Furthermore, FEP HSR + 1/8th VNRX-5133 HSR resulted in ≥1-log reduction in the initial bacterial burden in 16 out of 24 isolates.

**Conclusion.** FEP/VNRX-5133 combination showed potent in vivo efficacy against serine β-lactamase-producing Gram-negative isolates. The extent of bacterial killing achieved with 1/8th VNRX-5133 HSR attested to the robustness of the inhibitor activity. These data support the consideration of FEP/VNRX-5133 combination for the treatment of serious infections due to these organisms in clinical trials.

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1406. Augmented Renal Clearance Using Aminoglycoside Population-Based Pharmacokinetic Modeling with Bayesian Estimation in Children in the Pediatric Intensive Care Unit

Sean Avedissian, Pharm.D.1; Nathaniel Rhodes, PharmD, MS2; Yuna Kim, BS3; John Valdez, BS5; John Bradley, MD, FAAP5 and Jennifer Le, PharmD, MAA6; FCCP, FCSP, BCPS-ID1; Pharmacy Practice, Midwestern University Chicago College of Pharmacy/Northwestern Memorial Hospital, Downers Grove, Illinois, 1Department of Pharmacy, Northwestern Medicine, Chicago, Illinois, 2University of California San Diego Skaggs School of Pharmacy, San Diego, California, 3Pediatric Infectious Disease, University of California San Diego, San Diego, California, 4Pharmacy/Infectious Diseases, University of California San Diego Skaggs School of Pharmacy, La Jolla, California

**Session:** 145. PK/PD Studies
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**Background.** Augmented renal clearance (ARC) in critically ill pediatric patients has been evaluated in limited studies. We evaluated ARC using clearance of aminoglycosides (CL\textsubscript{AMP}) derived from population-based pharmacokinetic modeling.

**Methods.** A retrospective, cohort study was conducted at two pediatric hospitals in patients who received aminoglycosides from 1999 to 2016. ARC was defined as a CL\textsubscript{AMP}×0.75/min/1.73 m\textsuperscript{2} within the first 24 hours of therapy. Pharmacokinetic (PK) models with nonparametric parameter estimation were constructed using Pmetrics in R, with the ultimate model selected by Akaike score and rule of parsimony. Covariate modifiers considered included: age, total body weight (TBW), serum creatinine (SCr) and sex. Noncompartmental analysis was performed on the Bayesian posteriors from the first dose to generate CL\textsubscript{AMP} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC\textsubscript{24}], maximum concentration [C\textsubscript{MAX}], etc.) derived from population-based pharmacokinetic model. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]). Allometric scaling of CL\textsubscript{AMP} utilized a fixed exponent of 0.75 and volume of distribution (VD) scaling utilized a fixed exponent of 0.5. Covariate modifiers considered included: age, total body weight (TBW), serum creatinine (SCr) and sex. Noncompartmental analysis was performed on the Bayesian posteriors from the first dose to generate CL\textsubscript{AMP} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC\textsubscript{24}], maximum concentration [C\textsubscript{MAX}], etc.) derived from population-based pharmacokinetic model. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]). Allometric scaling of CL\textsubscript{AMP} utilized a fixed exponent of 0.75 and volume of distribution (VD) scaling utilized a fixed exponent of 0.5. Covariate modifiers considered included: age, total body weight (TBW), serum creatinine (SCr) and sex. Noncompartmental analysis was performed on the Bayesian posteriors from the first dose to generate CL\textsubscript{AMP} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC\textsubscript{24}], maximum concentration [C\textsubscript{MAX}], etc.) derived from population-based pharmacokinetic model. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]).

**Results.** ARC was identified in 34 of 117 (29%) subjects using 275 aminoglycoside serum concentrations. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]). Allometric scaling of CL\textsubscript{AMP} utilized a fixed exponent of 0.75 and volume of distribution (VD) scaling utilized a fixed exponent of 0.5. Covariate modifiers considered included: age, total body weight (TBW), serum creatinine (SCr) and sex. Noncompartmental analysis was performed on the Bayesian posteriors from the first dose to generate CL\textsubscript{AMP} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC\textsubscript{24}], maximum concentration [C\textsubscript{MAX}], etc.) derived from population-based pharmacokinetic model. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]). Allometric scaling of CL\textsubscript{AMP} utilized a fixed exponent of 0.75 and volume of distribution (VD) scaling utilized a fixed exponent of 0.5. Covariate modifiers considered included: age, total body weight (TBW), serum creatinine (SCr) and sex. Noncompartmental analysis was performed on the Bayesian posteriors from the first dose to generate CL\textsubscript{AMP} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC\textsubscript{24}], maximum concentration [C\textsubscript{MAX}], etc.) derived from population-based pharmacokinetic model. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]). Allometric scaling of CL\textsubscript{AMP} utilized a fixed exponent of 0.75 and volume of distribution (VD) scaling utilized a fixed exponent of 0.5. Covariate modifiers considered included: age, total body weight (TBW), serum creatinine (SCr) and sex. Noncompartmental analysis was performed on the Bayesian posteriors from the first dose to generate CL\textsubscript{AMP} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC\textsubscript{24}], maximum concentration [C\textsubscript{MAX}], etc.) derived from population-based pharmacokinetic model. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]). Allometric scaling of CL\textsubscript{AMP} utilized a fixed exponent of 0.75 and volume of distribution (VD) scaling utilized a fixed exponent of 0.5. Covariate modifiers considered included: age, total body weight (TBW), serum creatinine (SCr) and sex. Noncompartmental analysis was performed on the Bayesian posteriors from the first dose to generate CL\textsubscript{AMP} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC\textsubscript{24}], maximum concentration [C\textsubscript{MAX}], etc.) derived from population-based pharmacokinetic model. A two-compartment model fit the data well (See Figure 1: Population [a], Bayesian [b]).

