***Results.*** During 25 admissions, 12 patients had a first $AUC_{24}$ at goal and 13 patients had a first $AUC_{24}$ below goal. Of 41 $AUC_{24}$ calculations, 27 $AUC_{24}$s were ≥400 mg hours/L (group 1), and 14 $AUC_{24}$s were <400 mg hours/L (group 2). Median $AUC_{24}$ was 561 mg hours/L for group 1 vs. 344.5 mg hours/L for group 2 ($P < 0.001$). Correlating Cmin and Ctrough (Ctr) for group 1 and group 2 were 12 mg/L and 13.5 mg/L vs. 6.4 mg/L and 7.3 mg/L, respectively ($P < 0.001$). Figure 1 shows the pharmacokinetic parameters for each group. Spearman correlation between $AUC_{24}$ and Cmin was 0.87. Of the 35 subtherapeutic VAN STCs, 20 (57.1%) achieved an $AUC_{24}$ ≥400 mg hours/L (P = 0.08). Subgroup analysis of $AUC_{24}$ 400–600 mg hours/L showed a median $AUC_{24}$ of 519 mg hours/L with correlating Cmin and Ctr of 10.6 mg/L and 11.9 mg/L, respectively. The MIC was <1 in 90.9% of cases (Figure 2). The mean VAN dose required to achieve an $AUC_{24}$ ≥400 mg hours/L was 77.7 mg/kg/day; dosing frequency did not appear to affect $AUC_{24}$ outcome. Time to culture clearance was 2 days in group 1 and 6.5 days in group 2 (P = 0.24). No cases of nephrotoxicity were identified despite $AUC_{24}$ values ranging from 265–1294 mg hours/L.

***Conclusion.*** $AUC_{24}$ monitoring using a 2-sample trapezoidal method was successfully implemented at this institution. The results of this study align with previous pediatric studies, supporting the use of lower serum trough concentration goals of 10–15 mg/L.

Figure 1: Pharmacokinetic Data

| Pharmacokinetic Parameters | Total (n = 41) | $AUC_{24}$ ≥400 mg-hr/L (n = 27) | $AUC_{24}$ <400 mg-hr/L (n = 14) | P-value |
|---|---|---|---|---|
| $AUC_{24}$ (mg-hr/L) (median, IQR) | 494 (365-576) | 561 (494-776) | 344.5 (314-365) | <0.001* |
| AUC/MIC (median, IQR) (n=21) | 446 (365-863) | 516 (429-1028) | 329 (286-365) | -- |
| Ke ($hr^{-1}$) (median, IQR) | 0.247 (0.201-0.282) | 0.231 (0.189-0.282) | 0.259 (0.238-0.282) | 0.06 |
| Half-life ($t_{1/2}$) (hr) (mean, +/-SD) | 3 (2.2-3.8) | 3.1 (2.3-3.9) | 2.7 (2.2-3.2) | 0.07 |
| Cmax (mg/L) (median, IQR) | 35 (27.1-40.9) | 37.7 (33.9-50.6) | 26 (22.7-27.1) | <0.001* |
| Cmin (mg/L) (mean, +/- SD) | 10.1 (6.3-13.9) | 12 (8.8-15.2) | 6.4 (5.3-7.5) | <0.001* |
| Ctrough^ (mg/L) (mean, +/-SD) | 11.4 (7.3-15.5) | 13.5 (10.1-16.9) | 7.3 (6.1-8.5) | <0.001* |
| Volume of distribution (L/kg) (mean, +/- SD) | 0.65 (0.43-0.87) | 0.6 (0.4-0.8) | 0.75 (0.57-0.93) | 0.03* |
| Clearance (L/hr) (median, IQR) | 2.8 (1.7-4) | 2.5 (1.1-4) | 3.05 (1.9-4.9) | 0.22 |

