results in highly variable drug exposures. Thus, intravenous (IV) vancomycin was used to assess pharmacokinetic-toxidynamic (PK-TD) relationships with nephrotoxicity.

Methods. Male Sprawley-Dawley rats received IV vancomycin via an internal jugular vein catheter. Total daily doses ranging from 150 to 400 mg/kg/day were administered as a single or twice daily injection over 24 hours. Controls received IV saline. Plasma sampling was conducted via a second dedicated catheter, with up to eight samples in 24 hours. Twenty-four-hour urine was collected during this time and assayed for kidney injury molecule 1 (KIM-1), osteopontin (OPN) and clusterin using the MILLIPLEX Rat Kidney Panel. Vancomycin in plasma was quantified via LC-MS/MS. PK analyses were conducted using Pmetrics for R. PK exposures during the first 24 hours (i.e., \( \text{AUC}_{0-24} \), \( \text{C}_{\text{max}} \)) were calculated from Bayesian posteriors. PK-TD relationships were assessed with Spearman's rank coefficient and the best fit mathematical model (e.g., exposure response curve fitting in GraphPad v.7).

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Background. Limited data exists regarding antivirals and extracorporeal membrane oxygenation (ECMO). We present a case of pharmacokinetics (PK) of ganciclovir in an immunocompromised patient with respiratory failure requiring veno-venous ECMO support without continuous renal replacement therapy (CRRT). A 6-year old with a stage IV rhodoblast tumor s/p autologous bone marrow transplant rescue after chemotherapy 80 days prior to illness, developed acute respiratory failure. Patient was started on cefepime, vancomycin, trimethoprim/sulfamethoxazole, ganciclovir and micafungin. On Day (D) 7 of ICU stay, ECMO initiated due to concerns for air leak syndrome. Bronchovascular lavage on D8 resulted positive for Pneumocystis and CMV by PCR. Prior to ECMO initiation, CMV levels were <500 IU/mL. After the initiation of ECMO, patient had up-trending CMV PCR that peaked at 139,000 IU/mL with concerns for antiviral resistance or ganciclovir underdosing (5 mg/kg/dose) on ECMO.

Methods. Peak and random plasma levels to calculate AUC24 were drawn after concerns for under dosing on ICU D16/ECMO D9. Ganciclovir concentrations were determined by HPLC in the Special Chemistry Department at Cincinnati Children's Hospital Medical Center. After dose adjustments on ICU D17/ECMO D10, repeat peak/random levels were obtained on ICU D19 after steady state was achieved.

Results. Ganciclovir dosing of 5 mg/kg every 12 hours was subtherapeutic, both clinically and based upon PK analysis. 0.5 and 5 hours post-infusion levels were 5.47 and 0.76 μg/mL respectively with a calculated AUC24 to be 26 mg hour/L. After increasing the dose to 10 mg/kg every 12 hours, repeat levels at 1 and 5 hours were 4.53 and 1.48 μg/mL respectively, achieving the AUC24 goal of 50 mg hour/L.

Conclusion. This is the first case report of ganciclovir PK in either pediatric or adult ECMO populations. Standard recommended dosing of 5 mg/kg every 12 hours provided a low, subtherapeutic AUC24 with increased CMV viral load. With dose increase to 10 mg/kg, targeted AUC24 of 50 for ganciclovir was achieved clinically, CMV viral loads decreased and remained suppressed. Higher doses of ganciclovir may be required in ECMO patients, especially without concurrent CRRT, although further pharmacokinetic/pharmacodynamic studies are needed in these critically ill patients.

Disclosures. All authors: No reported disclosures.

1421. IV Brincidofovir (BCV): Pharmacokinetics (PK) and Safety of Multiple Ascending Doses (MAD) in Healthy Subjects
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Background. BCV is a lipid conjugated nucleotide analog that has shown rapid viral clearance with oral administration in patients with adenovirus infection, and improved survival in animal models of smallpox. Phase I single ascending dose evaluation of IV BCV demonstrated that 2 hour infusions of 10, 25, and 50 mg were well tolerated and not associated with significant adverse events (AEs) or laboratory abnormalities. This study evaluated the safety and PK of multiple ascending doses of IV BCV in healthy subjects.

Methods. Twenty-eight subjects were randomized 3:1 to receive blinded IV BCV or placebo in sequential MAD cohorts (Table A). Study drug was given twice a week (BIW) for 2 weeks or once a week (QW) for 4 weeks. Plasma PK samples were collected on Day 1 and after the last dose and assayed by HPLC-MS. Plasma PK parameters were determined by noncompartmental analysis and dose proportionality and accumulation was assessed. Safety assessments were performed during the dosing period through 14 days post last dose.

Results. Twenty-seven male and female subjects (29–65 years, 93% White) were enrolled and 26 completed the study. Plasma BCV \( C_{\text{max}} \) and AUC increased in proportion to dose with no accumulation (Table A). AEs were generally mild and included diarrhea and headache. Alanine aminotransferase (ALT) elevations were asymptomatic and resolved upon cessation of dosing. No serious AEs occurred.

