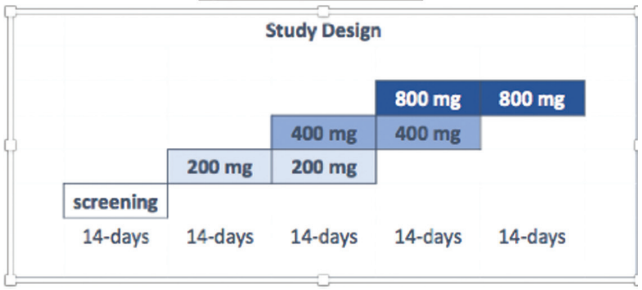
Figure 1: Dose Escalation Schedule



Background. Piperacillin/tazobactam (PTZ) is a carbapenem-sparing option for AmpC-repressed organisms. Current strategies of dosing PTZ focus on prolonging *f*T > minimum inhibitory concentration (MIC), lowering C:MIC ratios. The objective of this study was to determine the effect of physiologic PTZ concentration on the emergence of resistance among clinical isolates of *Klebsiella aerogenes* (KA).

Methods. Fifteen clinical KA from respiratory cultures had MICs determined by broth microdilution for PTZ and Etest for ceftriaxone (CRO) and cefepime (FEP). The presence of resistant mutants was determined using Muller–Hinton agar with increasing concentrations of CRO and PTZ. Five isolates with the highest selected MIC underwent time-kill (TK) studies with PTZ compared with CRO and FEP at high inoculum (HI) (7.0 $\log_{10}$ CFU/mL) and low inoculum (LI) (5.0 $\log_{10}$ CFU/mL). Concentrations used in TK studies simulated lung epithelial lining fluid for free peak of a prolonged infusion of PTZ (20 µg/mL; PTZ20) and the average AUC_{0-24} (10 µg/mL; PTZ10), continuous infusion FEP (8 µg/mL), and the average AUC_{0-24} concentration of CRO (6 µg/mL).

Results. MICs for PTZ, FEP and CRO ranged from 2 to 8, 0.47 and 0.094 to 0.125 µg/mL, respectively. Mutant selection for both PTZ and CRO occurred for five isolates. In TK studies at HI, FEP was the only agent to demonstrate bactericidal activity with reduction of 5.0 ± 0.7 $\log_{10}$ CFU/mL. Reductions for PTZ20 and PTZ10 were 0.21 ± 0.18 and 0.05 ± 0.16 $\log_{10}$ CFU/mL, respectively. CRO demonstrated regrowth of 0.5 ± 0.3 $\log_{10}$ CFU/mL. Interestingly, the susceptibility before and after TK did not differ for the PTZ groups, whereas all CRO-exposed isolates had become resistant. At LI, PTZ20 and PTZ10 had improved activity with reductions of 3.0 ± 0.4 and 2.8 ± 0.5 $\log_{10}$ CFU/mL, respectively. CRO was also more active at LI but with regrowth for 2/5 isolates.

Conclusion. In studies simulating conditions of pneumonia, PTZ demonstrated significant inoculum-dependent killing regardless of baseline MIC. CRO demonstrated selection for resistance at HI and variably at LI. FEP was the only antimicrobial associated with bactericidal activity at HI. Resistance to PTZ was seen on agar plates although not in TK studies. Dosing strategies to optimize cidality are warranted.

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

1415. Implementation and Validation of a Vancomycin AUC/MIC Calculator and Dosing Protocol at a Large Community Hospital

Megan Seddon, PharmD[1]; Kevin Scorgie, PharmD, BCPS[2]; Sara Kutner, PharmD[2]; Andre McMahon, PharmD[2] and Jamie Kisgen, PharmD, BCPS (AQ-ID)[2]; [1]University of South Carolina and Palmetto Health, Columbia, South Carolina, [2]Department of Pharmacy, Sarasota Memorial Health Care System, Sarasota, Florida