**Conclusion.** Oxacillin may be associated with overall improved safety compared with nafcillin based on reporting signals from FAERS. Our results support previous limited observational data. With the likely equal efficacy of these agents, clinicians may want to consider prescribing oxacillin over nafcillin if an antistaphylococcal penicillin is indicated for an invasive MSSA infection. However, given the limitations of reporting systems, further evaluation is warranted.

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1408. Population Pharmacokinetic (PK) Model to Describe Epithelial Lining Fluid (ELF) Penetration of ASN-1 and ASN-2 after ASN100 Administration to Healthy Subjects

Scott A. Van Wart, PhD, MS1; Christopher Stevens, MD2; Zoltan Magyarics, MD, PhD3; Steven A. Luperchio, PhD, CMP4; Christopher M. Rubino, PharmD5 and Paul G. Ambrose, PharmD, FIDSA1; 1ICPD, Schenectady, New York, 2Arasan, Inc., Waltham, Massachusetts, 3Arasan Biosciences GmbH, Vienna, Austria

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**Background.** ASN100 is a combination of two co-administered fully human monoclonal antibodies (mAbs), ASN-1 and ASN-2, that together neutralize the six cytotoxins critical to S. aureus pneumonia pathogenesis. ASN100 is in development for prevention of S. aureus pneumonia in mechanically ventilated patients. A population PK model was developed to characterize the time-course of ASN-1 and ASN-2 in ELF following intravenous administration of ASN100 in healthy subjects.

**Methods.** A total of 42 healthy subjects received a single dose of ASN-1 or ASN-2 alone (200–4,000 mg) or ASN100 (3,600 or 8,000 mg; 1:1 ratio of ASN-1:ASN-2). All subjects contributed 13–17 serum samples for ASN-1/ASN-2 assay. Twelve subjects contributed 2 bronchoalveolar lavage (BALF) samples each for ELF concentration assay (Day 1 or 2 and Day 8 or 30 after dosing). A previously reported, linear, two-compartment population PK model for serum [ID Week 2017, Poster #1849] was expanded and fit to the ELF concentration–time data. Sequential analysis was used to fix serum PK as the driver for ELF PK; only those parameters controlling transfer into and out of the ELF were fit.

**Results.** An effect-site model adequately described the time-course of ELF concentrations. To allow for estimation of interindividual variability in the elimination from ELF, residual variability in ELF was fixed to that previously estimated for the same PK data. Separate rate constants for transfer from serum to ELF were estimated for the 3,600 and 8,000 mg ASN100 dose groups to reflect the less than dose-proportional increase in ELF concentrations for both ASN-1 and ASN-2. Goodness-of-fit plots did not reveal any appreciable biases. A visual predictive check indicated that the model could adequately capture the observed data (Figure 1). Predicted ELF

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penetration using the ratio of ELF:serum AUC₀–ₚ was 33.0% for ASN-1 and 20.3% for ASN-2 following the selected clinical dose of 3,600 mg.

**Conclusion.** A population PK model adequately described the time-course of ASN-1 and ASN-2 in ELE. ELF penetration was 20–33% following administration of the ASN100 clinical dose. These results should be interpreted with caution given the limited sample size (six subjects per dose group) and limitations of urea-based normalization of BALF to ELF volume.

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1409. **Evaluation of Alternative Piperacillin–tazobactam Dosing Strategies Against ESBL-Producing Enterobacteriaceae Using a Hollow Fiber Infection Model**

Hennieta Abodakpi, Pharm.D.; Kai-Tai Chang, Ph.D.; Ana Maria Sánchez-Díaz, Ph.D.; Rafael Cantón, Pharm.D.; and Vincent Tam, Pharm.D.; Pharmaceutical and Pharmacological Sciences, University of Houston College of Pharmacy, Houston, Texas; Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas; Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCS), Madrid, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; and Pharmaceutical and Pharmacological Sciences, Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas

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**Background.** Extended-spectrum β-lactamases (ESBLs) present a serious challenge to the treatment of Gram-negative pathogens. ESBL-producing Enterobacteriaceae (ESBL-PE) are resistant to most β-lactams which may be reversed with the addition of an active β-lactamase inhibitor (such as tazobactam, relebactam, and avibactam). However, various ESBLs may display different susceptibilities to these inhibitors, which could impact efficacy. We propose a framework for comparing the efficacy of these inhibitors when combined with the same β-lactam.

