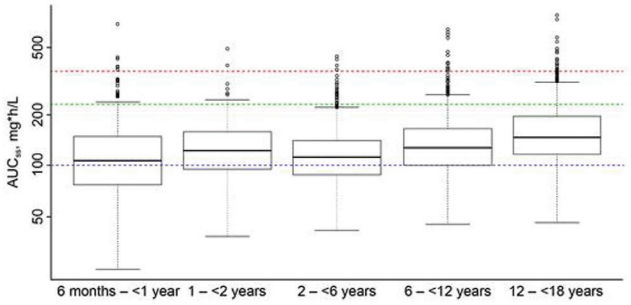
Figure: Box plot of predicted AUC_{ss} by age group for a 6 mg/kg dose (ages 6 months to <1 year) or 10 mg/kg dose (all other groups).



Dashed blue line is the lowest targeted median exposure. Dashed green and red line were the minimum (230 mg*h/L) and mean (330 mg*h/L) AUC_{ss} in a high-dose adult study (1116 mg) with increased toxicity. The box is the interquartile range (IQR) representing the 25th to 75th percentile. The whiskers represent the last point within 1.5 times the IQR of the 25th and 75th percentile. Circles represent all points beyond these thresholds.

Disclosures. **A. Desai**, Astellas Pharma, Inc.: Employee, Salary. **L. Kovanda**, Astellas Pharma, Inc.: Employee, Salary. **C. Lademacher**, Astellas Pharma, Inc.: Employee, Salary. **W. Hope**, F2G: Grant Investigator and Scientific Advisor, Consulting fee and Research grant. Astellas: Grant Investigator and Investigator, Grant recipient and Research grant. Pfizer: Grant Investigator, Research support. Gilead: Consultant and Scientific Advisor, Consulting fee. **P. Bonate**, Astellas Pharma, Inc.: Employee, Salary. **A. Edginton**, Astellas Pharma Global Development, Inc.: Independent Contractor, Consulting fee.

1397. Comparative Efficacy of Human-Simulated Epithelial Lining Fluid (ELF) Exposures of Tedizolid (TZD) Against Methicillin-resistant *Staphylococcus Aureus* (MRSA) in Neutropenic (I–) vs. Immunocompetent (I+) Murine Models of Pneumonia

James M. Kidd, PharmD, BCPS, Kamilia Abdelraouf, PhD and David P. Nicolau, PharmD, FCCP, FIDSA; Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut

Session: 145. PK/PD Studies
Friday, October 5, 2018: 12:30 PM

Background. TZD is an oxazolidinone with potent *in vitro* activity against Gram-positive pathogens, including MRSA. Limited data currently exist on the efficacy of TZD in the presence of neutropenia. Herein, we investigate the comparative efficacy of human-simulated ELF exposures of TZD against MRSA in I– and I+ murine models of pneumonia.

Methods. Four MRSA isolates with TZD broth microdilution MICs of 0.5 mg/L were studied. BALB/c mice in I– groups were made neutropenic with cyclophosphamide. Lungs of I– mice were inoculated intranasally with bacterial suspensions of 10^7 CFU/mL; a higher inoculum of 10^9 CFU/mL was required to induce infection in I+ mice. Single daily doses of TZD simulating human ELF exposures after doses of 200 mg q24h were determined in both I+ (40 mg/kg) and I– (32 mg/kg) models. Three hours after inoculation, human-simulated doses of TZD were administered q24h for up to 72 hours while control mice were vehicle dosed. A group of control and another of treatment ($n = 6$) per isolate were sacrificed at 24, 48, or 72 hours for lung harvest. Bacterial densities were determined by quantitative culture and averaged across all isolates. Mice that succumbed to infection before the scheduled time of sacrifice were included in the next group due for sacrifice. Changes in $\log_{10}$ CFU/lungs at 24 hours were compared with 0 hour controls.

Results. The average bacterial burdens at 0 hour were 5.86 ± 0.21 and 8.10 ± 0.24 $\log_{10}$ CFU/lungs among I– and I+ mice, respectively. At 24 hours, average burdens in control mice were comparable among I– and I+ mice at 7.91 ± 0.62 and 9.01 ± 0.69 $\log_{10}$CFU/lungs, respectively. Mean changes in bacterial density are reported in the table. No I+ control mice survived past 48 hours.

		Change in $\log_{10}$ CFU/Lungs (Mean ± SD)	
		I–	I+
24 hours	Control	2.06 ± 0.62	0.91 ± 0.69
	TZD	−1.18 ± 0.58	−1.23 ± 0.81
48 hours	Control	2.54 ± 0.31	0.61 ± 0.17
	TZD	−1.99 ± 0.90	−2.17 ± 0.84
72 hours	Control	2.85 ± 0.60	ND
	TZD	−2.78 ± 0.74	−3.64 ± 1.03

ND, no data.

Conclusion. Human-simulated ELF exposures of TZD demonstrated substantial and sustained efficacy in both I– and I+ murine models of pneumonia. These preclinical data utilizing clinically achievable bronchopulmonary exposures suggest that the efficacy of TZD for treatment of MRSA lung infections is not compromised by neutropenic status of the host. Further validation of these findings in patients is warranted.

Disclosures. **D. P. Nicolau**, Merck: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Speaker honorarium.

