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.

Disclosures. **D. P. Nicolau**, VenatoRx Pharmaceuticals, Inc.: Grant Investigator, Research grant

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

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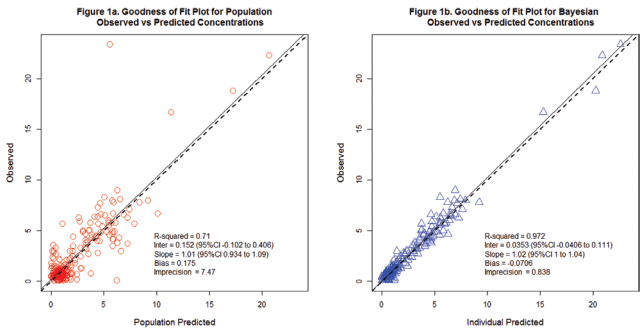
Background. Augmented renal clearance (ARC) in critically ill pediatric patients has been evaluated in limited studies. We evaluated ARC using clearance of aminoglycosides (CL_{AMINO}) derived from population-based pharmacokinetic modeling.

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_{AMINO} of ≥130 mL/minute/1.73 m^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_{AMINO} within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC_{24}], maximum concentration [C_{MAX}]). Summary of patient demographics and statistical analysis were performed using GraphPad Prism version 7.

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_{AMINO} utilized a fixed exponent of 0.75 and volume of distribution (VD) scaling utilized a fixed exponent of 1 in the final model. The final population model for CL_{AMINO} (L/hour) was $3.45 \times (TBW/40)^{0.75} + 0.05 \times 10^{(SCr/AGE)}$ and VD was $10.64 \times (TBW/40)^{1}$. Median age and baseline SCr were similar in those with and without ARC (13 [IQR 10–16] vs. 11.0 [5.0–15.0] years, $P = 0.11$, and 0.37 [0.27–0.49] vs. 0.38 [0.28–0.50] mg/dL, $P = 0.67$, respectively). Median TBW was found to be significantly higher in those with vs. without ARC (44.9 [26.9–61.7] vs. 34 [17.6–54.9] kg $P = 0.04$). Median 24 hours CL_{AMINO} was also found to be significantly higher in those with vs. without ARC (147.3 [138.7–163.9] vs. 94.5 [79.4–112.9], mL/minute/1.73 m^2, $P < 0.001$). Patients with vs. without ARC had significantly lower AUC_{24} and C_{MAX} (40.7 [33.3–54.4] vs. 55.7[46.7–66.4] mg hour/L, $P \leq 0.001$ and 5.06 [4.11–6.76] vs. 6.32 [5–7.44], μg/mL, $P = 0.01$).

Conclusion. The incidence of ARC observed was similar to adult studies. Patients that exhibited ARC had lower AUC_{24} and C_{MAX}; thus, higher doses may be warranted.



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

1407. Disproportionality Analysis of Safety with Nafcillin and Oxacillin with the FDA Adverse Event Reporting System (FAERS)

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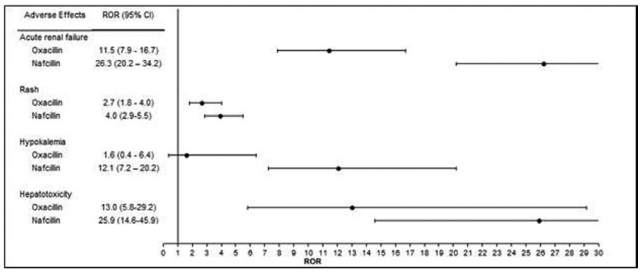
Background. Antistaphylococcal penicillins including oxacillin and nafcillin are among the drugs of choice for severe and invasive MSSA infections. While alternative agents such as cefazolin are associated with improved safety compared with antistaphylococcal penicillins, comparative safety data between individual antistaphylococcal penicillins is limited and has shown possible improved safety with oxacillin among adults. The objective of this study was to determine the relative adverse events (AEs) reporting for these agents among the FDA Adverse Event Reporting System (FAERS) database.

