**Session:** P-62. PK/PD Studies

**Background.** ADG20 is a fully human IgG1 monoclonal antibody engineered to have potent and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential as well as an extended-half-life. ADG20 is administered intramuscularly (IM). A QSP/PBPK model was constructed to support dose selection for a COVID-19 Phase 2/3 prevention trial (EVAIDE: NCT04895137).

**Methods.** A QSP/PBPK model and a CDC reference adult body weight distribution (45–150 kg) were used to simulate 1000 concentration-time profiles for candidate single-dose regimens of ADG20 (150–450 mg IM). As serum virus neutralizing antibody (sVNA) titers are reportedly a key correlate of protection from COVID-19, a regression equation between time-matched serum ADG20 concentrations (following a 300 mg IM dose) and sVNA titers was developed using measured titers against authentic SARS-CoV-2 determined by a plaque reduction neutralization assay. Projected ADG20 serum concentrations relative to neutralization potency in vitro (90% inhibitory concentration [IC90]) for authentic SARS-CoV-2 were also evaluated.

**Results.** The measured 50% neutralization titer (MN50; geometric mean [coefficient of variation, %]) was 1382 (32.7%) 13 days after a single 300 mg IM dose of ADG20. This was within the range of peak AVNA titers reported for COVID-19 vaccine recipients. Using the linear equation relating serum ADG20 concentration to time matched individual MN50 titers and the QSP/PBPK median PK prediction, the anticipated median MN50 exceeded the threshold for protection from SARS-CoV-2 infection established in a non-human primate adoptive transfer model for up to 52 weeks. Based on the QSP/PBPK median PK prediction, median ADG20 serum concentrations are projected to remain >10-fold above the ADG20 IC50 value of 0.011 mg/L against authentic SARS-CoV-2 for up to 52 weeks (Figure).

**Conclusion.** Following administration of a single 300 mg IM dose, sVNA titers and concentrations of ADG20 are projected to remain above thresholds anticipated to be required for protection against COVID-19 for up to 52 weeks. These data support the evaluation of a single ADG20 300 mg IM dose for the prevention of COVID-19.

Predicted median serum ADG20 concentration is shown with the dotted line representing 100x in vitro IC90 of 0.011 mg/L or 1.1 mg/L; the solid black line represents the simulated median; the shaded area represents the 90% prediction interval. The predicted median half-life of ADG20 300 mg IM exceeded 74 days. PBPK model inputs include Ln-normal Kd, FcRn of 9.55 nM (10% IIV); IM bioavailability of 100%; Kd, dissociation constant; Ln, log-normal; RC, reflection coefficient.

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**1090. Does calculation method matter for targeting vancomycin AUC?**

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**Background.** Vancomycin (VAN) guidelines recommend targeting an area under the curve (AUC) concentration of 400–600 for treatment of methicillin-resistant *Staphylococcus aureus* infections. Multiple strategies for calculating AUC exist, including first order pharmacokinetic (foPK) equations and Bayesian models. Most clinical applications of foPK assume unchanged patient status and project ideal administration times to estimate exposure. Bayesian modeling provides the best estimate of true drug exposure and can incorporate changing patient covariates and exact doses. We compared two commonly used foPK methods to Bayesian estimates of VAN AUC.

Graphs depict calculated AUCs using the three different methods: 1) Population PK estimated (foPOP PK) 2) Two-level first dose estimated (foFDPK) 3) Bayesian estimated.

**Method.** First order equations were performed using population PK estimates (foPOP PK) to estimate steady state (SS) AUC and initial doses. Two concentrations after first dose were used to estimate SS AUC (foFDPK). A 2-compartment Bayesian model allometrically scaled for weight and adjusted for creatinine clearance was used to determine 24-48 hour AUCs. Differences between AUCs were compared using a mixed-effects analysis, and correlation of foPK equations to Bayesian estimates was described using Spearman's correlation. Patient results from each method were classified as below (< 400), within (400-600), or above (>600) targets.

**Results.** 65 adult patients were included. The median 7Q2 for calculated AUCs using foPOP PK, foFDPK, and Bayesian methods were 495.6 (IQR: 76.6), 498.2 (IQR: 107.4), and 472.1 (IQR: 177.9), respectively with p >0.65 for both foPK methods vs. the Bayesian method. AUCs predicted by foPK equations were poorly correlated with Bayesian AUCs (Spearman's r=0.08, p=0.53), while AUCs from foFDPK better correlated with Bayesian AUCs (Spearman's r=0.48, p=0.00). AUCs were within, above, and below target for 54%, 20%, and 26% for the Bayesian model; 95%, 5% and 0% for foPOP PK; and 74%, 12%, and 14% for foFDPK. foPK AUC estimates concurred with Bayesian estimates only 52% of the time.

**Conclusion.** AUCs calculated by the three methods did not differ on average, but dosing recommendations for foPK at the patient level varied substantially compared to the Bayesian method. This difference is because Bayesian estimation incorporates actual patient exposures while foPK equations rely on idealized dose timing to predict AUCs.

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**1091. Validation of an Allometrically Scaled Body Weight Equation to Predict Vancomycin Clearance and Guide 24-Hour Vancomycin AUC Dosing in Obese Patients**

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**Session:** P-62. PK/PD Studies

**Background.** Accurately determining empiric vancomycin (VAN) doses in obese patients represents a clinical challenge. A recent population pharmacokinetic (PK) study provided an equation to estimate vancomycin clearance (CL) based on age, sex, serum creatinine (Scr), and allometrically scaled body weight. The purpose of this study was to validate this equation in a population of obese adults treated with vancomycin at eight community-based hospitals and use the CL estimate to guide empiric VAN dosing.