1398. β-Lactam Probability of Target Attainment (PTA) and Penetration into Epithelial Lining Fluid (ELF) Based on Multiple Bronchoalveolar Lavage (BAL) Sampling Time Points in a Swine Pneumonia Model

Ana Motos, MSc[1,2]; Joseph L. Kuti, PharmD[2]; Gianluigi Li Bassi, MD, PhD[1,3,4]; Antoni Torres, MD, PhD, FERS[1,3,4] and David P. Nicolau, PharmD, FCCP, FIDSA[2,5]; [1]Division of Animal Experimentation, Department of Pulmonary and Critical Care Medicine, Hospital Clinic of Barcelona, Barcelona, Spain, [2]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, [3]August Pi i Sunyer Biomedical Research Institute (IDIBAPS), CIBERES, Barcelona, Spain, [4]University of Barcelona, Barcelona, Spain, [5]Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut

Session: 145. PK/PD Studies
Friday, October 5, 2018: 12:30 PM

Background. Defining ELF concentrations is desired for antibiotics developed for pneumonia. For ethical reasons, BAL sampling in humans is routinely done at a single time point, thereby creating ambiguity in the precise ELF profile. It is unknown if additional sampling of the ELF would lead to more accurate estimates of exposure. The swine pneumonia model was used to characterize the full ELF profiles (5-BAL) of two β-lactams for comparison with models employing 1-BAL (1B) and 2-BAL (2B) sampling time points only.

Methods. Sixteen ventilated swine were infected with *Pseudomonas aeruginosa* to establish pneumonia and then treated for 72 hours with ceftolozane/tazobactam (C/T) 50 mg/kg q8h ($n = 8$) or piperacillin/tazobactam (TZP) 200 mg/kg q8h ($n = 8$). Plasma and BAL concentrations were measured in each swine at 1, 2, 4, 6, and 8 hours after the first dose. Urea correction was used to calculate ELF values. Ceftolozane and piperacillin plasma and ELF data were fitted to a two compartment model using the nonparametric adaptive grid program in Pmetrics. Hypothetical models were refitted after randomly selecting either 1B or 2B sampling time points from each swine. A 5,000 subject Monte-Carlo simulation was performed for each model to define PTA (60% free time above the MIC) and ELF penetration [area under the curve in ELF (AUC_{ELF}) vs. free AUC_{plasma}]. The KS-test was used to analyze distribution differences, reporting maximum vertical deviation (D) as percent difference; $D < 20\%$ was defined as negligible.

Results. Thirty-two C/T and 34 TZP plasma samples and 29 and 32 BAL samples were available for the full model, respectively; 1B and 2B sampling models used eight and 16 BAL samples. All models adequately fitted the data. C/T PTA at 4 mg/L was 94.8, 96.1, and 98.0%, for the full, 1B and 2B models. TZP PTA at 16 mg/L was 55.8, 46.8, and 46.7%, respectively. C/T median [interquartile range] penetration differences were negligible between the full (65% [25−−109]) and 1B (72% [45−−125], $D = 15\%$) or 2B models (62% [32−−111], $D = 6\%$). TZP penetration differences were also minimal between the full (32% [9−−67]) and 1B (17% [5−−49], $D = 18\%$) or 2B models (27% [9−−44], $D = 15\%$).

Conclusion. These data suggest that antibiotic ELF models constructed from a single BAL time point result in similar exposure estimates to full ELF profiles.

Disclosures. **G. Li Bassi**, MSD: Grant Investigator, Grant recipient. **A. Torres**, MSD: Grant Investigator, Grant recipient.

1399. Efficacy of Daptomycin Combination with β-Lactams for Daptomycin-resistant *Enterococcus faecium* Harboring LiaSR Substitutions

Razieh Kebriaei, PhD[1]; Seth Rice, BSc[2]; Kavindra Singh, PhD[3]; Kyle Stamper, BSc[4]; An Dinh, BS[5]; Rafael Rios, MSc[6]; Lorena Diaz, PhD[6]; Barbara Murray, MD[7]; Jose M. Munita, MD[8]; Truc T. Tran, PharmD[5]; Cesar Arias, MD, PhD, FIDSA[9] and Michael J. Rybak, PharmD, MPH, PhD[10]; [1]Antiinfective Research Laboratory, Department of Pharmacy Practice, Wayne State University, Eugene Applebaum College of Pharmacy & Health Sciences, Detroit, Michigan, [2]Pharmacy Practice, Wayne State University, Detroit, Michigan, [3]Center for Antimicrobial Resistance and Microbial Genetics (CARMiG), University of Texas McGovern Medical School, Houston, Texas, [4]Wayne State University, Detroit, Michigan, [5]Department of Internal Medicine, University of Texas McGovern Medical School at Houston, Houston, Texas, [6]Molecular Genetics and Antimicrobial Resistance Unit - International Center for Microbial Genomics, Universidad El Bosque, Bogota, Colombia, [7]Internal Medicine, University of Texas McGovern Medical School at Houston, Houston, Texas, [8]Instituto De Ciencias e Innovacion En Medicina (ICIM), Clinica Alemana Universidad del Desarrollo, Santiago, Chile, [9]Microbiology and Molecular Genetics, University of Texas McGovern Medical School, Houston, Texas, [10]259 Mack Ave, Suit 4131, Eugene Applebaum College of Pharmacy and Health Sciences Bldg, 259 Mack Ave, Detroit, Michigan

Session: 145. PK/PD Studies
Friday, October 5, 2018: 12:30 PM

Background. Daptomycin (DAP) is one of the mainstay treatments for *Enterococcus faecium* infections. However, development of resistance threatens its continued viability as a treatment option. 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 repulsion of the drug from cell exterior and diversion from the cell septum. Previous data suggest that combination of DAP with β-lactams has the potential to improve patient outcomes. In this investigation, we