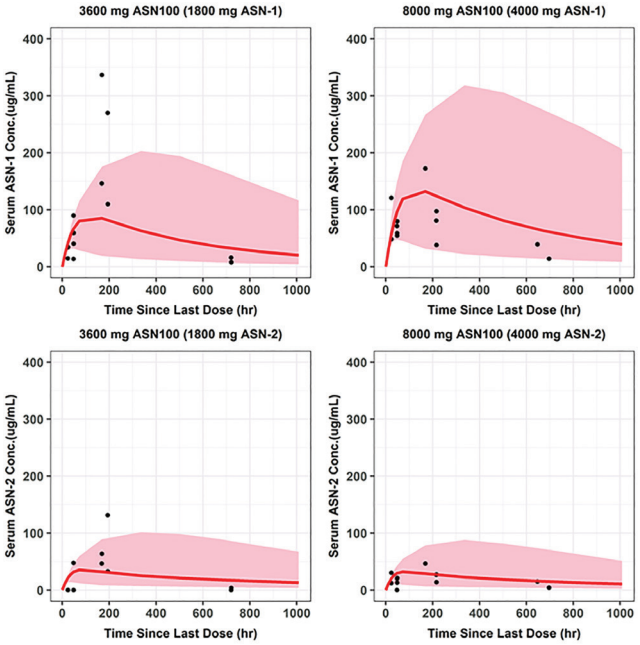
penetration using the ratio of ELF:serum $AUC_{0-\infty}$ was 33.0% for ASN-1 and 20.3% for ASN-2 following the selected clinical dose of 3,600 mg.

Conclusion. A population PK model adequately described the time-course of ASN-1 and ASN-2 in ELF. ELF penetration was 20–33% following administration of the ASN100 clinical dose. These results should be interpreted with caution given the limited sample size (six subjects per dose group) and limitations of urea-based normalization of BALF to ELF volume.

Figure 1. Visual predictive check for the population PK model fit to the ASN-1 and ASN-2 ELF data following administration of either 3600 mg or 8000 mg of ASN100



Red (Simulated) 80% Prediction Interval; Black Dots are All Observed Data (incl. LLOQ)

Disclosures.. **S. A. Van Wart**, Arsanis, Inc.: Research Contractor, Research support. **C. Stevens**, Arsanis, Inc.: Employee and Shareholder, Salary and stock options. **Z. Magyarics**, Arsanis Biosciences GmbH: Employee and Shareholder, Salary and stock options. **S. A. Luperchio**, Arsanis, Inc.: Employee and Shareholder, Salary and stock options. **C. M. Rubino**, Arsanis, Inc.: Research Contractor, Research support. **P. G. Ambrose**, Arsanis, Inc.: Research Contractor, Research support.

1409. Evaluation of Alternative Piperacillin–tazobactam Dosing Strategies Against ESBL-Producing Enterobacteriaceae Using a Hollowfiber Infection Model

Henrietta Abodakpi, Pharm.D[1]; Kai-Tai Chang, Ph.D[2]; Ana Maria Sánchez-Díaz, Ph.D[3]; Rafael Cantón, Pharm.D, Ph.D[4] and Vincent Tam, Pharm.D[5]; [1]Pharmacological and Pharmaceutical Sciences, University of Houston College of Pharmacy, Houston, Texas, [2]Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas, [3]Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain, [4]Hospital Universitario Ramon y Cajal, Madrid, Spain and [5]Pharmacological and Pharmaceutical Sciences, Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas

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

Background. Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae exhibit variable response to treatment with piperacillin–tazobactam. Current clinical practice with piperacillin–tazobactam involves dosing the components simultaneously at a fixed ratio of 8:1 piperacillin to tazobactam. However, it remains unclear whether this ratio is optimal for enzyme inhibition and bactericidal activity. Using a hollowfiber infection model (HFIM), we evaluated the efficacy of various exposures of piperacillin–tazobactam against ESBL-producing Enterobacteriaceae.

Methods. A clinical strain of *K. pneumoniae* expressing CTX-M-15 was used as a reference isolate. Piperacillin minimum inhibitory concentrations (MIC) were determined using a range of tazobactam concentrations and fitted to an inhibitory E_{max} model. An HFIM was used to simulate and evaluate the impact of escalating tazobactam dosing in the context of a fixed piperacillin exposure (equivalent to 4 g every 8 hours). Serial samples were collected to verify the pharmacokinetic simulations (by LC–MS/MS) and determine bacterial density for up to 120 hours. Measured drug concentrations were incorporated in the E_{max} model to determine the free-time above instantaneous MIC (*f*T>MICi) associated with each experimental exposure. The target *f*T>MICi associated with growth suppression was subsequently validated using a clinical strain of *E. coli* (producing SHV-12) and a second *K. pneumoniae* (producing CTX-M-15).

Results. For the reference strain, a clinical regimen of 4 g piperacillin and 0.5 g tazobactam administered every 8 hours resulted in a *f*T > MICi of 39.6% and bacterial regrowth. An exposure equivalent to 1.5 g tazobactam (*f*T > MICi of 55.1%) was needed to suppress growth. These regrowth findings were validated with the two other ESBL-producers with tazobactam exposures characterized by *f*T > MICi of 36.8 and 43.8%.

