1534. Polymyxin Antimicrobial Susceptibility (AST) Testing and Breakpoints for *P. aeruginosa*, *A. baumannii*, and Enterobacteriaceae: Recommendations from the United States Committee on Antimicrobial Susceptibility Testing (USCAST)

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Background. Polymyxins are important antimicrobial agents for the treatment of infections due to carbapenem-resistant and other multidrug-resistant organisms. Recently, the CLSI and EUCAST have set breakpoints for colistin (EUCAST and CLSI) and polymyxin B (CLSI) with slight differences in recommendations. However, there are issues unique to the polymyxin class that warrant additional guidelines. Herein, we assess data related to breakpoint setting and make additional recommendations for polymyxin AST interpretive criteria.

Methods. Data sources included longitudinal (2011–2017) US surveillance reference broth microdilution (BMD) MIC distributions (128,573 isolates) for colistin and polymyxin B (PB); published data on accuracy of various AST methodologies, in vivo pharmacokinetic/pharmacodynamic (PK-PD) models, prior polymyxin guide lines and agency package insert dosing recommendations, and population PK-PD and toxicodynamic (TD) data. Epidemiological cut-off, PK-PD (and TD), and clinical data were all considered for susceptible (S) breakpoint determinations.

Results. Data demonstrate that the most commonly utilized AST methodologies (disk diffusion, Etest, and automated MIC susceptibility panels), as well as agar dilution testing cannot reliably detect resistance; and BMD is the preferred AST. Importantly, colistin S is a reliable surrogate for PB with >90% of isolates in each pathogen group. Breakpoint recommendations can be found in the Table with emphasis on applying combination therapy. Key recommendations include an S breakpoint of ≤2 mg/L for each pathogen (both colistin and PB). However, based on a lack of preclinical efficacy in murine pneumonia models, PK/PD concerns, and poor clinical outcome data, we strongly suggest that no breakpoints are applied for pneumonia and that alternative therapies should be used where available. Additionally, due to a lack of significant renal excretion, PB will suggest that no breakpoints are applied for pneumonia and that alternative therapies should be used.

Conclusion. The polymyxins have compromised dosing strategies in obese populations that make them suboptimal antimicrobials when used alone, and additional caveats are required for AST breakpoint interpretive criteria and stewardship programs.

1535. Pharmacokinetic (PK) and Pharmacodynamic (PD) Evaluation of Cefepime (CPM) in Obese and Non-Obese Patients

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Background. Appropriate application of antimicrobial PK/PD properties is crucial to optimizing patient outcomes. Although β-lactams are among the most utilized antimicrobial and anti-infective agents, AST breakpoints available are largely un-known. The objective of this study was to compare PK/PD of CPM in non-obese (NO; weight ≤100kg) and obese (O; weight >100 kg) patients.

Methods. A prospective comparative PK/PD analysis was conducted in NO and O patients receiving CPM. Blood samples were obtained at 36, 60, 120, 240, 360, and 480 minutes after CPM infusion. CPM concentrations were determined by reversed-phase high-performance liquid chromatography. Non-compartmental PK analyses were performed, followed by Monte Carlo simulations (Oracle Crystal Ball®, 5,000 simulated patients) to estimate probability of target attainment (PTA) against common Gram-negative pathogens. The desired PD target for CPM was 95% above unbound drug (%T>MIC) ≥70%. Chi-squared and Mann–Whitney U tests were used for analysis.

Results. Seventeen patients were enrolled and most (94%) received CPM 2 g q8h. A greater PK/PD discrepancy in actual body weight and body mass index was observed (P < 0.001). There were no differences in other baseline or PK characteristics between the two groups. Utilizing CPM 2 g q8h, PTA ≥90% was not observed for organisms with an MIC of 8 µg/mL, the current CLSI breakpoint for *P. aeruginosa* and *A. baumannii* (PTA = 88% vs. 81% in NO and O groups, respectively). With a 6 g continuous infusion (CI), however, ≥90% PTA was achieved in both groups (PTA = 100% for organism with an MIC of 8 µg/mL, while a regimen of 2 g q8h (infused over 3 hours) [EI]) also provided PTA of ≥90% in both groups (PTA < 98% vs. 92% in NO and O groups, respectively). Goal PTA was not achieved in either group for organisms with an MIC of ≥4 µg/mL with CPM 1 g q8h or 2 g q12h (i.e., CLSI recommended dosing for organisms with MICs of 4 µg/mL).