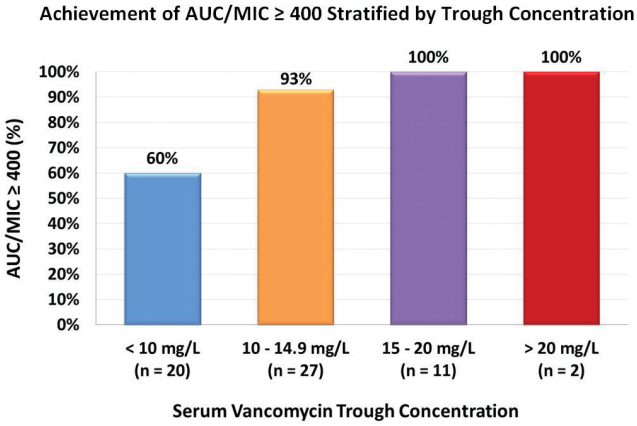
Session: 145. PK/PD Studies
Friday, October 5, 2018: 12:30 PM

Background. Current IDSA guidelines recommend targeting a vancomycin trough between 15 and 20 mg/L to achieve an AUC/MIC ≥ 400; however, recent literature shows increased rates of nephrotoxicity within this range and the target AUC/MIC ratio may be achieved with lower troughs. We sought to determine whether a vancomycin AUC-based dosing protocol and spreadsheet-based calculator, using one-compartment population-based dosing and two steady-state serum levels, accurately predicted AUC/MIC ratio in patients with moderate to severe *Staphylococcus aureus* infections.

Methods. A retrospective analysis of 60 adult patients treated with vancomycin for culture-confirmed *S. aureus* was conducted. The primary outcome was percent of patients who met the AUC/MIC goal of ≥400. Secondary outcomes included: mean initial trough concentration in patients who met the AUC/MIC goal compared with those who did not; correlation of two different methods of AUC-estimation with the patient's actual AUC; percentage of patients meeting AUC/MIC goal stratified by initial trough concentrations, age, weight, and indication; and percentage of patients meeting the AUC goal stratified by the same variables. Results were analyzed using descriptive statistics and calculations were performed using SPSS.

Results. The median age (range) was 55 (22–86) and 52% were male. Eighty-three percent of patients achieved an initial AUC/MIC ≥ 400, including 93% with serum troughs between 10 and 14.9 mg/L. Patients who met the AUC/MIC goal had an average trough of 13.5 mg/L, whereas those who did not had an average trough of 7.8 mg/L ($P < 0.001$). AUC estimation using population pharmacokinetics was significantly correlated with actual AUC ($P = 0.011$); however, this was not a strong correlation ($r = 0.340$). Subgroup analysis based on age, weight, and indication identified areas for improvement in the empiric dosing protocol at our institution.

Conclusion. Use of the vancomycin AUC-based dosing protocol and calculator resulted in achievement of efficacy goal in the majority of patients, including many with vancomycin troughs between 10 and 15 mg/L. More accurate estimation of AUC and other pharmacokinetic variables using local patient data is important for improving the reliability of vancomycin dosing protocols.



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

1416. Piperacillin/Tazobactam Therapeutic Drug Monitoring: True Interpatient Variability or Compound Instability?

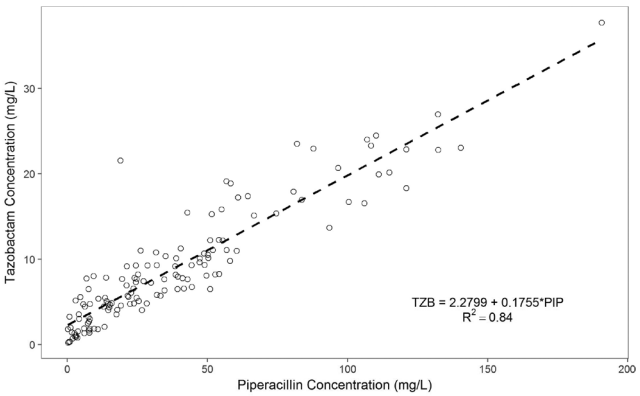
Ryan L. Crass, PharmD[1]; Praveen Kumar, PhD[1]; Twisha S. Patel, PharmD, BCPS[2] and Manjunath P. Pai, PharmD[1]; [1]College of Pharmacy, University of Michigan, Ann Arbor, Michigan, [2]Michigan Medicine, Ann Arbor, Michigan

Session: 145. PK/PD Studies
Friday, October 5, 2018: 12:30 PM

Background. β-Lactam exposure is frequently documented to be inadequate in critically ill patients implying that therapeutic drug monitoring (TDM) may be necessary to optimize efficacy. Practical barriers to implementation of TDM for β-lactam/β-lactamase inhibitor combinations include potential chemical instability as well as the need to assay both drug components.

