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 | 98.4 | 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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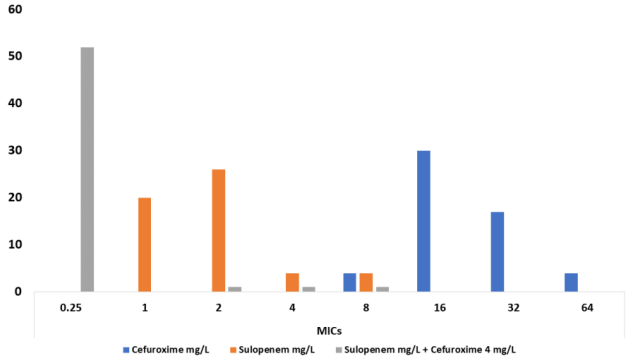
**Session:** P-71. Treatment of Antimicrobial Resistant Infections

***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.

***Disclosures.*** Robert A. Bonomo, MD, Entasis, Merck, Venatorx (Research Grant or Support)

### 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/ml, 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

for ACM or CR; this was not unexpected, since the trial showed non-inferiority of the two HABP/VABP therapies. No interactions between the significant predictors and treatment arm were observed.

***Conclusion.*** This analysis validated known predictors for mortality and clinical outcomes in pts with HABP/VABP and supports the main study results by showing no interactions between predictors and treatment arm.

Table 1. Candidate baseline variables pre-selected for inclusion

| | |
|---|---|
| Treatment arm: IMI/REL vs. PIP/TAZ | Concurrent bacteremia with any pathogen: Yes vs. no |
| Patient age: <65 vs. ≥65 years old | Number of LRT pathogens: Monomicrobial vs. polymicrobial vs. none |
| Patient sex: Female vs. male | Renal impairment: None[a] vs. mild[b] vs. moderate/severe[c] |
| Patient race: White vs. non-White vs. missing | Renal function: Augmented renal clearance[d] vs. normal[e] vs. impaired[f] |
| Region patient was enrolled in: Americas vs. Asia-Pacific vs. Europe | Treatment duration: ≥7 vs. <7 days |
| Type of pneumonia: Nonventilated HABP vs. ventilated HABP/VABP | *K. pneumoniae*: Present vs. not detected |
| APACHE-II score: <15 vs. ≥15 | *P. aeruginosa*: Present vs. not detected |
| CPIS: ≤5 vs. ≥6 | *E. coli*: Present vs. not detected |
| Hospital service unit: Neurology vs. other | *A. calcoaceticus-baumannii* complex: Present vs. not detected |
| In ICU: Yes vs. no | |

[a]Creatinine clearance ≥90 mL/min. [b]Creatinine clearance ≥60 to <90 mL/min. [c]Creatinine clearance ≥15 to <60 mL/min. [d]Creatinine clearance ≥150 mL/min. [e]Creatinine clearance ≥90 to <150 mL/min. [f]Creatinine clearance ≥15 to <90 mL/min.

Figure 1. Independent predictors of greater Day 28 all-cause mortality (MITT population; N=531)

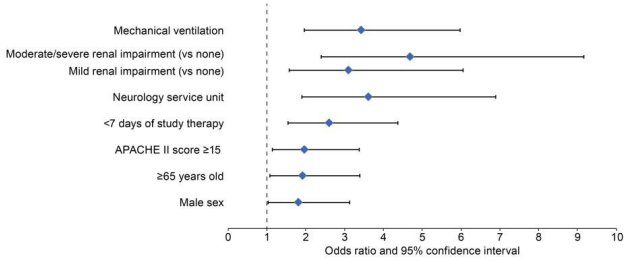
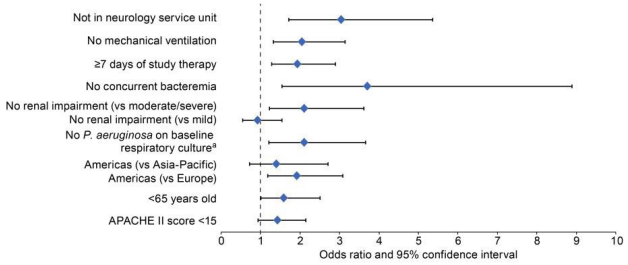



Figure 2. Independent predictors of favorable clinical response at EFU (MITT population; N=531)




[a]A total of 98 pts had no lower respiratory tract culture results.

