SPR206 to COL both alone and in combination with other antimicrobials against MDR *P. aeruginosa.*

***Methods.*** MIC susceptibility testing was performed against 15 carbapenem-resistant *P. aeruginosa* strains via broth microdilution. SPR206, COL, aztreonam (AZT) and ceftazidime/ avibactam (CAZ/AVI) were evaluated against the *P. aeruginosa* strains. Dual therapy and triple therapy combinations, either COL or SPR206-based, were tested against four representative strains in 24h time-kill experiments (TKE). Each antibiotic was tested at both 0.5 and 1x the MIC. A >2 $\log_{10}$ and a >3$\log_{10}$ reduction in CFU/ml were defined as synergistic and bactericidal activity, respectively.

***Results.*** The MIC testing revealed a lower range of MIC values for SPR206 compared to all agents tested, including COL, for the 15 MDR *P. aeruginosa* strains. A mean 2-fold reduction in MIC values was observed when comparing the activity of SPR206 to COL. Neither the SPR206 nor COL+CAZ/AVI combinations presented with synergistic activity in the TKEs. SPR206 or COL + CAZ/AVI +AZT, showed synergistic activity against each strain, irrespective of COL or SPR206 base and the tested concentration. At 0.5x MIC bactericidal activity was observed in two of the strains with either COL or SPR206 + AZT. However, at 1xMIC the SPR206+AZT combination exhibited bactericidal activity, equal to that of the triple therapy regimens, against each strain.

***Conclusion.*** The combination of SPR206 with other antibiotic agents showed promise in eradicating MDR *P. aeruginosa.* Further research is warranted to solidify the role of SPR206 in the current antibiotic armamentarium.

***Disclosures.*** Michael J. Rybak, PharmD, MPH, PhD, Paratek (Grant/Research Support)

### 1296. Efficacy of Human-Simulated Exposures of Meropenem/Vaborbactam (MVB) and Meropenem (MEM) against OXA-48 β-lactamase-producing Enterobacterales in the Neutropenic Murine Thigh Infection Model

Christian M. Gill, PharmD[1]; Tomefa E. Asempa, PharmD[2]; David P. Nicolau, PharmD[2]; [1]Center for Anti-Infective Research & Development, Hartford Hospital, Hartford, Connecticut; [2]Hartford Hospital, Hartford, CT

**Session:** P-59. PK/PD studies

***Background.*** OXA-48 exhibits variable hydrolytic activity toward carbapenems, with imipenem and meropenem MICs, though increased, often reporting within the 'susceptible' or 'intermediate' ranges defined by CLSI and EUCAST. Although vaborbactam (VAB) does not enhance MEM activity against OXA-48, ~ 1/3 of OXA-48-producing *Enterobacterales* will test susceptible to MVB due to its higher breakpoint. Clinical implications of this discordance warrant investigation.

***Methods.*** 26 isolates harboring OXA-48 (n=24) and KPC (n=2) were evaluated in the neutropenic murine thigh model. MICs were determined in triplicate per CLSI. Human-simulated regimens of MVB (simulating doses of 2-2 g IV q 8 hours (h) over 3 h) and MEM (2 g IV q 8 h over 3 h) were administered resulting in similar *f*%T >MIC and *f*AUC as humans for MEM and VAB, respectively. Mice received MVB, MEM, or sham control for 24 h. Efficacy was assessed on the resulting overall change in mean± SD $\log_{10}$ CFU/thigh as well as the achievement of ≥ 1 $\log_{10}$ reduction as an established surrogate marker predictive of success for serious infections.

***Results.*** MVB and MEM MICs ranged from 1- 64 and 2 - > 64 mg/L, respectively. Relative to 0 h control, the mean bacterial growth (mean ± SD, CFU/thigh) at 24 h in the untreated control mice was 2.69 ± 1.31. As anticipated for KPCs, MVB resulted in a mean bacterial reduction ≥ 1 $\log_{10}$ (-1.10 ± 0.26), whereas growth was observed on MEM (+1.45 ± 0.88). For all OXA-48 isolates, MVB resulted in variable bacterial densities ranging from -2.54 to +2.68, similarly MEM resulted in -2.18 to +2.66. Addition of vaborbactam did not enhance MEM activity for any isolate. For isolates with MVB MICs ≥ 16 (n=5), 8 (n=5, EUCAST breakpoint), 4 (n=9, CLSI breakpoint), and ≤ 2 (n=5) mg/L, 0%, 0%, 44%, and 60% of isolates treated with MVB or MEM achieved the target reduction of ≥ 1 $\log_{10}$ kill, respectively.