**Methods.** The study period was November 1, 2020 and March 30, 2021. Patients were included if they were ≥ 18-year-old with a body mass index (BMI) ≥ 30 kg/m^2^, had an empiric dose targeting an AUC24 determined using the above referenced equation, and had a calculated AUC24. Only the first vancomycin course and AUC calculation for each patient were included. Patients with a creatinine clearance < 30mL/min and pregnant women were excluded. AUC24 and other PK parameters were calculated using two levels and noncompartmental analysis. Observed versus predicted CL and AUC24 were plotted to determine correlation.

**Results.** Sixty patients were included, of which 60% were male and 33% had a confirmed methicillin-resistant *Staphylococcus aureus* infection. The mean age, BMI, and baseline Scr were 61.8 years, 37.8 kg/m^2^, and 0.99 mg/dL, respectively. Fifty-three
(88%) patients received a loading dose, with a mean dose of 20.3mg/kg. The mean initial total daily maintenance dose was 239.7mg. The mean predicted AUC24 was 476.4mg*h/L while the mean observed AUC24 was 556.3mg*h/L. For CL, the correlation between observed and predicted values was $R^2=0.38$ (Figure 1). The percentage of patients with observed AUC24 values of < 400mg*h/L, 400-600mg*h/L, and >600mg*h/L were 23%, 40%, and 37%, respectively. The relationship between calculated minimal concentration (Cmin) and AUC24 is shown in Figure 3. 65% of patients with a therapeutic AUC achieved it with a Cmin < 15mg/L while 4.5% of patients with a supratherapeutic AUC had a Cmin > 60mg/L.

Conclusion. The correlation between observed and predicted CL was 0.38. Using these CL estimates to guide empiric VAN dosing resulted in only 40% of patients achieving a therapeutic AUC24.

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1092. Population Pharmacokinetics of Cephalexin in Non-Obese and Obese Hospitalized Patients with Infectious Diseases
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Background. Obesity is a significant global health problem and has been associated with altered pharmacokinetics (PK) and pharmacodynamics (PD) of many drugs. Cephalexin is a commonly prescribed antibiotic as an oral drug for the treatment of mild to moderate infections; however, little is known regarding cephalexin pharmacokinetics in obese patients. The objective of this study was to investigate the population PK of cephalexin in non-obese and obese patients.

Methods. Hospitalized patients who were 18 years or older with a suspected or documented infection were studied. Patients weighing < 120 kg were defined as non-obese patients whereas those weighing ≥ 120 kg as obese. All included patients received cephalexin 1000 mg every 6 hours orally. After ≥ 3 days of therapy, serial blood samples were collected. Ultrafiltration was used to separate the unbound drug from the protein-bound fractions, and both total and unbound serum concentrations were determined by HPLC. The concentration-time data for cephalexin were analyzed by a non-linear mixed effects modeling approach using NONMEM.

Results. Overall, 255 serum concentrations from 19 patients (10 males, 4 in an ICU) were included: ten patients were non-obese (total body weight [TBW] ≤ 120 kg) and nine were obese (TBW ≥ 120 kg). A 1-compartment model with first-order absorption, absorption lag-time, first-order elimination, and linear protein binding best fit the concentration-time data. Creatinine clearance (CrCl) was the only covariate significantly associated with cephalexin PK, specifically systemic clearance (CL): CL (L/h) = 12.3 + [0.0837 x (CrCl – 81.8)]. No other covariates significantly affected the model-derived PK parameters including CL, volume of distribution (V), first-order absorption rate constant (Ka), unbound fraction (fu) with the fixed estimate of 0.776, and absorption lag-time (Tlag).

Conclusion. In conclusion, cephalexin PK is comparable between non-obese and obese patients. Dosing adjustments based solely on body size may not be necessary. Further analyses are warranted to suggest optimal cephalexin dosages in obesity through large-scale population PK-PD modeling and simulation.

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1093. Bypassing Penicillin Skin Testing in favor of Direct Oral Challenge: A Pharmacy-driven Inpatient Program
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Background. Patient interview, penicillin skin testing (PST) and/or an oral challenge can be used to evaluate penicillin allergies. Programs favor PST prior to oral challenge, but there is interest in bypassing PST and directly oral challenging for logistical and financial reasons. Data on the safety and efficacy of a direct challenge in the inpatient setting when the index reaction is moderate to severe (e.g. swelling of throat, angioedema, anaphylaxis) is lacking.

Methods. Adult patients (≥ 18 years) admitted with a penicillin allergy were evaluated for eligibility between September 2019 and June 2021. Pregnant patients were excluded, while critically ill patients and those on anti-histamine medications were evaluated if clinical need was high. Institutional protocols allowing for patients to be challenged without PST if reaction was more than 10 years ago were used. Data collected included the number of patients challenged and delabeled, number of patients who had moderate to severe index reactions, number of patients who were relabeled without cause, and number of patients who declined further testing.

Results. Two hundred twenty-five patients were evaluated; 11 patients declined testing. Two hundred four patients were delabeled (95%) among those fully evaluated. One hundred twelve patients were delabeled by interview and chart review alone (52%), 99 by oral challenge (46%), and 2 by PST and oral challenge (1%). Twenty-nine patients with moderate to severe reactions were challenged and 27 were delabeled. Ten patients could not be delabeled due to mild or delayed reactions to challenge or subsequent treatment, including 2 patients with severe index reactions who had mild challenge reactions and required no rescue medications. No patients required epinephrine during challenge. Five patients were relabeled and then delabeled again as no new reaction had occurred.

Conclusion. All Authors: No reported disclosures

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