1546. Efficacy of Daptomycin Combinations Against Daptomycin-Resistant *Enterococcus faecium* Differs by β-lactam

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Background. We have previously demonstrated that daptomycin (DAP) combinations with β-lactams offer enhanced bactericidal activity and prevent the emergence of resistance in *Enterococcus faecium* infections. Although the mechanisms of DAP resistance in enterococci are not fully comprehended, they are associated with alterations in cell envelope phospholipids assembly which leads to either repulsion of the drug from cell exterior or diversion from the cell septum. In this context, we sought to evaluate combinations of DAP with a panel of β-lactams including ampicillin (AMP), amoxicillin (AMX), ceftaroline (CPT), ceftriaxone (CRO) and ertapenem (ERT).

Methods. *E. faecium* R497 harboring *liaSFR* mutations (DAP MIC of 16 mg/L) was evaluated in a simulated endocardial vegetation (SEV) pharmacokinetic and pharmacodynamic model over 336 h at a starting inoculum of 10^9 $\log_{10}$ CFU/g. DAP 10 mg/kg/day combinations with AMP, AMX (2 g continuous infusion), CPT 600 mg q 12 h, CRO 2g q 24 h or ERT 1 g q 24 h were evaluated. The emergence of DAP resistance was determined daily over the course of treatment.

Results. DAP alone was not bactericidal and high-level DAP resistance was observed (MIC increase from 16 to 64 μg/mL). Combination of DAP+AMP offered a significant reduction in $\log_{10}$CFU/g amounts (Up to 7 $\log_{10}$ CFU/g and to detection limits) in 24h in with no emergence of DAP resistance. DAP 10+ AMX caused 6–6.5 $\log_{10}$ CFU/g reduction and counts were maintained around the detection limit while demonstrating no increased resistance. Dose de-escalation with AMP indicated that even DAP 4 mg/kg/d with AMP (2g) combination, reached detection limit at 168 h with no further resistance. None of the CPT, CRO or ERT regimens in combination with DAP was effective against R497 and elevated DAP MICs (>64 μg/mL) was observed during the 14-day model.

Conclusion. Combination of DAP+AMP offered the most encouraging results against *E. faecium* R497, while DAP+AMX caused enhanced reduction. The reason for this discrepancy in various β-lactam activity may be related to diverse β-lactam targeting or affinity toward PBP proteins. Further dissection of our observations is warranted to understand the optimized DAP-β-lactam combination and consequently improve patient outcomes and prevention of resistance.

E. faecium R497 vs. DAP 10 combinations
DAP MIC= 16 mg/L

E. faecium R497 vs. DAP 10 combinations
DAP MIC = 16 mg/L
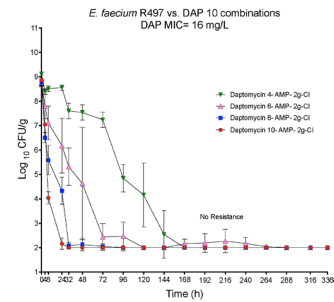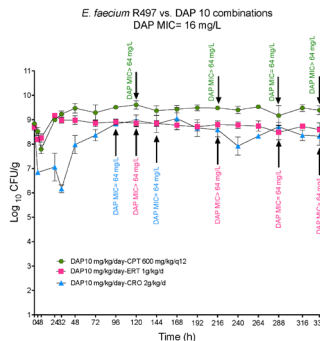
E. faecium R497 vs. DAP 10 combinations
DAP MIC= 16 mg/L
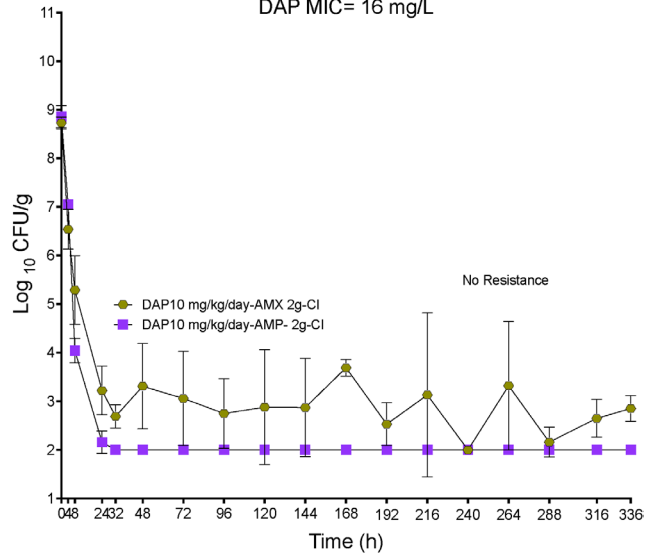
E. faecium R497 vs. DAP 10
DAP MIC= 16 mg/L
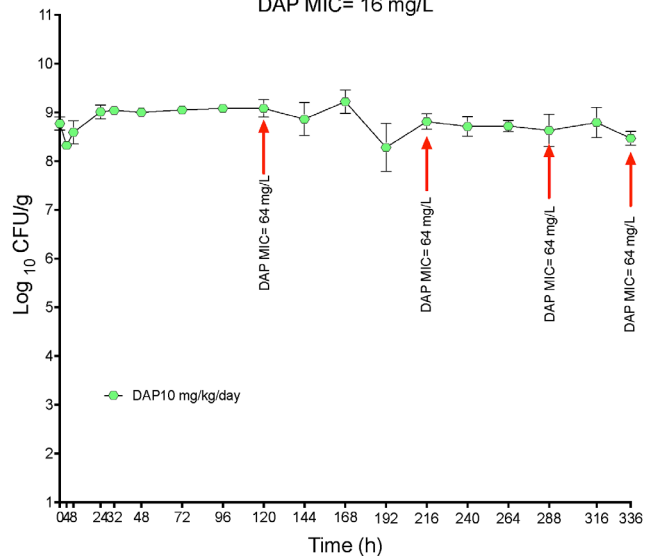
1547. Modeling Pharmacokinetics and Pharmacodynamics of Meropenem Utilizing a Novel Infusion Method of Bolus to Prolonged Infusion