***Disclosures.*** Robert Tipping, MS, Merck & Co., Inc. (Employee, Shareholder) Jiejun Du, PhD, Merck & Co., Inc. (Employee, Shareholder) Maria C. Losada, BA, Merck & Co., Inc. (Employee, Shareholder) Michelle L. Brown, BS, Merck & Co., Inc. (Employee, Shareholder) Katherine Young, MS, Merck & Co., Inc. (Employee, Shareholder)Merck & Co., Inc. (Employee, Shareholder) Joan R. Butterton, MD, Merck & Co., Inc. (Employee, Shareholder) Amanda Paschke, MD MSCE, Merck & Co., Inc. (Employee, Shareholder) Luke F. Chen, MBBS MPH MBA FRACP FSHEA FIDSA, Merck & Co., Inc. (Employee, Shareholder)Merck & Co., Inc. (Employee, Shareholder)

## 1575. Predictors of Negative Clinical Outcomes among Patients treated with Meropenem-Vaborbactam for Serious Gram-Negative Bacterial Infections: Impact of Delayed Appropriate Antibiotic Selection

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**Session:** P-71. Treatment of Antimicrobial Resistant Infections

***Background.*** Numerous number of studies have found a positive correlation between delayed appropriate antibiotic therapy and negative clinical outcomes (NCO) in Gram-negative bacterial infections (GNBI). The combination of meropenem with vaborbactam (MVB) received Food and Drug Administration approval for the treatment of complicated urinary tract infections and acute pyelonephritis caused by susceptible organisms in August 2017. We sought to determine the impact of delayed appropriate therapy with MVB on NCO among patients with GNBI.

***Methods.*** Multi-center, retrospective cohort study from October 2017 to March 2020. We included adult patients treated with MVB for >72 hours. We excluded patients who received alternative appropriate antibiotics for GNB prior to MVB and patients with unknown dates for index culture. NCO were defined as 30-day mortality and/or microbiological recurrence. All outcomes were measured from MVB start date. Classification and regression tree analysis (CART) was used to identify the time breakpoint (BP) that delineates the risk of NCO. Multivariable logistic regression analysis (MLR) was used to examine the independent association between the CART-derived-BP and NCO. Variables were retained in the model if P< 0.2 and removed in a backward stepwise approach.

***Results.*** A total of 86 patients were included from 13 institutions in the United States: median(IQR) age 55 (37-67) years, 67% male, and 48% Caucasian. Median(IQR) APACHE II and Charlson Comorbidity index scores were 18(11-26) and 4(2-6), respectively. Common sources of infection were respiratory (37%) and intra-abdominal (21%). The most common pathogens were *carbapenem-resistant Enterobacterales* (83%). CART-derived BP between early and delayed treatment was 48 hours, where NCO was increased (36% vs.7%; P=0.04). Delayed MVB initiation was independently associated with NCO in the MLR (aOR=7.4, P=0.02).

Results of Regression Analysis of Variables Associated With Negative Clinical Outcomes and Delayed Appropriate Therapy with Meropenem-vaborbactam

| Variable | Odds ratio, 95% confidence interval (CI) | Adjusted Odds Ratio |
|---|---|---|
| Respiratory infection source | 7.6, [0.94 – 61.1] | 11.2, [2.4 – 52.1] |
| Intensive care at index culture | 11.2, [1.7-82.2] | 14.4, [3.2 – 65.0] |
| Delayed MVB initiation (> 48 hours) | 15.6, [1.5 – 165.6] | 7.4, [1.4 – 40.3] |

***Conclusion:*** Our results suggest that delaying appropriate antibiotic therapy with MVB for >48 hours significantly increases the risk of NCO in patients with GNBI. Clinicians must ensure timely administration of MVB to assure best outcomes in patients with GNBI.

***Disclosures.*** **Kevin W. Garey, PharMD, MS, FASHP**, **Merck & Co.** (Grant/Research Support, Scientific Research Study Investigator) **Michael J. Rybak, PharmD, MPH, PhD**, **Paratek** (Grant/Research Support)

## 1576. Re-Evaluation of cefepime or piperacillin-tazobactam to Decrease Use of Carbapenems in ESBL-Producing *Enterobacterales* BloodStream Infections (REDUCE-BSI)

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**Session:** P-71. Treatment of Antimicrobial Resistant Infections

***Background.*** The ideal therapy for treatment of bloodstream infections (BSI) due to ESBL-producing organisms is widely debated. Although prior studies have demonstrated efficacy of non-carbapenems (CBPNs) for ESBL infections, results from the MERINO study group found increased mortality associated with piperacillin/tazobactam (PT) when compared with meropenem for treatment of ESBL BSI. The goal of this study was to investigate patient outcomes associated with the use of CBPN-sparing therapies (PT and cefepime (CEF)) for ESBL BSI. The primary outcome was in-hospital mortality between non-CBPN (PT and CEF) and CBPN groups. Secondary outcomes included clinical cure, microbiologic cure, infection recurrence, and development of resistance.

***Methods.*** This was a retrospective observational study of patients admitted to the hospital from May 2016 - May 2019 with a positive blood culture for an ESBL-producing organism. Patients receiving meropenem, ertapenem, PT, or CEF were