***Conclusion.*** Across the range of MICs evaluated, MVB and MEM humanized exposures *in vivo* resulted in similar reductions and growth in bacterial density for OXA-48-producing *Enterobacterales*. Moreover, these data highlight the poor efficacy of MVB for OXA-48 defined as susceptible using the current EUCAST and CLSI susceptibility criterion. Caution is therefore warranted when treating *Enterobacterales* testing susceptible to MVB without the genotypic profile.

***Disclosures.*** **David P. Nicolau, PharmD**, **Cepheid** (Other Financial or Material Support, Consultant, speaker bureau member or has received research support.)**Merck & Co., Inc.** (Consultant, Grant/Research Support, Speaker's Bureau)**Wockhardt** (Grant/Research Support)

### 1297. In-Vitro Antibacterial Activities of Cefiderocol (S-649266) Alone and With the Addition of Beta-Lactamase Inhibitors Against Multidrug-resistant Acinetobacter baumannii

Jacinda C. Abdul-Mutakabbir, PharmD, AAHIVP[1]; Logan Nguyen, BS[1]; Philip Maassen, BS[1]; Kyle Stamper, BS[1]; Razieh Kebriaei, PhD[1]; Katherine Lev, BS,MS[1]; Taylor Morrisette, PharmD[1]; Keith S. Kaye, MD, MPH[2]; Michael J. Rybak, PharmD, MPH, PhD[3]; [1]Wayne State University, Detroit, Michigan; [2]University of Michigan, Ann Arbor, Michigan; [3]Wayne State University / Detroit Medical Center, Detroit, Michigan

**Session:** P-59. PK/PD studies

***Background.*** Multidrug-resistant (MDR) infections caused by *Acinetobacter baumannii* continue to pose a serious public health threat. Cefiderocol (CFDC) is a new parental siderophore cephalosporin that has displayed potent activity against Gram-negative bacteria, more specifically non-fermenting Gram-negative bacilli, including *A. baumannii*. Although uncommon, elevated minimum inhibitory concentrations (MICs) to CFDC have been reported, when tested against *A. baumannii* isolates, *in-vitro*. The addition of beta-lactamase inhibitors has been shown to be successful in decreasing elevated CFDC MICs. The evaluation of sulbactam (SUL), tazobactam (TAZO), or clavulanic acid (CLAV) in addition to CFDC against *A. baumannii* isolates with elevated CFDC MICs, has yet to be reported. The objective of this study was to evaluate the activity of several beta-lactamase inhibitors in combination with CFDC against *A. baumannii* strains with high CFDC MICs.

***Methods.*** One hundred and fifty carbapenem-resistant *A. baumannii* strains were selected from the Anti-infective Research Laboratory. MIC susceptibility testing was performed for all of the strains via broth microdilution (BMD). Seven strains that exhibited elevated CFDC MICs,16-32 mg/L, were assessed via BMD, with the addition of the following beta-lactamase inhibitors: TAZO, SUL, AVI, and CLAV to CFDC. All *in-vitro* testing for CFDC was completed with the use of iron-depleted cation-adjusted Mueller-Hinton broth to ensure the induction of bacterial iron transporters per manufacturer standards.

***Results.*** A decline in elevated CFDC MIC values was observed in six of the seven *A. baumannii* strains, with the addition of each beta-lactamase inhibitor. AVI showed the most potent activity when added to CFDC, with an average 28- fold reduction in MIC values observed. SUL and CLAV produced similar fold reductions in the MIC values with an average 20-fold reduction observed with the addition of either agent to FDC. The addition of TAZO to CFDC also presented with a decline in MIC values, with an average 7-fold-reduction observed.

Cefiderocol (CFDC) strains with MICs of 16-32 mg/l plus Beta-Lactamase Inhibitors

| Strain # | R# | Species | CFDC MIC (mg/l) | CFDC+AVI MIC (mg/l) | CFDC+SUL MIC (mg/l) | CFDC+TAZO MIC (mg/l) | CFDC+CLAV MIC (mg/l) |
|---|---|---|---|---|---|---|---|
| 1 | 11248 | *A. baumannii* | 32 | 0.5 | 2 | 8 | 1 |
| 2 | 10141 | *A. baumannii* | 32 | 1 | 32 | 32 | 32 |
| 3 | 9755 | *A. baumannii* | 32 | 1 | 0.5 | 4 | 1 |
| 4 | 11357 | *A. baumannii* | 16 | 1 | 1 | 1 | 1 |
| 5 | 11189 | *A. baumannii* | 32 | 1 | 1 | 4 | 0.25 |
| 6 | 10053 | *A. baumannii* | 32 | 8 | 4 | 32 | 4 |
| 7 | 11340 | *A. baumannii* | 32 | 32 | 32 | 32 | 32 |

***Conclusion.*** The addition of several beta-lactamase inhibitors to CFDC has shown promise in decreasing elevated CFDC MICs. Further research is warranted to determine the role of BLIs on CFDC activity.

