rabbits and mice were observed at AUC/MIC ratios <0.2. These results further indicate reductions in target tissues in the animal models. Results support previously presented data of -1 in mice; and -2 in rabbits. AUC/MIC was an appropriate predictor of CFU reductions.

Mean log reduction of -4 logs in mice (Figure (b)). Treatment with DAP alone had log reductions 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 CFU reduction of 1.5 10^3 in the catheter, and -4 logs in mice (Figure (b)). Treatment with DAP alone had log reductions of -6 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 CFU reduction of 1.5 10^3 in the catheter, and -4 logs in mice (Figure (b)).

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 a predictor of efficacy. Maximum reductions in CFU in rabbits and mice were observed at AUC/MIC ratios <0.1. These results further indicate that Rabbits Cardiac Vegetation is the most appropriate efficacy model with MICs and antibacterial activity reflective of previously reported observations in human serum.

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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 equal to 65 mL/minute (figure), while each patient with detectable POD3 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.

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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 greater than 400 mg hours/L. The primary study objective was to compare AUC 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 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\textsubscript{24} at goal and 13 patients had a first AUC\textsubscript{24} below goal. Of 41 AUC\textsubscript{24} calculations, 27 AUC\textsubscript{24} were ≥400 mg hours/L (group 1), and 14 AUC\textsubscript{24} were <400 mg hours/L (group 2). Median AUC\textsubscript{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 (Cts) 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\textsubscript{24} and Cmin was 0.87. Of the 35 subtherapeutic VAN STCs, 20 (57.1%) achieved an AUC\textsubscript{24} ≥400 mg hours/L (P = 0.08). Subgroup analysis of AUC\textsubscript{24} 400–600 mg hours/L showed a median AUC\textsubscript{24}, of 519 mg hours/L, with corresponding Cmin and Ctrough 10.6 mg/L and 11.9 mg/L, respectively. The MIC was <1 in 90.9% of cases (Figure 2). The mean dose required to achieve an AUC\textsubscript{24} ≥400 mg hours/L was 77.7 mg/kg/day; dosing frequency did not appear to affect AUC\textsubscript{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\textsubscript{24}, values ranging from 265–1294 mg hours/L.

Conclusion. AUC\textsubscript{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.

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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 (AmBisome\textsuperscript{®}, 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. R. oryzae (ATCC MYA M4621) 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, d-0, d+3, d+4, and d+7 challenged intranasally with 1 × 10⁶ spores. In Study 1, mice (n = 16 mice/group) were given AmBi at 7.5 or 10 mg/kg IV for 4 days, or nebz AmBi for 20 minutes (1.33 mg/mL AmBi in reservoir) for 4 days. In Study 2, 16 mice/group 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/group) and morbidity (n = 8 mice/group) 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 (9 μg/g lung) (P = 0.003), even though both treatments were comparatively 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. AmBi dose d+6 indicated that nebz AmBi would be a less nephrotoxic, but still very effective route for drug delivery.

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