1101. Implementing a Beta-Lactam Therapeutic Drug Monitoring Program: Experience from a Large Academic Medical Center

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Session: P-62. PK/PD Studies

**Background.** Beta-lactams (BL) are the cornerstone of antimicrobial treatment for infections. Beta-lactam therapeutic drug monitoring (BL-TDM) optimizes drug concentrations to ensure maximal efficacy and minimal toxicity. The goals of this study were to describe the implementation process of a BL-TDM program and to further describe our experience using BL-TDM in clinical practice.

**Methods.** This was a retrospective review of adult patients with available BL-TDM between January 2016 and November 2019 at the University of Florida (UF) Health Shands Hospital. Total serum concentrations of BL were measured in the Infectious Diseases Pharmacokinetics Lab (IDPL) at UF using a validated ultrahigh pressure liquid chromatography assay with triple quadrupole mass spectroscopy (LC-MS-MS). At our institution, TDM is available for 11 BLs and in-house assays are performed from Mon-Fri for most BLs.

**Results.** A total of 3,030 BL concentrations were obtained. An analysis was performed on the first BL-TDM encounter in 1,438 patients. The median age was 57 years (IQR, 41-69) and the median BMI was 27.5 kg/m² (IQR, 22.5-34.5). On the day of BL-TDM, the median serum creatinine was 0.83 (IQR, 0.59-1.30). Fifty-one percent of patients (n=735) were in an ICU at the time of BL-TDM with a median day of BL-TDM, the median serum creatinine was 0.83 (IQR, 0.59-1.30). Fifty-one percent of patients (n=735) were in an ICU at the time of BL-TDM with a median day of BL-TDM was performed a median of 2 days (IQR, 1-4) from the start of BL therapy and resulted in a dosage adjustment in 26% (n=145).

**Conclusion.** BL-TDM was performed in older, non-obese patients with normal renal function. Over half of the evaluated patients were in an ICU at the time of TDM. This finding emphasizes the value of BL-TDM in the ICU setting because altered pharmacokinetics during critical illness has been linked to enhanced BL clearance. Interestingly, BL-TDM resulted in dosage adjustment in 1 in 4 patients who were receiving licensed BL dosing regimens, thus highlighting the role of TDM in dose individualization. BL-TDM was performed most commonly within the 72-hours of therapy initiation. Early BL-TDM has been shown to improve patient outcomes and should be promoted.

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1102. Evaluation of Vancomycin Accumulation in Patients with Obesity

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**Background.** Current vancomycin guidelines recommend using actual body weight for dosing. However, in patients with obesity, this may result in lower initial vancomycin concentrations that can accumulate with continued doses due to differences in volume of distribution. The objective of this study is to evaluate the incidence of vancomycin accumulation in patients with obesity and identify potential factors associated with accumulation.

**Methods.** This is a single-center, retrospective, observational study at a tertiary academic medical center. Adult patients with a BMI ≥ 30 kg/m² and with ≥ 2 vancomycin serum trough concentrations within the same encounter in 2019 were screened. Patients were excluded if they were pregnant, had unstable renal function or severe renal impairment, received < 3 doses before a concentration was drawn, or had inconsistent dosing prior to a concentration draw. Linear kinetics were used to correct for differences in timing of concentration or dose changes. The major endpoint was the incidence of vancomycin accumulation, defined as a 20% increase in trough concentration between the first and any subsequent trough concentrations within the first 10 days of therapy. Minor endpoints included the percentage of supratherapeutic concentrations and the incidence of acute kidney injury (AKI). Descriptive statistics were used to evaluate endpoints and multivariable logistic regression was used to evaluate factors associated with accumulation.

**Results.** We screened 543 patients, and 162 were included in our analysis. The median age was 56.5 years (interquartile range [IQR] 43 - 65.3), and 62.3% were male. The
median weight was 112.7 kg (IQR 99.8 - 122.6) and the median BMI was 36.8 kg/m² (IQR 33.1 - 41). The median total daily vancomycin dose at initiation was 287.8 mg/kg/day (IQR 25.4 - 31.2). Vancomycin accumulation occurred in 99 patients (61.1%) within the first 10 days of therapy and AKI occurred in 21 patients (14.9%). No factors studied, including age, gender, obesity class, initial dose, SCr, or frequency were associated with accumulation.

Discussion. Most patients with obesity experienced vancomycin accumulation within the first 10 days of therapy. Providers should be cautious when assessing a vancomycin concentration early in the treatment course.

1103. Minocycline (MIN) Pharmacodynamics (PD) against Stenotrophomonas maltophilia (STM) in a Neutropenic Murine Thigh Infection Model

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Background. Antibiotic treatment options for serious STM infections are limited. MIN displays in vitro activity against STM; however, limited data supports optimal dosing for STM. Herein, we employed the murine neutropenic thigh infection model to assess MIN PD against STM.