**Methods.** Three clinical isolates of *K. pneumoniae* harboring CTX-M-15 and one *E. coli* with SHV-12 were used. The susceptibility of each isolate to piperacillin was determined using escalating concentrations of tazobactam, relebactam, and avibactam. Similar experiments were subsequently conducted with cefazidime. The resulting minimum inhibitory concentrations (MICs) were mapped as response to inhibitor concentration using an inhibitory endpoint (Eₚₑₜ). The final model was validated in a hollow-fiber infection model (HFIM).

**Results.** For the reference strain, a clinical regimen of 4 g piperacillin and 0.5 g tazobactam administered every 8 hours resulted in a T > MIC of 39.6% and bacterial regrowth. An exposure equivalent to 1.5 g tazobactam (T > MIC of 55.1%) was needed to suppress growth. These regrowth findings were validated with the two other ESBL-producers with tazobactam exposures characterized by T > MIC of 36.8 and 43.8%.

**Conclusion.** Improved bacterial killing was observed with increasing tazobactam exposures. As a novel PK/PD index, T > MIC may be used to characterize response to a β-lactamase inhibitor and provide efficacy targets to guide the development and clinical dosing of these inhibitors.

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1410. **Novel Framework to Compare the Effectiveness of Tazobactam, Relebactam and Avibactam Against Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae**

Hennieta Abodakpi, Pharm.D.; Kai-Tai Chang, Ph.D.; Ana Maria Sánchez-Díaz, Ph.D.; Rafael Cantón, Pharm.D.; and Vincent Tam, Pharm.D.; Pharmaceutical and Pharmacological Sciences, University of Houston College of Pharmacy, Houston, Texas; Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas; Pharmaceutical and Pharmaceutical Sciences; Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas; Pharm.D.; and Prof. Tural; Osman Dağ, DOCTOR and Murat Abdulkadir, PROF; Internal Medicine, Hacettepe University, Ankara, Turkey; Biostatistics, Hacettepe University, Ankara, Turkey; Infectious Diseases and Clinical Microbiology, Hacettepe University, Ankara, Turkey

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

**Background.** Resistance mediated by extended-spectrum β-lactamases (ESBLs) presents a serious challenge in the treatment of Gram-negative pathogens. ESBL-producing Enterobacteriaceae (ESBL-PE) are resistant to most β-lactams which may be reversed with the addition of an active β-lactamase inhibitor (such as tazobactam, relebactam, and avibactam). Similar experiments were subsequently conducted with cefazidime. The resulting minimum inhibitory concentrations (MICs) were mapped as response to inhibitor concentration using an inhibitory endpoint (Eₚₑₜ). The final model was validated in a hollow-fiber infection model (HFIM). We illustrated a simple structural model capable of comparing the performance of different inhibitors. This platform may be used to identify the optimal pairing of various β-lactams and β-lactamase inhibitors for individual isolates.

**Disclosures.** V. Tam, European Union’s Seventh Framework Programme: Grant Investigator, Research grant.

1411. **Teciploplatin (TEI) vs. Vancomycin (VAN) in Combination with Piperacillin-Tazobactam (TZP) or Meropenem (MER) as a Cause of Acute Kidney Injury (AKI)**

Abdullah Tariq Aslan, RESIDENT1; Tural Pashayev, RESIDENT1; Osman Dağ, DOCTOR and Murat Akova, PROF2; Internal Medicine, Hacettepe University, Ankara, Turkey; Biostatistics, Hacettepe University, Ankara, Turkey; Infectious Diseases and Clinical Microbiology, Hacettepe University, Ankara, Turkey

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**Background.** VAN has been shown to cause increased incidence of AKI when combined with TZP. The reason is unknown. TEI is a glycopeptide which may be less nephrotoxic. We compared both glycopeptides in combination with TZP or MER for use as AKI.

**Methods.** A retrospective cohort study was performed between May 2015 and December 2017 in a large tertiary care setting. Evaluation of AKI was made by using RIFLE criteria. Patients ≥18 years were included if they had a baseline serum creatinine ≥3 mg/dL, creatinine value ranging from 1.36 to 35.25 µg/mL for tazobactam, 2.32–15.82 µg/mL for relebactam, and 0.62–2.37 µg/mL for avibactam. Iₚₑₜ values were 4.75–69.9, 6.56–97.7, and 7.83–112.2 for tazobactam, relebactam, and avibactam, respectively. Similar trends in Iₚₑₜ and Iₚₑₜ were observed with cefazidime as the β-lactam.

**Conclusion.** We illustrated a simple structural model capable of comparing the performance of different inhibitors. This platform may be used to identify the optimal pairing of various β-lactams and β-lactamase inhibitors for individual isolates.

**Disclosures.** V. Tam, European Union’s Seventh Framework Programme: Grant Investigator, Research grant.