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Background. Dose optimization of antibiotics has been shown to increase the likelihood of achieving pharmacodynamic efficacy targets and improve clinical

outcomes. For carbapenems, achieving greater than 40% time above minimum inhibitory concentration (T>MIC) has been shown to be correlated with clinical efficacy. Increasing bacterial resistance and rising MICs makes it more difficult for clinicians to rely on traditional dosing strategies to meet pharmacodynamic goals. Further optimization methods beyond extended infusion may be necessary to achieve certain pharmacodynamics goals.

Methods. We performed a Monte Carlo simulation investigating a novel method of meropenem administration, bolus to prolonged infusion (BPI). Multiple meropenem dosing regimens utilizing BPI were evaluated over 5000 patients utilizing pharmacokinetic profiles from 30 total patients. Patients were studied in 3 separate groups: <120 kg, ≥120 kg/non-critically ill and ≥120 kg/critically-ill. Bolus doses varied from 250–1000 mg and were paired with infusion doses varying from 500–1500 mg. Bolus plus infusion time totaled 3 hours and each dose was modeled with an 8-hour interval for both first dose and at steady state; BPI dosing was utilized for each dose. The primary outcome was probability of target attainment (PTA) of 40% time above minimum inhibitory concentration (T>MIC). Secondary outcomes included PTA 54% T>MIC and PTA 100% T>MIC.

Results. All doses studied achieved > 90% PTA of 40% T>MIC for MICs of ≤8 µg/mL at both first dose and steady state in the <120 kg and ≥120 kg/non-critically ill patient groups. In the ≥120 kg/critically ill patient group, all doses achieved > 90% PTA of 40% T>MIC for MICs of ≤4 µg/mL.

Conclusion. BPI achieves high probability of target attainment at nonresistant MICs for *Pseudomonas aeruginosa* and enteric Gram-negative organisms across the 3 patient groups studied.

Disclosures. All authors: No reported disclosures.

1548. Characterizing Cefepime Neurotoxicity: Experience from a Tertiary Care Center Performing β-lactam Therapeutic Drug Monitoring

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Background. Based on prior studies, elderly patients and those with renal dysfunction are prone to cefepime (CFP) toxicity. The toxicokinetics and toxicodynamics for CFP are not well established. Lamoth et al. reported a 50% probability of CFP neurotoxicity at a serum trough concentration of ≥22 mg/L, whereas Huwyler et al. observed CFP neurotoxicity when concentrations exceeded 35 mg/L. The objectives of this study were to quantify the incidence of CFP neurotoxicity and to assess the association between CFP concentrations and neurotoxicity.

Methods. We conducted a retrospective review between March 2016 and May 2018, of adult patients with serum CFP trough concentrations ≥25 mg/L. To be considered a CFP neurotoxicity case, patients were required to fulfill at least two of the NCI criteria for neurological toxicity such as, presence of new-onset confusion, delirium, or drowsiness. Following this, cases were classified as (1) high likelihood of toxicity (HLT) if they either had a neurology consult or EEG findings consistent with CFP toxicity and if their symptoms improved after discontinuation of CFP, (2) possible toxicity (PT) if neurology consult or EEG was absent or if we were unable to assess improvement after CFP was discontinued, or (3) nontoxicity (NT). Cases were independently reviewed by an ID pharmacist and physician. Additional data such as comorbidities, renal function, and use of anti-epileptics were collected.

Results. One hundred and forty-two patients were included in the analysis. Neurotoxicity (HLT+PT) related to CFP occurred in 18/142 (13%) patients; 67% (12/18) were considered HLT. The median age in the HLT cohort was 68 years (interquartile range [IQR], 57–74), with toxicity occurring a median of 6 days (IQR, 5–8) after starting CFP. At the time of neurotoxicity, HLT patients had diminished renal function with a median SCr of 1.6 mg/dL (IQR, 1.2–2.4) and a corresponding CrCl of 35.8 mL/minute (IQR, 19.2–50.9). The median CFP trough concentration in the HLT patients was 62 mg/L (IQR, 50–73) vs. 70mg/L (IQR, 41–115) in the PT and 42 mg/L (IQR, 31–61) in the NT groups.

