Methods. The initial model includes adult and pediatric patients with a rich cefepime sampling design. All adults received 2 g CEFL while pediatric subjects received a mean of 49 (SD 5) mg/kg. One- and two-compartment models were considered as base models and were fit using a non-parametric adaptive grid algorithm within the PMetrics package 1.5.2 (Los Angeles, CA) for R 3.5.1. Compartamental model selection was based on Akaike information criteria (AIC). Covariate relationships with PK parameters were visually inspected and mathematically assessed. Predictive performance was evaluated using bias and imprecision of the population and individual prediction models. External validation was conducted using a separate adult cohort.

Results. A total of 45 subjects (n = 9 adults; n = 36 pediatrics) were included in the initial PK model build and 12 subjects in the external validation cohort. Overall, the data were best described using a two-compartment model with volume of distribution (V) normalized to total body weight (TBW/70 kg) and an allometric scaled elimination rate constant (Ke) for pediatric subjects (AIC = 4.138.36). Final model observed vs. predicted plots demonstrated good fit (population R² = 0.87, individual R² = 0.69). Figure 1a and b). For the final model, the population median parameter value (95% credibility interval) were V0 (total volume of distribution), 11.7 L (10.2–14.4); Ke for adult, 0.56 hour⁻¹ (0.38–0.78); Ke for pediatrics, 0.82 hour⁻¹ (0.64–0.85); KCP (rate constant from central to peripheral compartment), 1.4 hour⁻¹ (1.3–1.8). KPC (rate constant from peripheral to central compartment), 1.6 hour⁻¹ (1.2–1.8). The validation cohort has 12 subjects, and the final model fit the data well (individual R² = 0.75).

Conclusion. In this diverse group of adults and pediatrics, a two-compartment model described CEFL PK well and was externally validated with a unique cohort. This model can serve as a population prior for real-time PK software algorithms.

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1574. Predictive Ability and Bias of Vancomycin Population PK Models in an Obese Adult Population

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Background. Accurate dosing of vancomycin is difficult due to high inter-individual variability of vancomycin pharmacokinetics (PK), and is particularly challenging in obese patients. Vancomycin is hydrophilic, yet total body weight (TBW) has traditionally been used for dosing in the general population, and also into the obese population. The aim of this study was to evaluate the performance of published vancomycin PK models in a large set of routine clinical data obtained from an obese population.

Methods. De-identified data were available from 1717 courses of vancomycin administered to obese adults (BMI ≥30) from hospitals across the United States, EU, and Australia. Three population PK models, Buelga et al. (2005), Goti et al. (2018), and an obese-specific model, Adane et al. (2015), were used to predict plasma concentrations at the time of each recorded vancomycin assay, and their accuracy and bias were compared. Goodness of fit at both the population and individual level was assessed, and elastic net regression was used to identify any sources of predictive error in the obese-specific model. Model parameters for each model were then re-estimated, and a variety of body size metrics were evaluated.

Results. The Buelga et al. one-compartment model had the best predictive ability (Table 1). In all models, bias (calculated as MME, mean per-patient mean predictive error) by obesity class was observed at both the population and individual levels, and unexpectedly was largest in the obese-specific model. In the obese-specific model, predictive error correlated with the use of TBW as a model covariate. A set of models derived from Adane et al. model were then developed to correct for weight. Using ideal body weight (IBW) or BMI and no correction for weight on CL provided the best fit. The derived model accounted for 81% of variance in plasma concentration and exhibited negligible bias by obesity class (population MME = -0.75 (i), -0.06 (ii), and -0.5 (iii) mg/L).

Conclusion. Existing vancomycin population PK models for use in the obese population are biased in higher obesity classes due to the use of total body weight. A novel population PK model developed using ideal body weight exhibits negligible bias across obesity classes as well as improved predictive ability.

Table 1. Predictive ability of and bias of published vancomycin models in the obese

| Model | Buelga et al. (2005) | Goti et al. (2018) | Adane et al. (2015) |
|-------|----------------------|-------------------|--------------------|
| % Variance Explained | 76% | 86% | 60% |
| Obesity class* | | | |
| Population, mg/L | -0.88 | -0.03 | 0.1 |
| Individual, mg/L | -0.19 | -0.10 | 0.87 |

* Obesity class as defined in WHO (2014) – i: BMI < 18.5, ii: BMI ≥ 18.5, and m: BMI ≥ 40

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1575. Vancomycin Loading Doses and Nephrotoxicity on Medicine Teaching Services

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Background. IDSA guidelines recommend the usage of a loading dose when using vancomycin for seriously ill patients to rapidly achieve adequate trough concentrations. While the relationship between vancomycin and nephrotoxicity is the focus of many studies, and with the strength of that relationship still debated, few studies have examined the relationship between vancomycin loading doses and nephrotoxicity.