Methods. We reviewed adverse events reports from the FAERS database from Q4/2003-Q1/2018 and performed a disproportionality analysis of safety events for nafcillin and oxacillin including ADEs related to acute kidney injury (AKI), rash, hypokalemia, and hepatotoxicity. Measures of association evaluated included reporting odds ratio (ROR) and proportion reporting ratio (PRR).

Results. Reports of AKI were substantially more common with nafcillin (PRR 23.2, 95% CI 18.4––29.3) than oxacillin (PRR 10.9, 95% CI 7.6––15.5). Rash was slightly higher with nafcillin than oxacillin (PRR 3.7, 95% CI 2.8––5.1 vs. 2.6, 95% CI 1.8––3.8). Hypokalemia was substantially more common with nafcillin than oxacillin (PRR 11.8, 95% CI 7.1––19.4 vs. 1.6, 95% CI 0.4––6.4). Hepatotoxcitiy was slightly higher reported among nafcillin than oxacillin (PRR 25.3, 95% CI 14.5––44.3 vs. 12.9, 95% CI 5.8––28.6). Similar observations were seen with RORs (Figure 1).

Figure 1. Reporting Odds Ratios of AEs with Nafcillin and Oxacillin



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.

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

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

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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.

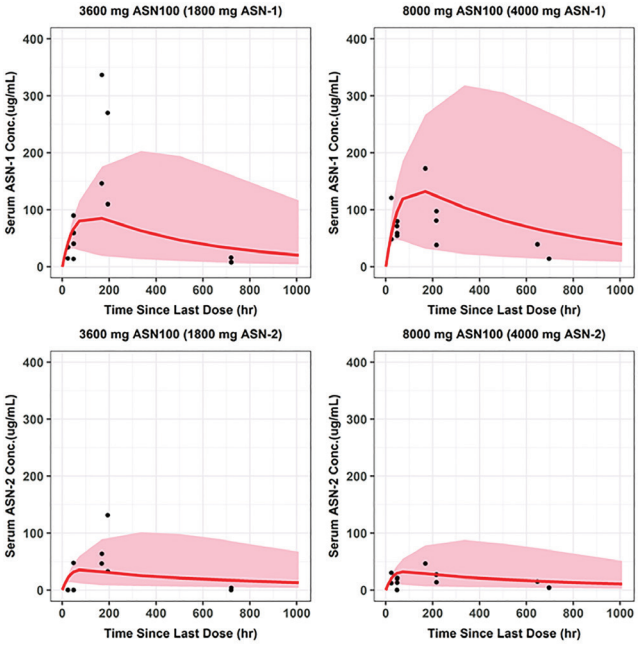
Methods. A total of 42 healthy subjects received a single dose of ASN-1 or ASN-2 alone (200–4,000 mg) or ASN100 (3,600 or 8,000 mg; 1:1 ratio of ASN-1:ASN-2). All subjects contributed 13–17 serum samples for ASN-1/ASN-2 assay. Twelve subjects contributed 2 bronchoalveolar lavage (BALF) samples each for 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 serum 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

penetration using the ratio of ELF:serum $AUC_{0-\infty}$ 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 ELF. 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.

Figure 1. Visual predictive check for the population PK model fit to the ASN-1 and ASN-2 ELF data following administration of either 3600 mg or 8000 mg of ASN100



Red (Simulated) 80% Prediction Interval; Black Dots are All Observed Data (incl. LLOQ)

Disclosures.. **S. A. Van Wart**, Arsanis, Inc.: Research Contractor, Research support. **C. Stevens**, Arsanis, Inc.: Employee and Shareholder, Salary and stock options. **Z. Magyarics**, Arsanis Biosciences GmbH: Employee and Shareholder, Salary and stock options. **S. A. Luperchio**, Arsanis, Inc.: Employee and Shareholder, Salary and stock options. **C. M. Rubino**, Arsanis, Inc.: Research Contractor, Research support. **P. G. Ambrose**, Arsanis, Inc.: Research Contractor, Research support.