***Disclosures.*** Michael J. Rybak, PharmD, MPH, PhD, Paratek (Grant/Research Support)

### 1298. Population Pharmacokinetics of Ceftazidime-avibactam among Critically-ill Patients with and without Receipt of Continuous Renal Replacement Therapy

Ellen G. Kline, MS[1]; Minh Hong T. Nguyen, MD[2]; Erin K. McCreary, PharmD[2]; Brett Wildfeuer, BS[2]; Josh Kohl, RN[2]; Kailey L. Hughes, MPH[2]; Chelsea E. Jones, BA[3]; Yohei Doi, MD, PhD[3]; Yohei Doi, MD, PhD[3]; Ryan K. Shields, PharmD, MS[3]; [1]University of Pittsburgh, School of Medicine, Pittsburgh, PA; [2]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [3]University of Pittsburgh, Pittsburgh, PA

**Session:** P-59. PK/PD studies

***Background.*** Ceftazidime-avibactam (CAZ-AVI) is used to treat multidrug-resistant infections. There are limited pharmacokinetic (PK) data among critically-ill patients (pts) and no dosing recommendations for those receiving continuous renal replacement therapy (CRRT).

***Methods.*** We conducted a PK study of CAZ-AVI among pts with and without CRRT. Serial blood samples were collected at 0 (pre-dose), 2, 4, 6, and 8 hours after CAZ-AVI administration. All doses were infused over 2h. Samples were centrifuged and plasma stored at -80°C until analysis by a Shimadzu Nexera XD UHPLC with a Shimadzu 8045 MS. Transitions were monitored in positive mode for CAZ (*m/z* 274.05 < 80.05) and negative mode for AVI (264.00 < 95.90). The assay was reproducible and linear over a range of 0.1 – 20 µg/mL for AVI and 1 – 200 µg/mL for CAZ. non-compartmental analyses were used.

***Results.*** 96 plasma samples from 20 pts were included in the study. Median age was 56 years (range: 31 – 74), 55% were male, and 90% were in the ICU at the time of collection. CZA dosing regimens included 2.5g IV q 8h (n=15), 1.25g IV q 8h (n=2), 0.94g IV q 24h (n=1), and 0.94g IV q 48h (n=2). 7 pts received CRRT (median blood and dialysate flow rates were 250 mL/min and 2.5 L/h, respectively; 86% received 2.5g IV q 8h) and 2 pts received intermittent hemodialysis (iHD). Among remaining pts, median creatinine clearance (CrCl) by Cockcroft-Gault was 91ml/min (range: 37 – 168 ml/min). PK values for CAZ and AVI are shown in the Table. Individual concentration-time profiles for patients receiving 2.5g IV q 8h are shown in the Figure. For patients receiving 2.5g IV q8h, CAZ and AVI median (IQR) AUCs were 525.6 hr*µg/ml (403.2, 762.0) and 83.7 (57.3, 129.5), respectively. For those on CRRT receiving the same dose, CAZ and AVI median (IQR) AUCs were 450.2 (450.0, 558.4) and 102.4 (100.7, 142.3), respectively. CAZ pharmacodynamics (PD) targets of 100% *f*T > 1x and 4x MIC were achieved in 90% and 55% of pts, respectively. AVI PD targets of 100% *f*T > 1 and 2.5µg/mL were achieved in 100% and 80% of pts, respectively. Treatment-emergent adverse events were not reported in any case.

Ceftazidime and avibactam pharmacokinetic parameters among critically-ill patients