Methods. We performed a retrospective cohort study examining vancomycin dosing for internal medicine teaching services’ patients over the 2014–15 academic year at one academic medical center. We generated a list of all hospitalized patients aged 18–85 who received vancomycin and were admitted to a teaching service. Patient data were extracted from the inpatient EMR via manual chart review. Patients were excluded if their pretreatment calculated glomerular filtration rate (GFR) was less than 50 mL/minute, if they received less than three doses of vancomycin, or if their initial dose was subtherapeutic (<10 mg/kg). Nephrotoxicity was determined by 7-day acute kidney injury (AKI) rate. Patients in the loading dose (>20 mg/kg) cohort were compared with those in the standard dose cohort (10–20 mg/kg). Our primary modeling used multi-variable logistic regression with AKI as our outcome of interest.

Results. 438 of the initial 804 patients were enrolled. The loading dose (n = 365, 83%) and standard dosing (n = 73, 17%) cohorts were not significantly different regarding demographics, GFR, nephrotoxic drug exposure, total vancomycin received, trough levels, or comorbidities, and were only significantly different regarding body mass index (BMI). The 7-day AKI rate was not significantly different between the two arms (6.3% in the standard dosing arm and 8.2% in the loading arm P = 0.6). AKI rate significantly increased in both arms in the setting of concurrent piperacillin–tazobactam and vancomycin administration (OR 2.5, P = .04). There was no association between BMI and AKI.

Conclusion. Few studies have examined the relationship between nephrotoxicity and vancomycin loading doses. The results of this study provide evidence that the use of loading doses is not significantly associated with increased 7-day AKI rate.

Table 2: Clinical Characteristics, Vancomycin Dosing, Concurrent Nephrotoxic Exposure, and 7-Day AKI Rate in Patients Treated with Standard Dose or Loading Dose Vancomycin

| Standard Dosing Cohort | Loading Dose Cohort | p-value (NS) |
|-------------------------|---------------------|--------------|
| Age in mean years (BMI<40) | 52.0 (17.2) | 50.4 (17.0) | .048 (n.s.) |
| Race | | | |
| Caucasian | 262 (65.6%) | 61 (65.6%) | |
| African American | 85 (19.1%) | 10 (11.3%) | |
| Other | 38 (8.4%) | 5 (5.6%) | |

Table 2: Clinical Characteristics, Vancomycin Dosing, Concurrent Nephrotoxic Exposure, and 7-Day AKI Rate in Patients Treated with Standard Dose or Loading Dose Vancomycin

| Standard Dosing Cohort | Loading Dose Cohort | p-value (NS) |
|-------------------------|---------------------|--------------|
| BMI, mean kg/m² (Standard Deviation, SD) | 38.1 (9.3) | 24.1 (9.9) | <0.001 (n.s.) |
| Baseline Creatinine (SD) | 0.85 (0.20) | 0.76 (0.20) | 0.06 (n.s.) |
| Baseline Glomerular Filtration Rate (SD) | 109 (64.7) | 116.2 (64.1) | 0.248 (n.s.) |
| Clacton Creatinine Clearance Score (SD) | 11.2 | 11.2 | 1.0 (n.s.) |
| ≤ 2 | 169 | 41 | |
| > 2 | 191 | 41 | |
| Inpatient (Piperacillin Tazobactam) | 96 (25.7%) | 27 (29.6%) | 0.54 (n.s.) |
| Piperacillin-Tazobactam Exposure | 63 (20.7%) | 21 (23.8%) | 0.56 (n.s.) |
| Other nephrotoxic exposure* | 42 (11.5%) | 40 (12.7%) | 0.99 (n.s.) |
| Concomitant Nephrotoxic exposure | 116 (32.6%) | 20 (21.7%) | |
| Total Vancomycin Received in gram (SD) | 5.9 (3.3) | 9.1 (3.4) | 0.03 (n.s.) |
| Vancomycin trough, mean (SD) | 15.7 (7.2) | 15.9 (6.1) | 0.90 (n.s.) |
| High trough (≥30 mg/L) | 20 (9.6%) | 5 (5.7%) | <0.05 (Fisher exact) |
| 7-day AKI Rate | 23 (5.2%) | 6 (0.7%) | 0.0 (n.s.) |