Conclusion. Optimizing PK/PD parameters through novel dosing strategies are essential for both the NO and OB populations for optimal CPM exposure in susceptible pathogens with higher MICs. CPM 6 gms/day by either CI or EI provides more optimal PK/PD characteristics in obese patients for pathogens with MICs at or near the current CLSI-recommended breakpoint.

1536. Population Pharmacokinetic Analysis of Baloxavir Morboxil, a Capsaicinoid Endonuclease Inhibitor, in Adult and Adolescent Healthy Subjects and Influenza Patients and Exposure-Response Relationships in the Patients at High-Risk of Influenza Complications

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Background. Baloxavir marboxil is a prodrug of baloxavir acid which is a se-3

Dependent Endonuclease Inhibitor, in Adult and Adolescent Healthy Subjects

1 Dependent Endonuclease Inhibitor, in Adult and Adolescent Healthy Subjects

Table 1. Baseline Characteristics and Pharmacokinetic/Pharmacodynamic Parameters

| Parameter                                    | Non-Obese (n = 7) | Obese (n = 10) | P-value |
|----------------------------------------------|-------------------|----------------|---------|
| Male, n (%)                                  | 6 (85.7)          | 6 (60.0)       | 0.338   |
| Actual body weight, kg                       | 87.8 (72.5–92.4)  | 124.5 (113.7–133.9) | < 0.001 |
| Ideal body weight, kg                        | 77.6 (71.9–83.4)  | 71.9 (63.3–77.0) | 0.230   |
| Body mass index, kg/m²                       | 26.5 (24.2–29.0)  | 40.7 (36.4–48.6) | < 0.001 |
| Age, years                                   | 62.0 (52.0–68.0)  | 52.0 (42.0–62.0) | 0.364   |
| Creatinine clearance, ml/min                 | 78.7 (70.5–103.1) | 103.9 (84.7–117.0) | 0.270   |
| Maximum concentration, mg/L                 | 67.6 (62.7–81.1)  | 82.6 (54.6–112.8) | 0.813   |
| Minimum concentration, mg/L                 | 9.7 (4.5–13.2)    | 10.6 (8.5–15.7)  | 0.536   |
| Clearance, l/hr/kg                           | 0.09 (0.07–0.12)  | 0.07 (0.06–0.10) | 0.364   |
| Volume of distribution, l/ug                 | 0.34 (0.29–0.38)  | 0.27 (0.22–0.37) | 0.601   |
| Half-life, hours                             | 2.48 (2.35–3.35)  | 1.87 (1.30–2.97) | 0.887   |

All data are reported as median (IQR) unless otherwise noted.

Disclosures. All authors: No reported disclosures.
was assessed on the PK of baloxavir acid. The individual C_{\text{max}} and AUC were estimated with an empirical Bayesian approach. Exposure-response analysis was conducted for TTIIS and virus titer in the high-risk patients.

**Results.** A 3-compartment model with first-order absorption and lag time was selected as a structural PK model, and well described the plasma concentrations. The population PK analysis suggested that (1) AUC in non-Asians was 30.7% lower than that in Asians, (2) body weight significantly affected the exposures to baloxavir acid, (3) the exposures in high-risk patients were similar to those in otherwise healthy patients, and (4) no PK differences were identified regarding the risk factors for influenza complications. The exposure-response analyses showed that the body weight-based dose regimen (40 mg for the patients weighing <80 kg and 80 mg for the patients weighing ≥80 kg) shortened TTIIS and reduced virus titer for both type A and B influenza, across the entire range of baloxavir acid exposures observed in CAPSTONE-2 although subject number in the lowest exposure group was limited and it was difficult to discuss the magnitude of the responses accurately.

