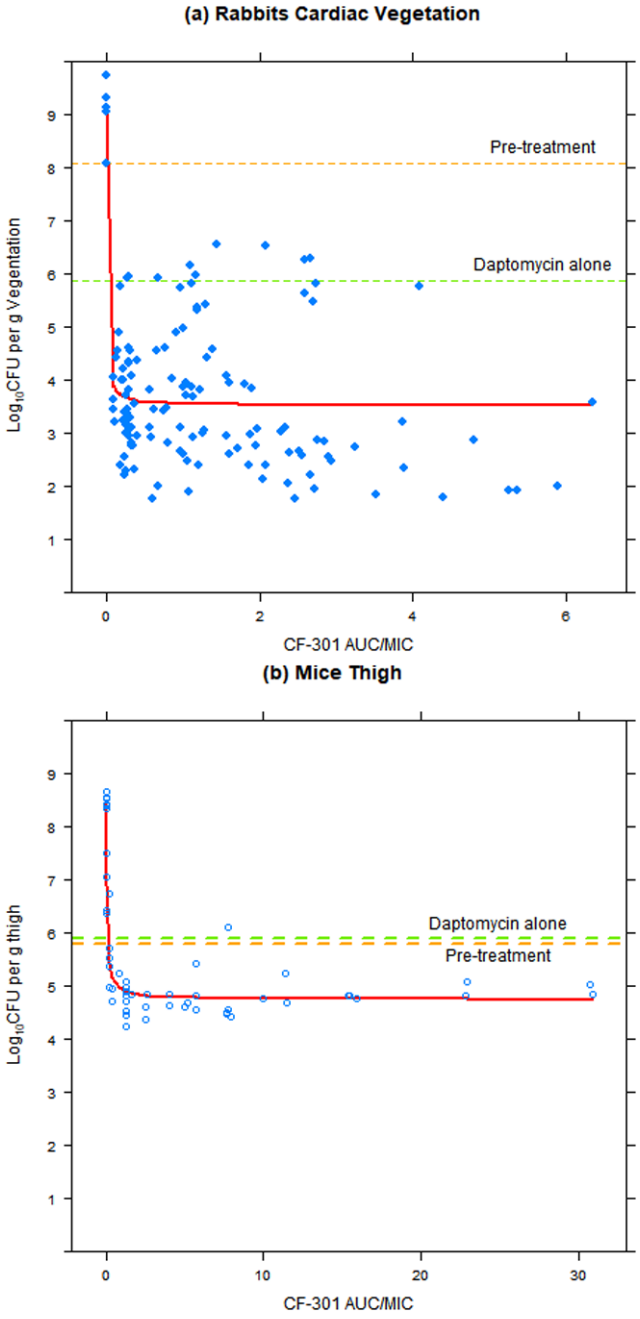
PK data using NONMEM and the most parsimonious model was selected by improvement in objective function value ($P < 0.01$). To evaluate efficacy, 349 animals with 177 mice (neutropenic thigh infection) and 172 rabbits (aortic valve infective endocarditis were treated with exebacase in addition to suboptimal doses of daptomycin (DAP). Full PK profiles were simulated for individual animals. Fifty-nine dosing regimens of exebacase in mice (0–90 mg/kg) and 18 regimens in rabbits (0–1.4 mg/kg) with q24h, q12h and q8h frequencies. Relationship between AUC/MIC, Cmax/MIC, T> MIC, and log-CFU was examined using a range of functions by comparing residual standard error (RSE).

Results. 3-compartment model with allometric scaling best described the PK data and was validated by bootstrap and Goodness of Fit. Maximum drop in $\log_{10}$CFU/g in target tissues was at AUC/MIC< 0.2 for exebacase when added to DAP that was associated with CF reduction of -5 logs in rabbits (Figure (a)) with similar magnitudes in cardiac vegetations, kidney and spleen, and -4 logs in mice (Figure (b)). Treatment with DAP alone had $\log_{10}$CFU reduction of -1 in mice; and -2 in rabbits. AUC/MIC was an appropriate predictor of CFU reductions.

Conclusion. PK model adequately described the data for 4 animal species. Exebacase addition to DAP has a synergistic effect on efficacy measured by CFU reductions in target tissues in the animal models. Results support previously presented determinations of AUC/MIC as predictor of efficacy. Maximum reductions in CFU in rabbits and mice were observed at AUC/MIC ratios <0.2. These results further indicate that rabbit is the most appropriate efficacy model with MICs and antibacterial activity reflective of previously reported observations in human serum.