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1576. Delaying the Start of Maintenance Vancomycin After a Loading Dose to Avoid a High 0–24h AUC

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**Background.** Vancomycin dosing guidelines recommend loading doses (LDs) (25–30 mg/kg TBW), and a maintenance regimen, usually started after a time period equal to the dosing interval. Studies of vancomycin exposure and nephrotoxicity conclude that a 0 to 24-hour area under the serum concentration–time curve (0–24 AUC) > 677 mg·hour/L results in a 3–to 4-fold increased risk of nephrotoxicity (Zasowski EJ, Antimicrob Agents Chemother 2018). For vancomycin LDs we compare the calculated LD and the maintenance dose, and delay initiation of the maintenance regimen when the LD exceeds the daily maintenance dose by > 50%. This study assessed the pharmacokinetic outcomes from this technique.

**Methods.** We retrospectively reviewed 68 consecutive adult patients receiving therapeutic doses of vancomycin. Patient age, sex, height, weight, serum creatinine, and indication were used to calculate the daily dose/intervals for a steady-state 24-hr AUC of 400 or 600 mg·hour/L. The total 0–24 AUC was calculated by adding the 0–24 AUC from a 25 mg/kg LD (max 3 gm) to the 0–24 AUC(s) for maintenance dose(s) within the first 24 hours. We compared the total 0–24 AUC when the first maintenance dose was timed for the next dosing interval (“scheduled”) to that when the maintenance dose was delayed according to our protocol (“delayed”). We tested the proportion of patients who would be exposed to a vancomycin 0–24 AUC > 677 mg·hour/L with the “scheduled” process and in none of the patients using the “delayed” protocol. However, for patients with a goal AUC of 600, the 0–24 AUC was > 677 mg·hour/L in 22/52 patients via the “scheduled” process vs. 4/52 patients via the “delayed” protocol.

**Conclusion.** For patients with severe gram-positive bacterial infections or severe aggressive dosing of vancomycin, delaying the start of maintenance dosing following a large LD is an effective way to ensure attainment of goal therapeutic AUC within the first 24 h without placing the patient at increased risk for nephrotoxicity.

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**1577. Particle Characterization of Nebulized Liposomal Amphotericin B and Its Use in the Treatment of Murine Pulmonary Aspergillosis**

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**Background.** Immunocompromised patients are very susceptible to pulmonary aspergillosis causing 50% mortality with present treatments, indicating a need for novel therapeutic strategies. To address this, we standardized a nebulization method for effectively delivering liposomal amphotericin B (Ambisome™, AmB) into lungs of Aspergillus fumigatus-infected mice. 

**Methods.** AmB particle characterization was done with a Cascade particle impactor and a Schuco S5000 nebulizer containing 1.33 mg/mL AmB. For in vivo studies, AmB was nebulized (nbd) into a 12 compartment mouse (one mouse/compartment), following immunosuppression with 28 mg/kg triamcinolone IP (3–d, 1–2 g/mL, 1–1.5 mg/kg). Mice were challenged d0 with 107 A. fumigatus (ATCC® 10373) and 4 h post-challenge, divided into 5 groups (n = 12/gp): 5 days of 20 min/day nbd AmB (Gp1), 5 days of 20 min/day nbd FLC (Gp2), 5 days of IV FLC (Gp3), 5 days of intravenous (IV) AmB 7.5 mg/kg/day (Gp4) and IV PBS (Gp5). Seven mice/gp were monitored for survival to d21 and lungs, livers, kidneys, spleens (7 mice/gp) analyzed for mean amphotericin B µg/g and CFU/g.

**Results.** 16/68 patients were diagnosed with SSTI (goal 24-hr AUC: 400 mg·hour/L) and 52/68 with sepsis, bacteremia/endocarditis, or pneumonia (24-hr AUC: > 250 mg·hour/L). Median daily maintenance dose was 1750 mg (range: 675–4000 mg). For patients with a goal AUC of 400, the 0–24 AUC was > 677 mg·hour/L in 157/162 patients via the “scheduled” process vs. 4/52 patients via the “delayed” protocol. 

**Conclusion.** For patients with severe gram-positive bacterial infections or severe aggressive dosing of vancomycin, delaying the start of maintenance dosing following a large LD is an effective way to ensure attainment of goal therapeutic AUC within the first 24 h without placing the patient at increased risk for nephrotoxicity.