*indicates statistical significance

Figure 2: Microbiology Data

| | Total | First AUC ≥400 mg*hr/L | First AUC <400 mg*hr/L | P-value |
|---|---|---|---|---|
| Positive culture (n, %) (n=25) | 15 (60) | 8 (53.3) | 7 (46.7) | 0.69 |
| Repeat cultures obtained (n, %) (n=15) | 8 (53.3) | 6 (75) | 2 (25) | 0.13 |
| Organism (n, %) (n=15) | | | | |
| Blood | | | | 0.41 |
| - *S. aureus* | 2 (13.3) | 2 (100) | 0 (0) | |
| - *B. cereus* | 1 (6.67) | 1 (100) | 0 (0) | |
| - *S. mitis* | 1 (6.67) | 1 (100) | 0 (0) | |
| CNS | | | | |
| - *S. epidermidis* | 3 (20) | 1 (33.3) | 2 (66.7) | |
| - *S. aureus* | 1 (6.67) | 1 (100) | 0 (0) | |
| - *S. intermedius* | 1 (6.67) | 1 (100) | 0 (0) | |
| Sputum | | | | |
| - *S. aureus* | 1 (6.67) | 0 (0) | 1 (100) | |
| - *S. pneumoniae* | 1 (6.67) | 0 (0) | 1 (100) | |
| Intra-abdominal Abscess | | | | |
| - *E. avium* | 1 (6.67) | 0 (0) | 1 (100) | |
| Islet cells | | | | |
| - *E. faecium* | 1 (6.67) | 0 (0) | 1 (100) | |
| Wound culture (bone) | | | | |
| - *S. aureus* | 1 (6.67) | 1 (100) | 0 (0) | |
| Wound culture (skin) | | | | |
| - *Coagulase-negative staphylococcus* | 1 (6.67) | 0 (0) | 1 (100) | |
| MIC available (n, %)(n=15) | 11 (73.3) | 6 (54.5) | 5 (45.5) | 1.0 |
| MIC result (n, %)(n=11) | | | | |
| - 0.5 | 5 (45.5) | 4 (80) | 1 (20) | 0.35 |
| - 1 | 5 (45.5) | 2 (40) | 3 (60) | |
| - 2 | 1 (10) | 0 (0) | 1 (100) | |

***Disclosures.*** **All authors:** No reported disclosures.

### 1553. Human-Simulated Pharmacokinetic Profiles of Cefiderocol and Meropenem Are Conserved in Murine Models of Thigh Infection With or Without Iron Overload

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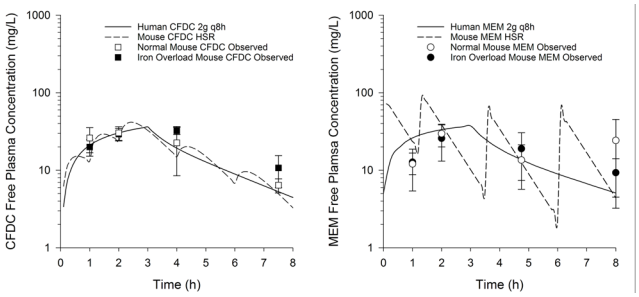
**Session:** 162. PK/PD and Susceptibility Testing
*Friday, October 4, 2019: 12:15 PM*

***Background.*** A translational murine model of thigh infection with comorbid iron overload was previously developed to study the efficacy of iron-dependent siderophore-antibiotic conjugates under conditions where the hypoferremic response of innate immunity may be compromised. Given the potential for functional organ damage from excessive tissue iron, which could alter the pharmacokinetic (PK) profiles of antibiotics being compared for efficacy using this model, the effects of iron overload on a siderophore-β-lactam conjugate, cefiderocol (CFDC), and a non-siderophore β-lactam, meropenem (MEM), were studied.

***Methods.*** Female CD-1 mice received iron dextran (Fe-D) 100 mg/kg intraperitoneally for 14 days as previously shown to produce vastly supranormal iron concentrations in serum, liver, and spleen (ASM Microbe 2019 abstract HMB-373). Age-matched control mice were not dosed with Fe-D. Mice were rendered neutropenic. On day 15, both thighs of iron-overloaded and control mice were inoculated intramuscularly with *Acinetobacter baumannii* suspensions of $10^7$ CFU/mL. Two hours after inoculation, mice in each model were dosed with previously developed human-simulated regimens (HSR) of CFDC or MEM simulating human PK profiles after doses of 2g q8h (3 hours infusion) for both drugs. At 4 time points per regimen, 6 mice per model were sacrificed for blood collection. Plasma total MEM and CFDC concentrations were measured with HPLC and LC-MS-MS, respectively. Free concentrations were calculated with murine protein binding. At each time point, mean free concentrations in both models were compared using Student's *t*-test.