Table A. BCV PK on Day 1 and Safety

| Plasma BCV PK | BCV 10 mg BIW | BCV 20 mg QW | 2-hour Infusion | 2-hour Infusion | 1-hour Infusion | Pooled Placebo |
|---------------|---------------|---------------|-----------------|-----------------|-----------------|---------------|
| (n = 9)       | (n = 6)       | (n = 5)       | (n = 7)         |                 |                 |               |
| C\(_{\text{max}}\) (ng/mL) | 553 (33%) | 1,110 (19%) | 1,720 (19%) | NA               |                 |               |
| AUC\(_{0-24}\) (ng*h/mL) | 1,374 (34%) | 2,982 (32%) | 2,919 (18%) | NA               |                 |               |
| Drug-related AEs in >2 subjects | | | | | | |
| Diarrhea | 0 | 3 (60%) | 1 (20%) | 0                |                 |               |
| Headache | 4 (44%) | 3 (60%) | 3 (60%) | 4 (57%) |                 |               |
| Fatigue | 2 (23%) | 0 | 0 | 0 |                 |               |

1. \( C_{\text{max}} \) and AUC\(_{0-24}\): geometric means (%CV).

Conclusion. Multiple doses of IV BCV given as 10 mg BIW or 20 mg QW were generally safe and well tolerated. Mild diarrhea was reported only after IV BCV 20 mg QW. As seen with oral BCV, ALT increases were reversible upon cessation of drug, and were not associated with hyperbilirubinemia. BCV exposure was dose-proportional.
and no accumulation was observed. The data support evaluation of repeat dose administration in virally infected patients.

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1422. Comparative Monte-Carlo Analysis of Aztreonam-Avibactam vs. Ceftazidime-Avibactam Against Carbapenem-Resistant Gram-Negative Pathogens

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**Background.** The new β-lactamase inhibitor, avibactam (AVI), has recently been combined with ceftazidime (CAZ) as CAZ-AVI. AVI is also in Phase 3 clinical trials combined with aztreonam as ATM-AVI. Both drug combinations have similar in vitro activity against some organisms, but ATM-AVI is more potent against metallo-β-lactama (MBL)-producing organisms. However, against P. aeruginosa (PA), CAZ-AVI is more potent. Since these compounds have similar pharmacokinetic (PK)/pharmacodynamic (PD) profiles, and there is a need for drugs for the treatment of resistant microorganisms, a Monte-Carlo analysis (MCA) was used to assess their potential efficacy and cost in resistant pathogen treatments.

**Methods.** MCA (n = 10,000) was performed for ATM-AVI and CAZ-AVI using PK parameters, CrCl vs. CI regression, PD targets, and recent MICs from peer-reviewed literature against five carbapenem-resistant (CR) organisms: P. aeruginosa (CR-PA), E. cloacae (CR-EC), K. pneumoniae (CR-KP), Enterobacteriaceae (CR-ENT), and MBL producing Enterobacteriaceae (MBL-ENT). Only MIC studies that directly evaluated both combinations were utilized. Our institution’s inpatient CrCl distribution (range: 10–120 mL/min) was used to assess drug clearance. The ATM-AVI regimen was 1.5 g q6h with a 3 hours infusion and adjusted for renal function) and the CAZ-AVI regimen was 2 g q8h with a 2-hour infusion and adjusted for renal function). PD targets (%T > MIC) for ATM-AVI were 40 and 60% and for CAZ-AVI were 40 and 70%.

**Results.** Target attainment (TA%) for each regimen and organism was:

| Drug | ATM-AVI | CAZ-AVI |
|------|---------|---------|
| Regimen | 1.5 g q6h (3h infusion) | 2 g q8h (2h infusion) |
| IT>MIC (% of interval) | 40 | 60 |
| CR-PA | 48 | 43 |
| CR-EC | 100 | 100 |
| CR-KP | 100 | 100 |
| CR-ENT | 100 | 100 |
| MBL-ENT | 100 | 99 |

**Conclusion.** Both ATM-AVI and CAZ-AVI displayed very high TA% (>95%) for CR-EC, CR-KP, and CR-ENT at both PD targets. However, TA% for MBL-ENT was very low for CAZ-AVI and 299% for ATM-AVI. Against CR-PA, CAZ-AVI was had much higher TA% than ATM-AVI (87–93% vs. 43–48%). These differences suggest different roles for each drug combination in clinical practice.

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1423. Plasma and Intrapulmonary Pharmacokinetics of Sitafloxacin in Thai Critically Ill Patients With Pneumonia

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**Background.** Pneumonia is a major cause of mortality in critically ill patients. Sitafloxacin, broad-spectrum fluoroquinolone, has an in vitro activity against many drug-resistant pathogens causing pneumonia. The objectives of this study were to determine epithelial lining fluid (ELF) concentrations of sitafloxacin and compare those with plasma, including pharmacokinetic (PK) parameters in Thai critically ill patients.

