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

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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.

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

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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.

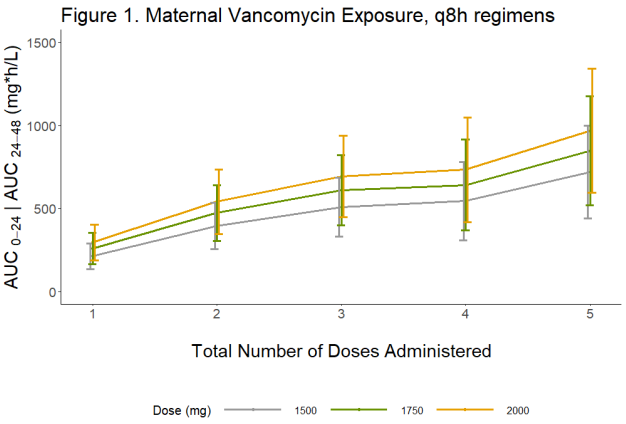

Figure 2.A