***Results.*** Observed murine-free plasma concentrations ± 95% CI of CFDC and MEM are overlaid with simulated human and murine profiles in the figure. In both models, these regimens approximated human exposures after clinical doses. For all time points and both drugs, concentrations were not significantly different ($P > 0.05$) between models with or without iron overload.

***Conclusion.*** Iron overload did not significantly alter PK profiles of a siderophore-β-lactam conjugate, CFDC, or a non-siderophore β-lactam, MEM. These data support the use of CFDC and MEM HSR for pharmacodynamic studies utilizing both iron-overloaded and standard murine thigh infection models.




***Disclosures.*** **All authors:** No reported disclosures.

### 1554. Nebulized Liposomal Amphotericin B for Treatment of Murine Pulmonary Mucormycosis

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**Session:** 162. PK/PD and Susceptibility Testing
*Friday, October 4, 2019: 12:15 PM*

***Background.*** Pulmonary mucormycosis, a life-threatening infection of immunocompromised individuals, can have a 95% mortality rate, even with treatment. Intravenous (IV) liposomal amphotericin B (AmBisomeâ, AmBi) is used to treat the infection, but rapid growth of the pathogen can limit the drug's effectiveness. In the present study we investigated whether nebulized (nebz) AmBi could improve treatment outcome using a neutropenic murine model of pulmonary mucormycosis.

***Methods.*** *Rhizopus oryzae* (ATCC MYA4621) was grown on Potato Dextrose Agar for 3–7 days, followed by spore harvesting, and determination of spore viability. Male ICR mice were immunosuppressed with 200 mg/kg of cyclophosphamide d-2, d0, d+2, d+4, and d0 challenged intranasally with $1 \times 10^6$ spores. In Study 1, mice ($n$ = 16 mice/gp) were given AmBi at 7.5 or 10 mg/kg IV for 6 days, or nebz AmBi for 20 minutes (1.33 mg/mL AmBi in reservoir) for 4 days. In Study 2, 16 mice/gp were given AmBi at 15 mg/kg IV for 6 days or nebz AmBi for 7 days. PBS was the control. Lungs and kidneys were collected d+6 to determine drug concentration by a bioassay ($n$ = 7–8 mice/gp) and morbidity ($n$ = 8 mice/gp) monitored to d+21.

***Results.*** In Study 1, survival was significantly better with nebz AmBi for 4 days (50%) or 10 mg/kg IV AmBi (33%) vs. 7.5 mg/kg IV AmBi (0%) ($P < 0.003$). In Study 2 with 13% survival in the PBS mice, 7 days of nebz AmBi produced 100% survival and 15 mg/kg IV AmBi gave 83% survival ($P < 0.02$ vs. PBS), underscoring the need for more intensive treatments. In Study 2, we also observed that average lung drug levels with nebz AmBi were significantly lower (3 μg/g lung) than with 15mg/kg AmBi IV (19 μg/g lung) ($P = 0.003$), even though both treatments were comparably effective. Kidney drug levels with 15 mg/kg AmBi IV were 13 μg/g and in comparison, nebz AmBi produced no detectable drug.

***Conclusion.*** Daily nebulization of AmBi for one week or a high dose of IV AmBi at 15 mg/kg for 6 days protected the mice from severe pulmonary mucormycosis caused by *R. oryzae*, delivering effective drug levels to the lungs. The IV treatment yielded elevated levels of drug in the kidneys, while nebulization with AmBi produced no detectable drug in the kidneys. This indicated that nebz AmBi would be a less nephrotoxic, but still very effective route for drug delivery.

***Disclosures.*** **All authors:** No reported disclosures.