Methods. First, ex-vivo stability studies of piperacillin/tazobactam (PIP/TZB) were performed at 1, 10, and 100 mg/L concentrations in human plasma. Spiked plasma samples were stored at room temperature for 4 hours and then at 4°C for 72 hours to mimic the conditions of routine handling. Second, a pilot study using discarded clinical laboratory samples was conducted to ascertain the feasibility of such a method for PIP/TZB TDM. Consecutive patients initiated on PIP/TZB within 24 hours of admission to the medical intensive care unit were screened for enrollment. Patients receiving less than 48 hours of therapy and those requiring renal replacement therapy were excluded. Laboratory samples were collected following their intended use and assayed for PIP and TZB using LC-MS/MS. Clinical patient data were obtained retrospectively.

Results. In the ex vivo studies, both PIP and TZB were stable at 100 mg/L for up to 48 hours at 4°C; however, at lower drug concentrations there was unacceptable (>15%) loss after 24 hours. Thirty-two subjects contributed a total of 136 clinical samples for secondary analysis. Patients were a mean (SD) of 64 (15) years old with estimated creatinine clearance of 97 (61) mL/minute. The assay was linear over a range of 1–100 µg/mL and 0.5–50 µg/mL for PIP and TZB, respectively. The median (fifth, 95th percentile) PIP and TZB concentrations were 26.30 (1.78, 112.00) and 7.55 (0.95, 23.00) mg/L, respectively. A strong linear relationship (R^2 0.84) was found between TZB and PIP concentrations (figure).



Conclusion. PIP and TZB concentrations are strongly correlated permitting evaluation of PIP as the key analyte. Plasma samples for PIP/TZB should be frozen

soon after collection for batch assay Methods. "Real-world" studies documenting high interpatient variability in PIP/TZB pharmacokinetics in the critically ill should account for pre-analytical variation due to sample degradation with clear sample handling protocols.

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

1417. Evaluating the Dissonance Between C_{max} and AUC with Clinically Utilized Aminoglycoside (AG) Dosing Regimens: Use of Tobramycin (TOB) Against *Pseudomonas aeruginosa* (PA) as a Case Study

Nikolas J. Onufrak, PharmD[1]; Sujata M. Bhavnani, PharmD, MS[1]; Jason M. Pogue, PharmD, BCPS-AQ ID[2,3] and Christopher M. Rubino, PharmD[1]; [1]ICPD, Schenectady, New York, [2]Detroit Medical Center, Detroit, Michigan, [3]Wayne State University, Detriot, Michigan