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**1578. Rifampicin Reduces Telzidol Concentrations When Co-Administered in Healthy Volunteers**

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**Session:** 162. PK/PD and Susceptibility Testing

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**Background.** Telzidol is an oxazolidinone used to treat skin and soft-tissue infections. Rifampicin is a rifamycin antibiotic which can also treat skin and soft-tissue infections, such as those caused by Staphylococcus aureus. Telzidol and rifampicin could therefore be used concurrently to treat infections. There is currently no clinical data on whether rifampicin affects telzidol concentrations. Rifampicin is known to be cleared by cytochrome P450s, but could be affected by other clearance mechanisms. Therefore we conducted a pharmacokinetic drug interaction study to investigate whether 2 weeks of rifampicin can affect telzidol concentrations.

**Methods.** We conducted a healthy volunteer study in 8 subjects. Subjects were first given linezolid 600 mg on day 1, telzidol 200 mg on day 4, rifampicin 600 mg daily from day 5 to 19 (28 mg/kg of rifampicin), and an additional dose of telzidol 200 mg on day 19. Blood was obtained at pre-dose, 1, 2, 3, 4, 5, 6, 8, and 24 hours post dose on days 4 and 19. Concentrations of telzidol were measured using a validated liquid chromatography / mass spectrometry method.

**Pharmacokinetic parameters were calculated by Non-Compartmental Analyses using Phoenix WinNonLin version 8.0.** The bioequivalence module was used to obtain ratios of PK parameters pre- and post-rifampicin.

**Results.** Eight subjects were included in the study. Median age (range) and weight were 34 (26–40) years and 77 (68–82) kg, respectively. Rifampicin was well tolerated in the study. Telzidol AUC (0–24 hours) was reduced after 2 weeks of rifampicin (GMR 0.80, 90% confidence interval 0.73–0.88), as was Cmax (0.54, 0.44–0.66) and Cmax (0.85, 0.79–0.91). Clearance/F of telzidol was significantly increased after rifampicin (1.35, 1.21–1.50).

**Conclusion.** Rifampicin given for 2 weeks has the potential to reduce telzidol concentrations, especially trough levels, which was reduced by 46%. Caution is recommended when using telzidol together with rifampicin, especially when telzidol MIC is high or treating difficult infections.

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1579. Multidrug-Resistant Candida auris Isolates From New York Hospitals and Healthcare Facilities Are Susceptible to Antifungal Combinations

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**Background.** Candida auris outbreak continues unabated in New York with the current case counts exceeding 300 patients. We used a modification of standard CLSI broth microdilution method (BMD) to 2-drug combinations are efficacious against C. auris isolates with high resistance to fluconazole (FZ, MIC > 256 µg/mL), and variable resistance to other broad-spectrum antifungal drugs.

**Methods.** BMD plates were custom-designed and quality controlled by TREK Diagnostic System. The combination tests of 15 drug-resistant C. auris involved microtiter wells with the initial 144 two-drug combinations and their two-fold dilutions (1/2–1/32) to get 864 two-drug combinations finally. We utilized MIC50 endpoints for the drug combination readings as reported earlier for the intra- and inter-laboratory agreements obtained against Candida species and Aspergillus fumigatus (Antimicrob Agents Chemother. 2015; 59:1759–1766). We also tested minimum fungicidal concentrations (MFC).

**Results.** We tested all possible 864 two-drug antifungal combinations for nine anti-fungal drugs in use to yield 12,960 MIC50 readings, and MFC readings for 15 C. auris isolates. Flucytosine (FLC) at 2.0 mg/L potentiates most successful combinations with other drugs. Micafungin (MFG), Anidulafungin (AFG), Caspofungin (CAS) at individual concentrations of 0.25 mg/L combined well with FLC (2.0 mg/L) to yield MIC50, as also fungicidal for 14 of 15 isolates. AMB / FLC (0.25/1.0 mg/L) yielded MFC for 13 isolates and MFC for three test isolates. Posaconazole (POS), and Isavuconazole (ISA) and Voriconazole (VRC) also combined well with FLC (0.25/2.0 mg/L) to yield MIC50 for 12, 13 and 11 isolates, respectively. POS/FLC combination was fungicidal for three isolates.

**Conclusion.** We identified seven two-drug combinations of antifungals efficacious against drug-resistant C. auris strains. The modified BMD combination susceptibility testing could be used by the clinical laboratories to assist providers with the selection of optimal treatment for C. auris candidemia.