**Conclusion.** The results of the population PK analysis and exposure-response analyses provide useful information for understanding the pharmacokinetic and pharmacodynamic characteristics of baloxavir marboxil.

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

1537. Multicenter Study with Therapeutic Drug Monitoring (TDM) of Voriconazole (VRCZ) in Japanese Patients

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**Background.** TDM of VRCZ might be useful, especially in Asian people because of CYP2C19 genetic polymorphisms. However, limited data are available because of the small sample size.

**Methods.** Patients who received VRCZ and had TDM were reviewed retrospectively at five institutions. Adequate VRCZ dosage was defined as a loading dose of 5–6 ± 0.5 mg/kg twice daily followed by a maintenance dose of 3–4 ± 0.5 mg/kg twice daily. For prophylaxis, the loading dose was left to the physician’s discretion. Optimal timing of TDM was defined as 4–7 days after starting therapy. Patients with adequate dosing and optimal timing of TDM were evaluated for analysis of trough levels (C_{\text{min}}). Target C_{\text{min}} was set at 1–5 μg/mL.

**Results.** The study included 584 patients (treatment: 402; prophylaxis: 182). TDM was conducted on days 4–7 in 66.5% of patients (>5, 30.2%). A low adequate dosage (44.5%) was observed for treatment mainly because of a low performance of the loading dose (46.6%). Achievement of target C_{\text{min}} was obtained in 62.7% (>5 μg/mL, 32.2%) in the treatment group and in 67.6% (11.0%) in the prophylaxis group. Seventy-one of 81 (81.7%) patients who required a dose reduction reached target C_{\text{min}} by the second TDM. In 38 patients whose dose was not altered at oral switching, C_{\text{min}} was significantly reduced from 2.5 ± 1.6 to 1.2 ± 1.3 μg/mL (P = 0.002), which indicated the necessity of TDM after oral switching. Hepatotoxicity occurred in 4.6% and visual symptoms in 7.9% of patients. Visual symptoms resolved without discontinuation of VRCZ in 73.9% of patients. Because of dosage adjustment based on TDM, high C_{\text{min}} did not cause hepatotoxicity. However, the incidence of visual symptoms was significantly higher in patients with a high C_{\text{min}} (12.7% vs. 5.4%, P = 0.002).

**Conclusion.** One-third of Japanese patients who underwent VRCZ treatment with a loading dose showed high C_{\text{min}}. Occurrence of hepatotoxicity was prevented with alteration of dosage in these patients (AMED, JP18fk0108045).

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

1538. Who Will Benefit From Therapeutic Drug Monitoring of Ganciclovir?

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**Background.** TDM of Ganciclovir (GCV) is indicated for the achievement of adequate trough concentrations. However, limited data are available regarding the necessity of TDM and its optimal timing.

**Methods.** TDM was conducted on days 4–7 in 66.5% of patients (>7, 30.2%). GCV therapy was initiated with a loading dose (44.5%) was observed for treatment mainly because of a low performance of the loading dose (46.6%). Achievement of target C_{\text{min}} was obtained in 62.7% (>5 μg/mL, 32.2%) in the treatment group and in 67.6% (11.0%) in the prophylaxis group. Seventy-one of 81 (81.7%) patients who required a dose reduction reached target C_{\text{min}} by the second TDM. In 38 patients whose dose was not altered at oral switching, C_{\text{min}} was significantly reduced from 2.5 ± 1.6 to 1.2 ± 1.3 μg/mL (P = 0.002), which indicated the necessity of TDM after oral switching. Hepatotoxicity occurred in 4.6% and visual symptoms in 7.9% of patients. Visual symptoms resolved without discontinuation of VRCZ in 73.9% of patients. Because of dosage adjustment based on TDM, high C_{\text{min}} did not cause hepatotoxicity. However, the incidence of visual symptoms was significantly higher in patients with a high C_{\text{min}} (12.7% vs. 5.4%, P = 0.002).

**Conclusion.** One-third of Japanese patients who underwent VRCZ treatment with a loading dose showed high C_{\text{min}}. Occurrence of hepatotoxicity was prevented with alteration of dosage in these patients (AMED, JP18fk0108045).

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