**Methods.** Sitafloxacin concentrations were determined using LC-MS/MS assay. Twelve critically ill patients with pneumonia were enrolled to receive oral sitafloxacin 200 mg single dose. Serial blood samples were collected in each patient (seven time points) prior to dose and over 12-hour interval. BAL samples were collected once in each patient simultaneously with plasma sampling. Intrapulmonary penetration was evaluated as the ELF to unbound plasma concentration ratio calculated by fraction unbound related to albumin concentration in each patient. A compartment model was applied to describe plasma PK parameters using WinNonLin software.

**Results.** The median age was 57 years with median weight was 52 kg. The highest penetration ratio of ELF to unbound plasma concentrations based on median value was 1.3, observed during 5–6 hours (Table 1). The data fitted to one-compartment model that described absorption, distribution and elimination. PK parameters are presented in Table 2.

**Conclusion.** Oral sitafloxacin well penetrate into ELF at a penetration ratio of 130% related to unbound plasma in Thai critically ill patients. Sitafloxacin is a promising agent for treatment of lower respiratory tract infections caused by susceptible pathogens in intensive care unit.

| Table 1: Penetration Ratio Based on Median of Sitafloxacin Concentrations in Each Sampling Time |
|---|---|---|---|---|
| BAL Fluid Sampling Time (hour) | Sample (nL) | ELF Conc. (µg/mL) | Unbound Plasma Conc. (µg/mL) | Ratio ELF: Unbound Plasma Penetration (%) |
| 0.5 - 2 | 3 | 0.09 | 0.29 | 0.3 | 30 |
| 3 - 4 | 3 | 0.50 | 0.91 | 0.6 | 50 |
| 5 - 6 | 3 | 0.84 | 0.64 | 1.3 | 130 |
| 7 - 9 | 3 | 0.22 | 0.42 | 0.5 | 50 |

**Table 2: PK parameters of sitafloxacin 200 mg single dose based on the median values (min–max).**

| PK Parameters | Plasma | ELF |
|---------------|--------|-----|
| T1/2 (h) | 3.7 (1–8) | 5.5 |
| Cmax (µg/mL) | 1.5 (0.48–1.82) | 0.84 |
| Kt (h−1) | 10.84 (3.64–48.49) | NA |
| CL/F (mL/minute) | 221.62 (45.13–533.22) | NA |
| AUC0–∞ (µg.hour/mL) | 146.92 (192.88–361.91) | NA |
| KC, absorption rate constant; NA, not applicable. |

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1424. Examining the Relationship Between Vancomycin Area Under the Concentration–Time Curve and Serum Trough Levels in Adults with Presumed or Documented Staphylococcal Infections

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**Session:** 145. PK/PD Studies

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**Background.** Recent studies evaluating area under the concentration–time curve (AUC)-guided vancomycin dosing have reported reduced drug exposure and nephrotoxicity as compared with traditional trough-guided (target 15–20 mg/L) dosing for invasive infections, but studies exploring the relationship between vancomycin trough concentration and AUC remain limited.

**Methods.** This was a retrospective observational study performed at two hospitals within a large health system. Patients receiving AUC-guided vancomycin dosing for a presumed or confirmed invasive staphylococcal infection between December 1, 2016 and July 31, 2017 were evaluated. Two steady-state serum vancomycin levels were obtained in each patient and used to determine the 24-hour AUC/MIC ratio; the AUC/MIC target was >600 mg.hour/L for endocarditis and >400 mg.hour/L for all other sources. The relationship between trough and AUC was explored using the Pearson product-moment correlation coefficient. Patient demographics and dosing details were also collected.

**Results.** Thirty-four patients were included in the study, with two patients having vancomycin levels drawn twice (36 sets of levels). Most patients were located in an ICU (91.2%) and 85.3% of patients had bacteremia, pneumonia or endocarditis. An organism was recovered from 28 patients (82.3%) of which 21 (75%) had a vancomycin MIC of 1 mg/L and 25 were S. aureus (89.3%). The mean vancomycin trough was 16.6 ± 6.1 mg/L and the mean AUC/MIC was 588 ± 156 mg.hour/L. There was a strong correlation between vancomycin trough and 24-hour AUC (R² = 0.731; P < 0.001; Figure 1). The rate of 24-hour vancomycin AUC/MIC target attainment was 91.2% (n = 31/34). Among patients with a trough >9 mg/L, 100% (n = 33) achieved AUC/MIC values >400 mg.hour/L and 94% were >500 mg.hour/L.

**Conclusion.** Targeting a vancomycin trough between 15 and 20 mg/L frequently results in an AUC/MIC in excess of the target identified for efficacy. Considering the strong correlation observed between trough and AUC alongside practical challenges associated with wide-scale implementation of AUC monitoring, a reduced target trough in conjunction with targeted application of AUC-guided dosing warrants further evaluation.