Session: 145. PK/PD Studies

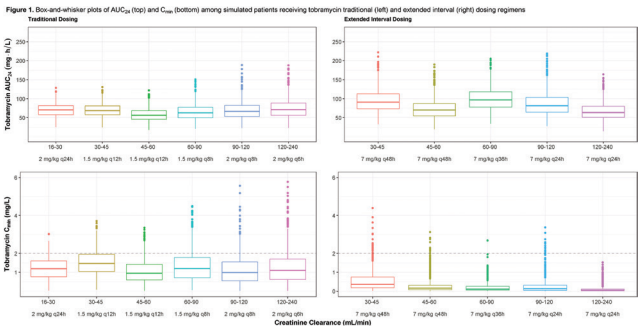
Friday, October 5, 2018: 12:30 PM

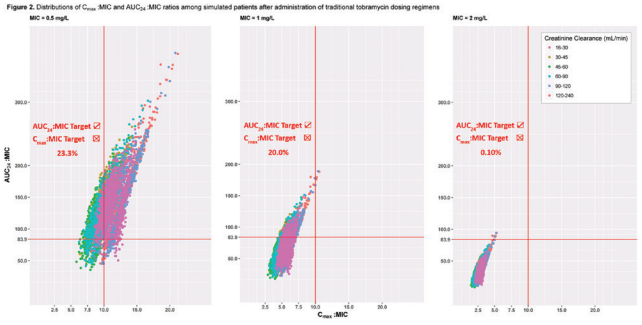
Background. Current dogma suggests optimizing AG doses based on peak concentration (C_{max}), without consideration of daily drug exposure (AUC_{24}). The correlation between attainment of the TOB pharmacokinetic-pharmacodynamic (PK-PD) targets, C_{max}:MIC and AUC_{24}:MIC ratio was explored using a TOB population PK (PPK) model, Monte Carlo simulation, and PA nonclinical PK-PD data.

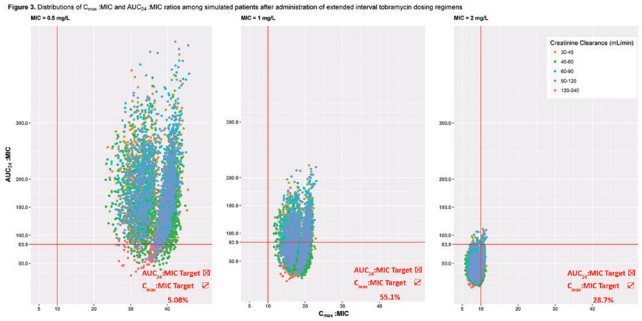
Methods. Simulated TOB plasma concentration-time profiles for traditional (TD) and extended interval (EID) dosing regimens were generated using a published PPK model [Aarons. *Br J Clin Pharmacol* 1989;28:305–14]. Simulations were performed by bootstrapping from a database of >1,400 infected patients enrolled in clinical trials to achieve n = 1,000 per renal function group defined by varying creatinine clearance ranges. Variability in average TOB AUC_{24} and C_{min} over 48 hours was assessed to determine dosing regimens that produced, for each renal group, (1) ≤50% difference in median AUC_{24} compared with that of normal renal function (90–120 mL/minute); (2) ≤25% of simulated AUC_{24} values beyond the fifth and 95th percentiles of the AUC_{24} distribution for normal renal function; and (3) ≤20% of C_{min} values >2 mg/L. Once these requirements were met across renal groups, the percentages of simulated patients achieving the C_{max}:MIC target ≥10 and AUC_{24}:MIC target for 1-log_{10}CFU reduction (≥83.9) at MIC values of 0.5–2 mg/L were assessed.

Results. Distributions of simulated TOB AUC_{24} and C_{min} values by renal group are shown in Figure 1. Figures 2 and 3 depict the discordance between C_{max}:MIC and AUC_{24}:MIC target attainment for TD and EID, respectively. Of 6,000 simulated patients receiving TD, 20.0% achieved the AUC_{24}:MIC target at an MIC = 1 mg/L without producing a C_{max}:MIC ≥10, whereas 55.1% of 5,000 simulated patients receiving EID failed to achieve the AUC_{24}:MIC target despite producing a C_{max}:MIC ≥10.

Conclusion. At clinically relevant MICs, AG TD regimens optimized based on C_{max} may result in patients receiving higher than necessary doses, while EID regimens may lead to underdosing. Given the transient nature of a peak concentration compared with overall drug exposure, the adequacy of AG dosing should consider variability in drug clearance (AUC_{24}) over variability in distributional volume (C_{max}).