Conclusion. Our data emphasize the need for careful dosing in older patients with renal insufficiency. Interestingly, our study reveals higher cefepime troughs (~3-fold higher) associated with neurotoxicity than previously reported.

Disclosures. All authors: No reported disclosures.

1549. Impact of New Fluoroquinolone Breakpoints on *Enterobacteriaceae* Susceptibility Rates and Clinical Outcomes

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Background. In January 2019, the Clinical and Laboratory Standards Institute (CLSI) lowered the Fluoroquinolone (FQ) susceptibility breakpoints for Enterobacteriaceae. The new breakpoints were updated primarily based on FQ pharmacodynamics, and only limited clinical data. We sought to evaluate clinical outcomes among patients who received an FQ for infection with Enterobacteriaceae with MIC values that would now be considered resistant, using the new interpretive criteria. We also assessed the potential impact of the new breakpoints on overall blood and urine Enterobacteriaceae susceptibility rates at our medical center.

Methods. All positive blood and urine cultures with Enterobacteriaceae between September 1, 2018 and February 28, 2019 were included. Enterobacteriaceae isolates with ciprofloxacin MICs of 0.5 and 1 µg/mL (based on new breakpoints, now considered non-susceptible) were identified. We assessed the length of stay (LOS), mortality, and 30-day readmissions among patients who received an FQ for treatment. The impact of the new breakpoints on overall Enterobacteriaceae susceptibilities from urine and blood isolates was also determined.

Results. A total of 1,761 cultures (191 blood, 1,570 urine) grew Enterobacteriaceae. One-hundred and twenty-five (7%) cultures grew isolates with a ciprofloxacin MIC of 0.5 or 1 µg/mL. Eighteen patients with Enterobacteriaceae isolated (4 blood, 14 urine) received an FQ. Among these patients, the median LOS was 4 days; one patient was readmitted within 30 days, and 0% mortality was observed. The patient readmitted within 30 days received an FQ for a blood isolate with MIC 0.5. Overall, with the revised breakpoints, we observed a 4.2% decrease in the number of Enterobacteriaceae that would be susceptible to ciprofloxacin (Figure 1).

Conclusion. The new FQ breakpoints for Enterobacteriaceae will have a marginal impact on overall FQ susceptibility rates at our medical center. In this single-center study, patients that received FQ antibiotics for Enterobacteriaceae with MIC values now considered intermediate or resistant did not appear to experience poor outcomes.

Table 1: Observed Outcomes for Patients That Received FQ for Non-susceptible Isolates (Ciprofloxacin MIC 0.5 and 1)

	All Isolates (n=18)	Urine Isolates (n=14)	Blood Isolates (n=4)
LOS (days), median	4	4	3
30d Readmission, n (%)	1 (5.5)	0 (0)	1 (25)
Mortality, n (%)	0 (0)	0 (0)	0 (0)

Figure 1: Percentage of Susceptible *Enterobacteriaceae* Isolates

Susceptibility of Enterobacteriaceae to Fluoroquinolones Using the Old and New CLSI Breakpoints
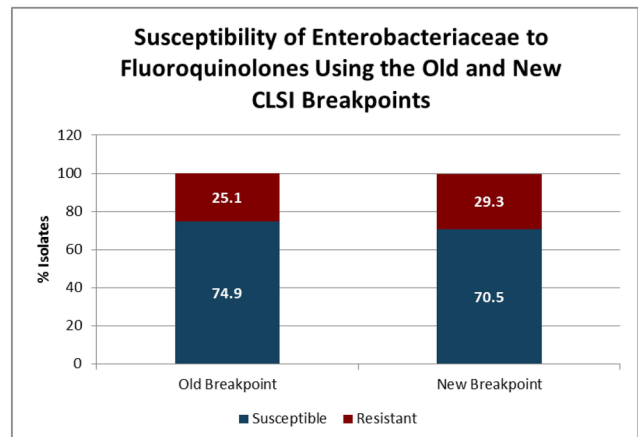
Disclosures. All authors: No reported disclosures.

1550. PK-PD Relationship and PK Driver of Efficacy of the Novel Antibacterial Lysin Exebacase (CF-301) in Pre-Clinical Models

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Background. Exebacase (CF-301) is a novel lysin with rapid bacteriolytic and anti-biofilm activity against *S. aureus*, pronounced synergy with antibiotics and low propensity for resistance. Exebacase has undergone Phase 1–2 trials. This work was to develop pharmacokinetic (PK) model in animal and determine the relationship between exebacase exposure and efficacy in animals.

Methods. PK data in 592 animals (4 species) included in population PK model. A range of linear and nonlinear mammillary models with allometric scaling fitted to the