| | All patients (n=20) | CrCl > 50ml/min (n=9); 2.5g IV q8h | CRRT (n=6); 2.5g IV q8h | Other (n=5); various doses |
|---|---|---|---|---|
| **Ceftazidime** | | | | |
| Cmax (µg/ml) | 78.1 (61.1, 109.5) | 95.1 (71.2, 124.0) | 94.1 (74.0, 118.5) | 59.4 (23.9, 61.7) |
| Cmin (µg/ml) | 34.5 (23.5, 47.6) | 29.8 (23.6, 36.2) | 45.8 (34.6, 62.7) | 38.6 (7.0, 46.3) |
| Ke (1/hr) | 0.13 (0.06, 0.16) | 0.15 (0.14, 0.19) | 0.07 (0.05, 0.14) | 0.04 (0.04, 0.07) |
| $t_{1/2}$ (hr) | 5.2 (4.3, 12.6) | 4.5 (3.7, 5.1) | 10.1 (5.5, 15.1) | 15.7 (8.9, 16.5) |
| Vd (L) | 34.6 (22.5, 49.3) | 26.0 (16.3, 36.1) | 43.2 (31.3, 56.9) | 40.7 (33.1, 55.1) |
| Cl (L/h) | 3.6 (2.3, 5.2) | 5.3 (3.6, 6.2) | 4.0 (3.0, 4.7) | 2.3 (1.8, 2.3) |
| **Avibactam** | | | | |
| Cmax (µg/ml) | 17.0 (12.0, 21.5) | 16.8 (12.2, 19.3) | 22.3 (18.7, 27.0) | 8.9 (7.6, 12.0) |
| Cmin (µg/ml) | 7.6 (2.7, 10.3) | 3.7 (2.5, 9.0) | 10.9 (8.7, 13.9) | 7.0 (1.7, 8.7) |
| Ke (1/hr) | 0.15 (0.07, 0.21) | 0.21 (0.16, 0.23) | 0.07 (0.05, 0.13) | 0.07 (0.05, 0.07) |
| $t_{1/2}$ (hr) | 4.6 (3.3, 10.2) | 3.3 (3.0, 4.2) | 10.3 (5.6, 15.2) | 9.8 (9.3, 12.6) |
| Vd (L) | 43.2 (23.4, 58.9) | 32.1 (20.6, 43.8) | 56.1 (35.4, 78.9) | 43.8 (42.6, 57.7) |
| Cl (L) | 4.5 (3.3, 6.2) | 6.6 (5.6, 9.6) | 4.2 (3.3, 4.9) | 3.0 (1.6, 3.6) |

All values are expressed as the median with inter-quartile range in paratheses

***Conclusion:*** Among this cohort of critically-ill pts, CAZ and AVI exposures varied; however, most pts achieved PD targeted exposures, including those patients receiving CRRT and a standard dosing regimen of 2.5g IV q 8h.

***Disclosures.*** **Erin K. McCreary, PharmD**, **Entasis** (Advisor or Review Panel member)**Summit** (Advisor or Review Panel member) **Ryan K. Shields, PharmD, MS**, **Allergan** (Advisor or Review Panel member, Research Grant or Support)**Entasis** (Advisor or Review Panel member)**Melinta** (Research Grant or Support)**Menarini** (Consultant)**Merck** (Advisor or Review Panel member, Research Grant or Support)**Shionogi** (Advisor or Review Panel member, Research Grant or Support)**Summit** (Advisor or Review Panel member)**Tetraphase** (Research Grant or Support)**Venatorx** (Advisor or Review Panel member, Research Grant or Support)

**1299. *In Vitro-In Vivo* Discordance with β-lactams against Metallo-β-lactamase-Producing Enterobacterales: Implications for Susceptibility Testing**

Kamilia Abdelraouf, PhD[1]; Sergio Reyes, MD[2]; David P. Nicolau, PharmD[1]; [1]Hartford Hospital, Hartford, CT; [2]St. Vincent's Medical Center, Bridgeport, Connecticut

**Session:** P-59. PK/PD studies

***Background.*** Using murine models of thigh and lung infection, we previously reported the potent *in vivo* activity of carbapenem human-simulated regimens against metallo-β-lactamase-producing Enterobacterales despite the observed resistance *in vitro* (JAC 2020 Apr 1;75(4):997-1005, AAC 2014;58(3):1671-7). In the current study, we examined the *in vivo* activity of cefepime human-simulated regimen against metallo-β-lactamase-producing Enterobacterales in a murine thigh infection model.

***Methods.*** A population of clinical (n=21) and isogenic engineered (n=5) metallo-β-lactamase-producing Enterobacterales isolates expressing VIM, IMP or NDM but not co-expressing ESBLs or serine carbapenemases were utilized. KPC-producing strains (n=3) were included as positive controls. MICs of cefepime, piperacillin-tazobactam and meropenem were determined using broth microdilution in conventional cation-adjusted Muller Hinton and EDTA-supplemented broth at EDTA concentration of 300 mg/L (zinc-limited). The *in vivo* efficacy of a cefepime human-simulated regimen (2 g q8h as 2 h infusion) was determined in the neutropenic murine thigh infection model against the test isolates. Efficacy was measured as the change in $\log_{10}$cfu/thigh at 24 h compared with 0 h controls.