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

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Background. Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae exhibit variable response to treatment with piperacillin–tazobactam. Current clinical practice with piperacillin–tazobactam involves dosing the components simultaneously at a fixed ratio of 8:1 piperacillin to tazobactam. However, it remains unclear whether this ratio is optimal for enzyme inhibition and bactericidal activity. Using a hollowfiber infection model (HFIM), we evaluated the efficacy of various exposures of piperacillin–tazobactam against ESBL-producing Enterobacteriaceae.

Methods. A clinical strain of *K. pneumoniae* expressing CTX-M-15 was used as a reference isolate. Piperacillin minimum inhibitory concentrations (MIC) were determined using a range of tazobactam concentrations and fitted to an inhibitory E_{max} model. An HFIM was used to simulate and evaluate the impact of escalating tazobactam dosing in the context of a fixed piperacillin exposure (equivalent to 4 g every 8 hours). Serial samples were collected to verify the pharmacokinetic simulations (by LC–MS/MS) and determine bacterial density for up to 120 hours. Measured drug concentrations were incorporated in the E_{max} model to determine the free-time above instantaneous MIC (*f*T>MICi) associated with each experimental exposure. The target *f*T>MICi associated with growth suppression was subsequently validated using a clinical strain of *E. coli* (producing SHV-12) and a second *K. pneumoniae* (producing CTX-M-15).

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

Conclusion. Improved bacterial killing was observed with increasing tazobactam exposures. As a novel PK/PD index, *f*T > MICi 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.

Disclosures. **A. M. Sánchez-Díaz**, European Union's Seventh Framework Programme: Grant Investigator, Research grant. **R. Cantón**, European Union's Seventh Framework Programme: Grant Investigator, Research grant. **V. Tam**, European Union's Seventh Framework Programme: Grant Investigator, Research grant.

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

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Background. Resistance mediated by extended-spectrum β-lactamases (ESBLs) presents a serious challenge in the treatment of Gram-negative pathogens. ESBLs confer resistance 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 by broth dilution using escalating concentrations of tazobactam, relebactam and avibactam. Similar experiments were subsequently conducted with ceftazidime. The resulting minimum inhibitory concentrations (MICs) were mapped as response to inhibitor concentration using an inhibitory E_{max} model. The best-fit model parameters were compared for each isolate-inhibitor combination.

Results. In all scenarios, MIC reductions were observed in the presence of increasing inhibitor concentrations. The MIC reduction for each isolate was well fitted to inhibitor concentrations ($r^2 \geq 95\%$). IC_{50} estimates reflected the sensitivity of the isolates to each inhibitor, while I_{max} captured the maximum extent of MIC reduction. With piperacillin, IC_{50} values ranged from 1.36 to 35.25μg/mL for tazobactam, 2.32–15.82 μg/mL for relebactam and 0.62–2.37 μg/mL for avibactam. I_{max} values were 4.75–6.99, 6.56–9.77 and 7.83–11.22 for tazobactam, relebactam and avibactam, respectively. Similar trends in IC_{50} and I_{max} were observed with ceftazidime 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.

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

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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 causing 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 available and received one of the combinations tested for at least 48 hours. Exclusion criteria were renal replacement therapy, pregnancy, <48 hours antibiotic therapy and no follow-up.

Results. Overall 456 patients were screened and 379 included in the study. After controlling for residual differences (age, Charlson comorbidity index score, presence of AKI, GFR value, presence of sepsis or septic shock, residing in intensive care unit at the time of antibiotic therapy and number of days of antibiotic therapy), AKI incidence was significantly higher in patients receiving TZP-VAN than those receiving TZP-TEI and also in patients receiving TZP-VAN than those with MER-VAN. No difference