or linezolid to either daptomycin-ertapenem or daptomycin-ceftaroline combinations resulted in synergy against this organism. Combinations of daptomycin-ertapenem and daptomycin-ceftaroline were synergistic against R496. Addition of linezolid, ceftriaxone or tigecycline to either daptomycin-ceftaroline or daptomycin-ertapenem combination did not increase killing activity against R496.

Conclusion. Differential affinity of β-lactams to specific PBP isotypes seems to be a key parameter for the success of daptomycin- β-lactam combinations against multi-drug resistant *E. faecium* . The optimized use of double β-lactam therapy in addition to daptomycin can potentially lead to improved patient outcomes and preserving antibiotic therapy for serious enterococcus infections.

Disclosures. Cesar A. Arias, MD, MSc, PhD, FIDSA, **Entasis Therapeutics** (Scientific Research Study Investigator)**MeMed** (Scientific Research Study Investigator)**Merck** (Grant/Research Support) **Michael J. Rybak, PharmD, MPH, PhD**, **Paratek** (Grant/Research Support)

1574. Multivariate Regression Analysis to Determine Independent Predictors of Treatment Outcomes in the RESTORE-IMI 2 Trial

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. In the RESTORE-IMI 2 trial, imipenem/cilastatin/relebactam (IMI/REL) was non-inferior to PIP/TAZ for treating hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) in the primary endpoint of Day 28 all-cause mortality (D28 ACM) and the key secondary endpoint of clinical response (CR) at early follow-up (EFU; 7-14 d after end of therapy). We performed a multivariate regression analysis to determine independent predictors of treatment outcomes in this trial.

Methods. Randomized, controlled, double-blind, phase 3, non-inferiority trial comparing IMI/REL 500 mg/250 mg vs PIP/TAZ 4 g/500 mg, every 6 h for 7-14 d, in adult patients (pts) with HABP/VABP. Stepwise-selection logistic regression modeling was used to determine independent predictors of D28 ACM and favorable CR at EFU, in the MITT population (randomized pts with ≥1 dose of study drug, except pts with only gram-positive cocci at baseline). Baseline variables (n=19) were pre-selected as candidates for inclusion (Table 1), based on clinical relevance. Variables were added to the model if significant (p < 0.05) and removed if their significance was reduced (p > 0.1) by addition of other variables.

Results. Baseline variables that met criteria for significant independent predictors of D28 ACM and CR at EFU in the final selected regression model are in Fig 1 and Fig 2, respectively. As expected, APACHE II score, renal impairment, elderly age, and mechanical ventilation were significant predictors for both outcomes. Bacteremia and *P. aeruginosa* as a causative pathogen were predictors of unfavorable CR, but not of D28 ACM. Geographic region and the hospital service unit a patient was admitted to were found to be significant predictors, likely explained by their collinearity with other variables. Treatment allocation (IMI/REL vs PIP/TAZ) was not a significant predictor