Methods. Four clinical STM isolates with MIN MICs 0.25 – 1 mg/L were included. Both thighs of neutropenic ICR mice were inoculated with bacterial suspensions in phosphate buffered saline (PBS) forming units (CFU)/mL. Mice received urinary nitrate on Day -3 to provide predictable renal impairment. Two hours after inoculation, MIN or control was administered subcutaneously. Pharmacokinetic (PK) studies of 2.5, 25, 50, and 100 mg/kg were conducted. Previously reported protein binding of 78.1% was used to define free exposure. Dose ranging studies were conducted on all STM to assess in vivo activity for a range of MIN exposures. MIN total daily doses (TDD) of 10, 20, and 50 mg/kg were fractionated q24h, q12h, and q6h against a single STM to determine the PD index best correlated with reductions in CFU/mL. Efficacy was measured in log CFU/thigh at 24h compared with 0h controls. Composite CPU data were fitted to an E_max model to determine the AUC/MIC exposure for stasis and 1 log reduction.

Results. MIN PK was linear up to 50 mg/kg and well described by a 1 compartment model with first order absorption and elimination. Mean PK parameters across the linear range were: Vd 2.97 L/kg; K01, 10.62 1/h; and K10, 0.35 1/h. Mean ± SD bacterial growth was 7.90±0.85 log CFU/thigh at 24h. A dose response was observed across all isolates using TDD of 2-300 mg/kg. PD indices correlated with CFU reductions as follows: AUC/MIC (R²=0.613), fmax/MIC (R²=0.590), and %T >MIC (R²=0.504). The AUC/MIC needed for stasis and 1 log reduction at 24h was 9.6 and 23.6, respectively.

Conclusion. These are the first data describing MIN PD against STM. Against these STM, MIN/AUC/MIC was the PD index best correlated with CFU reductions. The exposure thresholds defined in this study will be useful in designing optimal MIN dosing regimens for treating STM infections and re-assessment of the current susceptibility breakpoint.

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1104. Comparison of Antibiotic Sampling Techniques: Predicting Plasma Vancomycin Concentrations Using Volumetric Absorptive Microsampling (VAMS) from Capillary and Venous/Arterial Whole Blood

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Background. Therapeutic drug monitoring (TDM) is paramount to optimize the safety and efficacy of vancomycin (VAN). In children, TDM is challenged by difficulty in obtaining venous samples, impeding timely sampling. We assessed the ability of volumetric absorptive microsampling (VAMS) as a novel, whole blood sampling technique to predict plasma VAN concentrations in plasma.

Methods. We conducted a prospective pilot study among critically ill children prescribed VAN for clinical care. Coincident with VAN TDM in plasma (P), we collected 20 μL of capillary whole blood (C) and venous/arterial whole blood (V) using VAMS. Paired VAMS-P samples drawn >5 mins apart and VAMS samples with over- or under-filtered tip on visual inspection were excluded. Plasma concentrations were measured via chemiluminescent immunoassay in the Chemistry Laboratory. VAMS C and V concentrations were measured using LC/MS in the Bioanalytic Core Laboratory. Plasma concentrations were predicted from whole blood VAMS with Passing-Bablok regression using 3 methods: 1) uncorrected VAMS measures, 2) hematocrit-corrected VAMS, and 3) lab-corrected VAMS (Figure 1). We then assessed bias, imprecision, and accuracy of plasma predictions from VAMS (C and V) as compared to coincident P concentrations for each technique (Figure 1).

Results. Paired samples were collected from 31 enrolled subjects (Figure 2), with a median age of 3.3 years (range 0.1-17.9). Measured P concentrations ranged from 4.6 - 54.9 mg/L. 11 C samples (29%) and 3 V samples (10%) were excluded due to collection issues. Prediction results are shown in Figure 3. The 3 prediction techniques had similar performance characteristics, with each method displaying minimal bias (R² =0.2-0.2). The accuracy of prediction of P concentrations using VAMS was better for V than C samples.

Conclusion. VAMS has the potential to become a capillary blood sampling technique that aligns with the 2019 revised guidelines for appropriate TDM in children. Further studies are required to establish this as a routine TDM approach.

Abbreviations: C-P, capillary VAMS-plasma; V-P, venous/arterial VAMS-plasma; VAMS, volumetric absorptive microsampling.

Figure 1. Methods for relating whole blood vancomycin concentrations collected via VAMS to plasma concentrations and measure to evaluate predictive performance.

Figure 2. Flow diagram from sample collection to evaluation.

Figure 3. Performance of 3 techniques to predict plasma vancomycin concentrations using whole blood collected via VAMS.