Results. Unique cytological signatures strongly correlated with antifungal MOA: FCZ resulted in rounded cells that lacked lyraphal forms; APX001A resulted in abundant intracellular membrane labeling at 4 hours, consistent with an endoplasmic reticulum stress response, with cell death (Sytox Green Staining) at 24 hours.

Conclusion. FCP is a rapid and accurate method to establish MOA and distinguish between antifungals that inhibit specific biosynthetic pathways (e.g., cell wall and sub-pathways (glucan vs. chitin synthesis). In addition, this technology can be useful in drug discovery program to determine on-target vs. off-target activity of newly synthesized molecules.

Disclosures. M. Sharp, Linnaeus: Employee. Salary. Q. Soltoff, Amplyx Pharmaceuticals Inc.: Employee, Salary. K. J. Shaw, Amplyx Pharmaceuticals Inc.: Employee, Salary. Linnaeus: Consultant, Consulting fee. J. Pogliano, Linnaeus: Employee, Salary.

1523. Fosfomycin (FOS) Plus Meropenem (MER) Suppresses Resistance Emergence Against P. aeruginosa (PA) PA01 in the Hollow Fiber Infection Model (HFIM)
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Background. FOS (ZTI-01, fosfomycin for injection) is an epoxide antibiotic that covalently binds MurA, an earlier step in cell wall synthesis inhibition. FOS has demonstrated synergistic killing with other classes of agents, including carbapenems. PA, among other non-fermenters, are difficult to treat pathogens and combination therapy is important to ensure killing and suppress emergence of resistance. Here, we examine the combination of FOS + MER in the HFIM against PA.

Methods. The experimental design was fully factorial (3 FOS and 3 MER arms and all combinations). Simulated FOS doses were 4, 6 and 8 g 8 hourly (Q8). MER doses were 0.5, 1 and 2 g Q8. The experiment lasted 10 days. Concentrations from the central compartment were measured in all arms by LC/MS/MS. Total bacterial burden and resistant subpopulations for both drugs were measured. Resistance plates were infused with 3XBaseline MIC. Starting inoculum was 6.86 Logs.

Results. FOS/MER MICs were 64 mg/L (broth) and 0.5 mg/L. Mutational frequency to resistance were -5.27 (FOS) and -6.7 (MER). There were 15 drug-containing arms and a no-treatment control. All drug arms had concentration–time profiles accurately reproduced. All FOS alone arms had rapid resistance emergence. MER 0.5 gm alone had resistance emerge at Day1. FOS 4 g + MER 0.5 g allowed resistance to both agents as did FOS 6g + MER 0.5 g. FOS 6 g + MER 1 g allowed MER resistance, but not FOS. All other combination regimens fully suppressed all resistant mutants. The effect of combination therapy is shown in Figures 1–3. MIC’s for MER-resistant isolates were 2 mg/L early and up to 16 mg/L late (day4 and after). FOS-resistant isolates generally had MIC values between 128 and >1024 mg/L.

Conclusion. The combination of FOS + MER is promising for therapy of a wild-type PA. Doses of FOS of 6 and 8 g Q8 tended to suppress resistance emergence to either agent when combined with 1 or 2 g Q8 of MER. We intend on examining the impact of resistance mutations to MER (oprD downregulated andMexAB upregulated) with this combination to identify any potential therapeutic advantage of this combination regimen

Disclosures. G. L. Drusano, Zavante: Scientific Advisor, Consulting fee.

1524. Good Correlation of Cefiderocol Between In Vivo Efficacy Murine Thigh/Lung Infection Models and MIC Determined in Iron-Depleted Conditions
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Background. Cefiderocol (S-649266) is a novel siderophore cephalosporin active against a wide variety of carbapenem-resistant Gram-negative bacteria such as Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii and Stenotrophomonas maltophilia. This potent activity is mainly due to its efficient penetration through the outer membrane via active iron transporter systems and its high stability to both serine- and metallo-carbapenemases. The antibacterial activity is evaluated under iron-deficient conditions to mimic the infection sites in human. In this study, the efficacy in murine infection models was evaluated in order to show that the MIC under iron-deficient conditions is more predictive for the in vivo efficacy.

Methods. A total of 19 strains of E. coli, K. pneumoniae, P. aeruginosa and A. baumannii were used for the in vivo efficacy studies using neutropenic murine thigh or lung infection models. The efficacy was evaluated by the bacterial reduction at 24 hours after treatment by subcutaneous q3h administration of cefiderocol which was initiated at 2 hours post-infection. MIC of cefiderocol was determined by broth microdilution methods according to CLSI instruction using both CAMHB and iron-depleted CAMHB (ID-CAMHB). The PK/PD analysis was conducted by calculating the percentage fT>MIC value of free plasma concentrations (fT>MIC) in infected mice.

Results. The efficacy in murine thigh and lung infection models were evaluated by using 12 and 15 strains, respectively. The average fT>MIC value required for static effect and 1 log10 reduction was shown to be 75% and 85%, respectively irrespective...