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

1418. Pharmacokinetics (PK) and Toxicity of Intravenous Amikacin (AMK) Dosed Three Times a Week (TIW) for Treatment of Disseminated *Mycobacterium abscessus* Infection in Children

M. Tuan Tran, PharmD[1]; Felice C Adler-Shohet, MD[2]; Jasjit Singh, MD[2]; Delma Nieves, MD[2]; Negar Ashouri, MD[2] and Antonio Arrieta, MD, FIDSA[2]; [1]Pharmacy Services, CHOC Children's Hospital, Orange, California, [2]Infectious Diseases, CHOC Children's Hospital, Orange, California

Session: 145. PK/PD Studies

Friday, October 5, 2018: 12:30 PM

Background. AMK exhibits concentration-dependent bactericidal activity where larger intermittent doses with higher peaks (C_{max}) may be less toxic than more frequent dosing while achieving similar efficacy. An AMK containing regimen was used for treatment of *M. abscessus* odontogenic outbreak infections in children. Additionally, synergy has been observed between AMK and clofazimine (CFZ). Previous reports of daily AMK for *M. abscessus* infection in children resulted in high rates of toxicity. This is the first report of PK and safety of AMK dosed TIW for disseminated *M. abscessus* infections in children.

Methods. Treatment regimen initially included high dose AMK TIW with azithromycin (AZM) and a β-lactam followed by lower dose AMK with CFZ and AZM. Data collected included demographics, weekly laboratories, treatment details and adverse effects. AMK levels were drawn at 2- and 6-hour postdose for PK determination and to attain a C_{max} of 8 × minimum inhibitory concentration. Audiograms were obtained every 2 weeks.

Results. Of 27 children who received treatment, 13 were male, mean age was 5.8 years (3.0–9.4 years) and mean weight was 21.4 kg (14–37 kg). Dissemination (lung nodules (16 [59.3%]) and granulomatous cervical lymphadenitis (10 [37%]) was common. All patients underwent oral surgical debridement. Mean total treatment duration was 135 ± 19 days (mean ± SD). Initial AMK dose was 23.7 ± 5 mg/kg to achieve a C_{max} 58.7 ± 6.3 mg/L. Dosage was reduced to 12.6 ± 2.2 mg/kg after addition of CFZ at 65 ± 14 days to target C_{max} 25 ± 5 mg/L. No nephrotoxicity was noted, however a transient increase in serum creatinine of 50% from baseline was seen in seven (25%) patients. Two children experienced mild–moderate hearing loss during treatment which normalized by final audiogram. All children showed evidence of jaw healing with resolved or improving lung nodules at 12-months follow-up.

Conclusion. TIW AMK containing regimen is well tolerated and potentially less toxic than daily dosing for treatment of *M. abscessus* infection in children.

AMK PK Parameters (Mean ± SD)	k_e ($hour^{-1}$)	$t_{1/2}$ (hour)	V_d (L/kg)	C_{max} (mg/L)	CL (mL/minute)	AUC (mg hour/L)
	0.46 ± 0.07	1.5 ± 0.25	0.38 ± 0.11	58.7 ± 6.3	59.3 ± 17.7	145.6 ± 24.6

Disclosures. **A. Arrieta**, Melinta Therapeutics: Investigator, Research support.

1419. 24-Hour Pharmacokinetic Relationships for Intravenous Vancomycin and Novel Urinary Biomarkers of Acute Kidney Injury

Sean Avedissian, PharmD[1]; Jiajun Liu, PharmD[2]; J Nicholas O'Donnell, PharmD, MSc[3]; Gwendolyn Pais, PhD[4]; Leighton Becher, BS[5]; Medha Joshi, PhD[5]; Walter Prozialeck, PhD[5]; Peter Lamar, BS[5]; Thomas P. Lodise, Jr., PharmD, PhD[6] and Marc H. Scheetz, PharmD, MSc, BCPS AQ-ID[7]; [1]Pharmacy Practice, Midwestern University Chicago College of Pharmacy/Northwestern Memorial Hospital, Downers Grove, Illinois, [2]Pharmacy, Edward Hines, Jr. VA Hospital, Hines, Illinois, [3]Albany Medical Center, Albany, New York, [4]Midwestern University, Downers Grove, Illinois, [5]Midwestern University Chicago College of Pharmacy, Downers Grove, Illinois, [6]Albany College of Pharmacy and Health Sciences, Albany, New York, and [7]Department of Pharmacy, Northwestern Medicine, Chicago, Illinois

Session: 145. PK/PD Studies

Friday, October 5, 2018: 12:30 PM

Background. Vancomycin induces exposure-related acute kidney injury; yet only troughs are generally monitored in patients. In rat models, intraperitoneal dosing