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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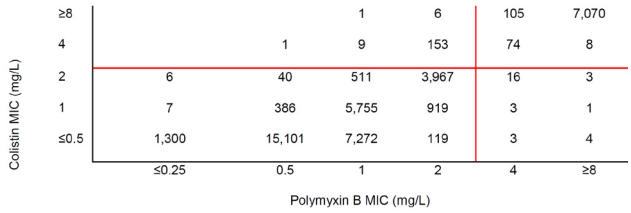
Background. Polymyxins are important antimicrobial agents for the treatment of infections due to carbapenem-resistant and other multidrug-resistant organisms. Recently, the CLSI and EUCAST have set breakpoints for colistin (EUCAST and CLSI) and polymyxin B (CLSI) with slight differences in recommendations. However, there are issues unique to the polymyxin class that warrant additional guidances. 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 guidelines 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 S with cross-S accuracy at > 99% 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 also have no S breakpoint recommendation for lower urinary tract infections.

Conclusion. The polymyxins have compromising characteristics that make them suboptimal antimicrobials when used alone, and additional caveats are required for AST breakpoint interpretive criteria and stewardship programs.

Figure 1: Concordance (cross susceptibility) of colistin and polymyxin B MICs by reference broth microdilution tests for 43,033 Enterobacteriaceae, *P. aeruginosa*, or *Acinetobacter* spp.



* Vertical and horizontal lines (red) are S breakpoints

Figure 2: USCAST susceptibility breakpoint recommendations when testing the polymyxins against *P. aeruginosa*, *A. baumannii*, and Enterobacteriaceae.

Polymyxins[1]	MIC breakpoint (mg/L)		Disk Content (µg)	Zone diameter breakpoint (mm)		Notes
	S≤	R≥		S≥	R≤	
Colistin [2,3] (No breakpoints for respiratory infections)	≤ 2	≥ 4	10 µg	Note[A]	Note[A]	1. Polymyxin therapies should be combined with a second active agent, whenever possible. 2. Polymyxin MIC determinations should be performed with broth microdilution method. Colistin susceptibility results can infer susceptibility to polymyxin B at ≤2 mg/L. 3. Colistin dosing based on EMA package insert or dosing algorithm in polymyxin guidelines. 4. Polymyxin B dosing at 2.5 mg/kg/day, with no renal adjustments A. Use only broth microdilution MIC methods, disk diffusion cannot reliably determine susceptibility
Polymyxin B [2,4] (No breakpoints for respiratory or urinary tract infections)	≤ 2	≥ 4	300 units	Note[A]	Note[A]	

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

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 and effective antibiotics, optimal dosing strategies in obese populations are largely unknown. The objective of this study was to compare PK/PD of CPM in non-obese (NO, weight 80–100 kg) 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 30, 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 % time above MIC of unbound drug (%fT > MIC) ≥ 60%. 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 significant difference 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 organisms 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 obtained 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 in both the NO and O populations for optimal CPM exposure in susceptible pathogens with higher MICs. CPM 6 grams/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.

Table 1. Baseline Characteristics and Pharmacokinetic Parameters

	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 (82.5-92.4)	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/m^2	26.5 (24.3-29.0)	40.7 (36.4-48.4)	< 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 (62.7-83.1)	82.6 (54.6-111.9)	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/kg	0.34 (0.29-0.38)	0.27 (0.22-0.37)	0.601
Half-life, hours	3.20 (2.11-3.35)	2.68 (2.35-3.59)	0.887
All data reported as median (IQR) unless otherwise noted.			

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

1536. Population Pharmacokinetic Analysis of Baloxavir Marboxil, a Cap-Dependent 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 selective inhibitor of cap-dependent endonuclease. The global Phase 3 study conducted in the influenza patients at high-risk of influenza complications (CAPSTONE-2) enrolled adult and adolescent patients from 2016 to 2018. Baloxavir marboxil demonstrated significantly shorter time to improvement of influenza symptoms (TTIIS) than placebo. The aim of this study was to build a population pharmacokinetic (PK) model of baloxavir acid and to evaluate the exposure-response relationships in high-risk patients.

Methods. The population PK analysis was conducted on the pooled data from 13 clinical studies: 10 phase 1 studies, a phase 2 study, and 2 phase 3 studies. A total of 11846 plasma concentrations from 1827 subjects were used for this analysis. The influence of background characteristics including risk factors of influenza complications