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 and 12 hours after LD. During MD, samples were collected before and at 1, 2 and 8 hours after the ninth and ninth 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, 10% received meropenem and 5(25%) received ticagrelol. Clinical cure rate was 50(10%) and mortality rate was 25(5%). 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 colistinCss avg was 2.25 ± 1.3 mg/L and 7.8 ± 4.5 mg/L in CC and CF groups, respectively. The mean AUC Css/MIC ratio of MD colistin was 92.76 ± 65.7 and 51.8 for CC and CF groups, respectively (P = 0.27). In pneumonia, AUC Css/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). Acute renal injury was observed in 80% 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 Csa averaged 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 and extended-spectrum β-lactamases as well as 20 patients 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 was associated with average net growth of 2.76 ± 0.75 log 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 a 2-log reduction in the initial bacterial burden in 16 out of 24 isolates.

**Conclusion.** FEP/VNRX-5133 combination potent showed 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 inhibitory 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

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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_auro) 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_auro ≥ 10 mL/min/1.73 m2 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_auro within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC24]). 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). Pharmacokinetic 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_auro within the first 24 hours and other PK exposure metrics (i.e., area under the curve for first 24 hours [AUC24]). Maximum concentration ([C_max]). Summary of patient demographics and statistical analysis were performed using GraphPad Prism version 7.

**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

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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 Day 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