Conclusion. Incorporation of eGFR calculated using the Cr- and CysC-based full age spectrum equation improved population PK model fit for VAN among critically ill children compared with $Schwartz_{bed}$. Clinical use of CysC may help estimate VAN CL among critically ill children compared with use of Cr alone.

Disclosures. **K. Downes**, Merck, Inc.: Investigator, Research support. Pfizer, Inc.: Investigator, Research support.

1403. Daptomycin Combined with Low Dose Ceftriaxone Prevents the Emergence of Daptomycin Resistance against *Streptococcus mitis-oralis* Group in an *In vitro* Model of Simulated Endocardial Vegetations (SEVs)

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Background. The viridans group streptococci (VGS) are a heterogeneous group of microorganisms that form portion of the normal oral flora of humans. Among the VGS, *S. mitis-oralis* is the most common cause of infective endocarditis in the developing world, as well as the leading cause of the "toxic Strep syndrome" in neutropenic cancer patients. Therapeutic options are often limited by frequent β-lactam resistance, as well as vancomycin tolerance. Daptomycin (DAP) has been suggested as an alternative therapeutic option for invasive *S. mitis-oralis* infections. However, the ability of these strains to rapidly evolve high-level and durable DAP-resistance (DAP-R) is problematic. Recent data have suggested the potential for combined DAP +β-lactam therapy to circumvent this issue.

Methods. Using human-simulated dosing, the activities of DAP (6, 8,10 or 12 mg/kg/day × 4 days) alone vs. DAP (6 mg/kg/day) +(CRO) (500 mg daily × 4 days or 500 mg, given once on day one) were assessed against two DAP-susceptible (DAP-S) *S. mitis-oralis*strains (SF100; 351) employing a PK-PD model of simulated endocardial vegetations (SEVs).

Results. DAP alone was not bactericidal at any dose-regimen, and regrowth of high-level DAP-R isolates was observed in both strains (MIC increase from 0.5 to >64 μg/mL). Combinations of DAP +CRO at either dose-regimen yielded significant reductions in log_{10}CFU/g amounts within SEVs for both strains (~6 log_{10} CFU/g and to detection limits) within 24 hours. In addition, no DAP-R strains were detected in either DAP+ CRO combination regimens over the 96-hour exposure period.

Conclusion. Combinations of DAP+ low-dose CRO (even single dosing) showed promise to forestall the emergence of DAP-R in *S. mitis-oralis* strains. Such regimens can potentially lead to optimizing treatment outcomes with DAP therapy, with minimal β-lactam exposures. Further research in relevant *in vivo* models and clinically is warranted to determine the most optimized DAP+ CRO dose-regimens for the prevention of emergence of DAP-R among *S. mitis-oralis* strains.

Disclosures. **J. M. Miro**, Abbvie: Consultant and Grant Investigator, Consulting honoraria and Research grant; Bristol-Myers Squibb: Consultant and Grant Investigator, Consulting honoraria and Research grant; Genentech: Consultant and Grant Investigator, Consulting honoraria and Research grant; Medtronic: Consultant and Grant Investigator, Consulting honoraria and Research grant; Novartis: Consultant and Grant Investigator, Consulting honoraria and Research grant; Gilead Sciences: Consultant and Grant Investigator, Consulting honoraria and Research grant; Pfizer: Consultant and Grant Investigator, Consulting honoraria and Research grant; ViiV Healthcare: Consultant and Grant Investigator, Consulting honoraria and Research grant. **C. Arias**, Merck & Co., Inc.: Grant Investigator, Research support; MeMed: Grant Investigator, Research support; Allergan: Grant Investigator, Research support. **A. Bayer**, Trellis: grant recipient, Grant recipient; Contrafect: grant recipient, Grant recipient; Theravance: grant recipient, Grant recipient. **M. J. Rybak**, Allergan: Consultant, Grant Investigator and Speaker's Bureau, Research grant and Research support; Achaogen: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Bayer: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Melinta: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Merck: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Theravance: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Sunovian: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Zavante: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; NIAID: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support.

1404. A Pharmacokinetic Study on CMS and Colistin and Its Impact on Clinical Cure and Acute Kidney Injury in Critically Ill Patients with Normal Renal Function from South India

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Background. Colistin has re-emerged as last line antimicrobial to combat MDR GNB. There is need for robust pharmacokinetic (PK) and pharmacodynamics (PD) data to guide dosing. This study assessed the PK of CMS and colistin and its impact on clinical cure (CC) and acute kidney injury (AKI) in critically ill patients with normal baseline renal function.

Methods. Adult critically ill patients with colistin susceptible MDR/XDR infections and normal renal function who were treated with intravenous CMS (9MU CMS loading dose (LD) followed by maintenance (MD) 3MU every 8 hour starting 24 hours after LD) were recruited into this prospective observational study. For PK sampling, 3mL venous blood was drawn immediately before LD and at 0.5, 1, 2, 4, 8 and 12 hours after LD. During MD, samples were collected before and at 1, 2 and 8 hours after the eight and nineth infusion. Colistin plasma concentrations were determined by LC–MS.