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

1551. Systemic Tobramycin Absorption Resulting from Antibiotic-Impregnated Cement Spacers for the Treatment of Prosthetic Joint Infection

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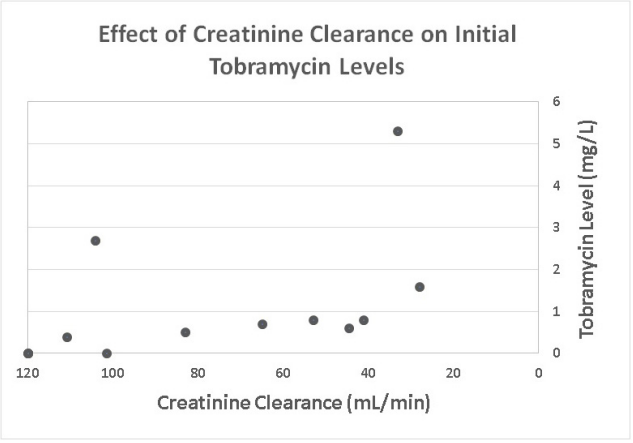
Background. Antibiotic-impregnated cement spacer (ACS) placement has been a cornerstone of two-stage surgical management of prosthetic hip and knee infection for decades. Utilized antibiotics have included aminoglycosides and vancomycin. Pharmacokinetic modeling studies have described peak systemic levels within the first 24–48 hours post-operatively, followed by rapid clearance. While this systemic exposure was previously felt insufficient to cause organ toxicity, a few studies have described antibiotic-induced nephrotoxicity.

Methods. We prospectively enrolled patients with prosthetic hip or knee infection, and subsequent ACS placement, containing vancomycin and tobramycin, from October 2017 to February 2019, at Allegheny General Hospital. Risk factors for post-operative nephrotoxicity, including patient comorbidities, receipt of potentially nephrotoxic medications, estimated creatinine clearance (CrCl), perioperative hypotension, total spacer tobramycin dosage, and post-operative day 1 (POD1) and 3 (POD3) serum tobramycin levels were recorded. Patients who had antibiotic cement spacer exchange, or had received systemic aminoglycoside therapy, were excluded.

Results. Thirteen patients were enrolled, comprising 4 hip and 9 knee ACS, with respective median (interquartile range (IQR)) tobramycin cement dosages of 3.8 (2.86–4.58) and 4.8 (4.8–9.6) grams. Tobramycin levels were measured at a median 16.5 and 60.7 hours on POD1 and POD3, respectively. Three hip and six knee ACS had respective, detectable POD1 median serum tobramycin levels of 0.6 (0.38–1.20) and 0.8 (0–0.8) µg/mL; three knees, but no hip ACS had detectable POD3 serum tobramycin levels. Six of the nine patients with detectable POD1 serum tobramycin levels had a CrCl of less than or equal to 65 mL/minute (figure), while each patient with detectable POD3 levels had a CrCl of less than 45 mL/minute. No significant changes in baseline CrCl were identified. A relationship between tobramycin cement dosage and detectable serum tobramycin levels was not observed.

Conclusion. Low baseline CrCl, but not the total tobramycin dosage or other nephrotoxicity risk factors, may be the single most reliable predictor of detectable postoperative systemic tobramycin levels in patients who have received hip or knee ACS.



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

1552. Correlation Between Vancomycin Serum Trough Concentrations and Area Under the Curve in Pediatric Patients

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Background. Despite years of experience with vancomycin (VAN), the optimal method to monitor VAN therapy in pediatric patients is still unknown. Recent pediatric data indicate serum trough concentrations lower than 10–20 mg/L or 15–20 mg/L based on indication may achieve an AUC_{24} > 400 mg hours/L. The primary study objective was to compare AUC_{24} to goal VAN serum trough concentrations (STC).

Methods. A retrospective chart review of pediatric patients who received intravenous VAN June 1, 2018 to December 31, 2018 was completed. AUC_{24} was calculated using a trapezoidal method with 2 steady-state serum concentrations. A serum peak concentration was drawn 1 hour and 15 minutes following the end of infusion and an STC was drawn 30 minutes prior to infusion.

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)	

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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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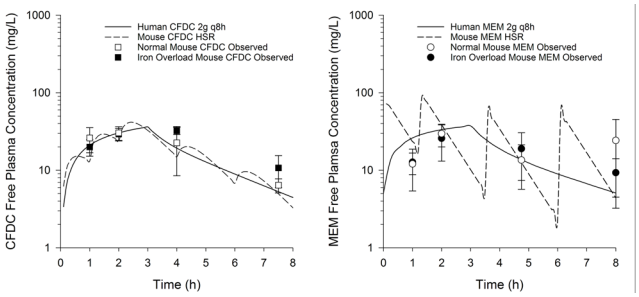
Background. A translational murine model of thigh infection with comorbid iron overload was previously developed to study the efficacy of iron-dependent siderophore-antibiotic conjugates under conditions where the hypoferremic response of innate immunity may be compromised. Given the potential for functional 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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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 1×10^6 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.