***Results.*** Metallo-β-lactamase-producing Enterobacterales were found to be cefepime, piperacillin-tazobactam and meropenem non-susceptible in conventional broth. Supplementation with EDTA resulted in multi-fold reduction in the MICs and restoration of susceptibility. In accordance with the MICs generated in the zinc-limited broth, the administration of cefepime human-simulated regimen was associated with substantial bacterial reductions among mice infected with the clinical as well as the isogenic engineered metallo-β-lactamase-producing isolates. As anticipated with serine-based resistance, absence of MIC reduction in zinc-limited broth and lack of *in vivo* activity against KPC-producers were observed.

***Conclusion.*** For metallo-β-lactamase-producing Enterobacterales, *in vitro* susceptibility testing to β-lactams with conventional media such as cation-adjusted Muller Hinton broth, a zinc-rich testing medium, is flawed since it does not recapitulate the host environment in which zinc concentrations are low.

***Disclosures.*** **David P. Nicolau, PharmD**, **Cepheid** (Other Financial or Material Support, Consultant, speaker bureau member or has received research support.)**Merck & Co., Inc.** (Consultant, Grant/Research Support, Speaker's Bureau)**Wockhardt** (Grant/Research Support)

**1300. ACOG Committee Opinion #797 and the Dose of Intrapartum Vancomycin: a Potential Danger to Mother and Newborn Alike**

Andras Farkas, PharmD[1]; KRISTINA M. FELDMAN, DO[2]; Krystina L. Woods, MD[3]; Arsheena Yassin, PharmD[4]; [1]Mount Sinai West Hospital, New York, NY; [2]MOUNT SINAI WEST HOSPITAL, NEW YORK, New York; [3]Mount Sinai West, NEW YORK, NY; [4]Mount Sinai St. Luke's Hospital, New York, NY

**Session:** P-59. PK/PD studies

***Background.*** Intra-partum (IP) IV vancomycin (VAN) 20 mg/kg every 8 hours is proposed by #797 for the prevention of early onset neonatal group B streptococcal disease (GBS), a recommendation for which the basis of scientific merit is poor. The goal of our study was to analyze the sparsely sampled published data and raise awareness about the underlying risk of VAN toxicity with this dosing approach.

***Methods.*** Plasma and cord-blood concentration-time data of IV VAN given to mothers in the IP period was analyzed. 5000 Monte Carlo runs were conducted to simulate maternal/fetal exposure ($AUC_{0\text{-}24;\ 24\text{-}48}$) for doses of 1500, 1750 and 2000 mgs q8h and for possible birth times at two-hour intervals. Neonatal VAN clearance was not possible to determine; hence, we used a validated PK model to calculate exposure for the first 24h of life for gestational ages (GA) of 33 to 40 weeks. The AUC range of 400 – 600, and > 600 mg*h/L were considered for indices of efficacy and toxicity, respectively.

***Results.*** Estimates from 30 pairs of serum and cord-blood concentrations analyzed with a 2-compartment model are shown in Table 1. Maternal VAN exposures seem acceptable up to 2 IP doses given with mean (SD) $AUC_{0\text{-}24}$ of 394 (140), 474 (167), and 540 (193) mg*h/L for the 1500, 1750 and 2000 mg regimens. Most mothers (up to 83%) who receive three or more doses will be subjected to nephrotoxic exposures (Figure 1.). Neonatal evaluations indicate similarly low PTAs for the three dosing regimens when the efficacy target is considered (Figure 2. A). On the other hand, the PTAs for potentially nephrotoxic exposure is expected to reach undesirable levels when three or more doses were to be administered. The risk is profoundly high in GA of 33 to 35 weeks and birth times beyond 20 hours after the initiation of intra-partum prophylaxis (Figure 2. B).

Figure 1.

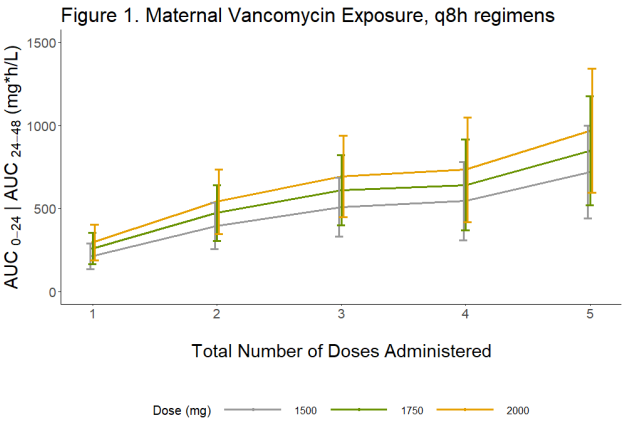


Figure 2.A