Results. A total of 280 serum samples were analyzed from 20 patients. Sixty percent had pneumonia. Predominant pathogens were *Klebsiella pneumonia* (12) and *Acinetobacter* spp. (8). Mean creatinine clearance (CrCl) was 115 ± 24 mL/minute (72.3–208.8). All patients received combination therapy with colistin, 18(90%) received meropenem and 5(25%) received tigecycline. Clinical cure rate was 50% (10/20) and mortality rate was 25% (5/20). Mean LD colistin Cmax were 3 ± 1.1 mg/L (1.75–5.14) and 2.37 ± 1.2 mg/L (1.52–5.54) among CC and CF groups, respectively (P = 0.13). MD colistin Css avg was 2.25 ± 1.3 mg/L and 1.78 ± 1.1 mg/L in CC and CF groups, respectively. The mean AUC_{0-24}/MIC ratio of MD colistin was 92.76 ± 65.5 and 76.59 ± 51.8 for CC and CF groups, respectively (P = 0.27). In pneumonia, AUC_{0-24}/MIC for *Acinetobacter* spp. was higher in the CC (71.18 ± 10.20) than in the CF group (40.88 ± 16.28) (P = 0.05). Renal injury was 5% at 7 days and 40% at end of therapy. Ten to 20% of patients with CrCl ≥ 100 mL/minute had Css avg ≥ 2 mg/L. Majority of CF with AKI had Css avg between 1 and 1.5 mg/L

Conclusion. Clinical cure was low at 50%. Sub-inhibitory Css avg and increased volume of distribution following MD could have contributed to high failure. Colistin exposures were similar to those reported in other published cohorts with no consistent exposure-response relationship. Based on these results, there is an important role for therapeutic drug monitoring with Colistin.

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

1405. Efficacy of the Human-Simulated Regimen (HSR) of Cefepime (FEP)/VNRX-5133 Combination Against Serine β-Lactamase-Producing Gram-negative Bacteria in the Neutropenic Murine Thigh Infection Model

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Background. VNRX-5133 is a new-generation β-lactamase inhibitor with potent activity against serine and metallo-β-lactamases. FEP/VNRX-5133 combination shows remarkable *in vitro* activity against multi-drug-resistant Gram-negative bacteria. The objective of this study was to assess the *in vivo* efficacy of HSR of the combination against a range of Enterobacteriaceae and *Pseudomonas aeruginosa* isolates expressing serine β-lactamases in the murine thigh infection model.

Methods. Twenty-four Enterobacteriaceae and *P. aeruginosa* clinical isolates producing KPC and extended-spectrum β-lactamases as well as *P. aeruginosa* with AmpC overexpression were utilized for *in vivo* studies. FEP and FEP/VNRX-5133 MIC ranges were 256 to >512 and 0.125––16 mg/L, respectively. ICR mice were rendered transiently neutropenic, and the thighs were inoculated with bacterial suspensions of 10^7 CFU/mL. HSR of FEP and VNRX-5133 equivalent to clinical doses of 2 g and 500 mg, respectively, each given q8h as 2 hours infusion were developed in the murine model. Treatment mice were administered either FEP HSR alone, FEP HSR + VNRX-5133 HSR combination, or FEP HSR + 1/8th the doses of VNRX-5133 HSR. Control mice were vehicle-dosed. Efficacy was assessed as the change in log_{10}CFU/thigh at 24 hours compared with 0 hour.

Results. The average log_{10}CFU/thigh at 0 hour across all isolates was 5.74 ± 0.53. At 24 hours, the bacterial burden increased by an average of 3.27 ± 0.53 log_{10} CFU/thigh in the untreated control mice. Treatment with FEP alone was associated with average net growth of 2.76 ± 0.75 log_{10}CFU/thigh. The co-administration of VNRX-5133 HSR was adequate to attain ≥ 2-log reduction in initial bacterial burdens at 24 hours in seven out of 24 isolates and ≥ 1-log reduction in the remaining 17 isolates.

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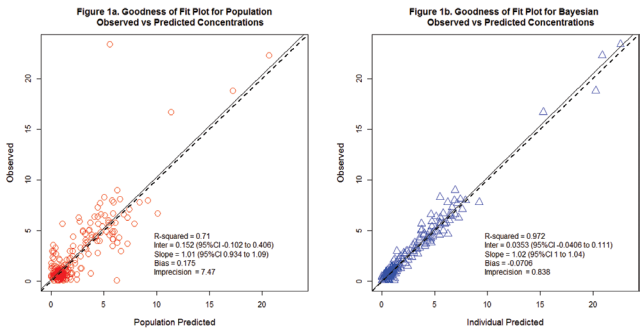
Background. Augmented renal clearance (ARC) in critically ill pediatric patients has been evaluated in limited studies. We evaluated ARC using clearance of aminoglycosides (CL_{AMINO}) derived from population-based pharmacokinetic modeling.

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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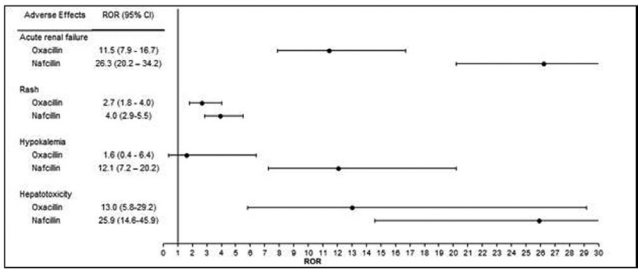
Background. Antistaphylococcal penicillins including oxacillin and nafcillin are among the drugs of choice for severe and invasive MSSA infections. While alternative agents such as cefazolin are associated with improved safety compared with antistaphylococcal penicillins, comparative safety data between 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