Conclusion. Improved bacterial killing was observed with increasing tazobactam exposures. As a novel PK/PD index, *f*T > MICi may be used to characterize response to a β-lactamase inhibitor and provide efficacy targets to guide the development and clinical dosing of these inhibitors.

Disclosures. **A. M. Sánchez-Díaz**, European Union's Seventh Framework Programme: Grant Investigator, Research grant. **R. Cantón**, European Union's Seventh Framework Programme: Grant Investigator, Research grant. **V. Tam**, European Union's Seventh Framework Programme: Grant Investigator, Research grant.

1410. Novel Framework to Compare the Effectiveness of Tazobactam, Relebactam and Avibactam Against Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae

Henrietta Abodakpi, Pharm.D[1]; Kai-Tai Chang, Ph.D[2]; Caitlan Byerly, B.S[1] and Vincent Tam, Pharm.D[3]; [1]Pharmacological and Pharmaceutical Sciences, University of Houston College of Pharmacy, Houston, Texas, [2]Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas, [3]Pharmacological and Pharmaceutical Sciences; Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, Texas

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

Background. Resistance mediated by extended-spectrum β-lactamases (ESBLs) presents a serious challenge in the treatment of Gram-negative pathogens. ESBLs confer resistance to most β-lactams which may be reversed with the addition of an active β-lactamase inhibitor (such as tazobactam, relebactam and avibactam). However, various ESBLs may display different susceptibilities to these inhibitors, which could impact efficacy. We propose a framework for comparing the efficacy of these inhibitors when combined with the same β-lactam.

Methods. Three clinical isolates of *K. pneumoniae* harboring CTX-M-15 and one *E. coli* with SHV-12 were used. The susceptibility of each isolate to piperacillin was determined by broth dilution using escalating concentrations of tazobactam, relebactam and avibactam. Similar experiments were subsequently conducted with ceftazidime. The resulting minimum inhibitory concentrations (MICs) were mapped as response to inhibitor concentration using an inhibitory E_{max} model. The best-fit model parameters were compared for each isolate-inhibitor combination.

Results. In all scenarios, MIC reductions were observed in the presence of increasing inhibitor concentrations. The MIC reduction for each isolate was well fitted to inhibitor concentrations ($r^2 \geq 95\%$). IC_{50} estimates reflected the sensitivity of the isolates to each inhibitor, while I_{max} captured the maximum extent of MIC reduction. With piperacillin, IC_{50} values ranged from 1.36 to 35.25μg/mL for tazobactam, 2.32–15.82 μg/mL for relebactam and 0.62–2.37 μg/mL for avibactam. I_{max} values were 4.75–6.99, 6.56–9.77 and 7.83–11.22 for tazobactam, relebactam and avibactam, respectively. Similar trends in IC_{50} and I_{max} were observed with ceftazidime as the β-lactam.

Conclusion. We illustrated a simple structural model capable of comparing the performance of different inhibitors. This platform may be used to identify the optimal pairing of various β-lactams and β-lactamase inhibitors for individual isolates.

Disclosures. **V. Tam**, European Union's Seventh Framework Programme: Grant Investigator, Research grant.

1411. Tecioplanin (TEI) vs. Vancomycin (VAN) in Combination with Piperacillin-Tazobactam (TZP) or Meropenem (MER) as a Cause of Acute Kidney Injury (AKI)

Abdullah Tarik Aslan, RESIDENT[1]; Tural Pashayev, RESIDENT[1]; Osman Dağ, DOCTOR and Murat Akova, PROF[3]; [1]Internal Medicine, Hacettepe University, Ankara, Turkey, [2]Biostatistics, Hacettepe University, Ankara, Turkey, [3]Infectious Diseases and Clinical Microbiology, Hacettepe University, Ankara, Turkey

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

Background. VAN has been shown to cause increased incidence of AKI when combined with TZP. The reason is unknown. TEI is a glycopeptide which may be less nephrotoxic. We compared both glycopeptides in combination with TZP or MER for causing AKI.

Methods. A retrospective cohort study was performed between May 2015 and December 2017 in a large tertiary care setting. Evaluation of AKI was made by using RIFLE criteria. Patients ≥18 years were included if they had a baseline serum creatinine available and received one of the combinations tested for at least 48 hours. Exclusion criteria were renal replacement therapy, pregnancy, <48 hours antibiotic therapy and no follow-up.

Results. Overall 456 patients were screened and 379 included in the study. After controlling for residual differences (age, Charlson comorbidity index score, presence of AKI, GFR value, presence of sepsis or septic shock, residing in intensive care unit at the time of antibiotic therapy and number of days of antibiotic therapy), AKI incidence was significantly higher in patients receiving TZP-VAN than those receiving TZP-TEI and also in patients receiving TZP-VAN than those with MER-VAN. No difference

in AKI was detected between patients with MER-VAN and with MER-TEI (table). Mortality at 7 and 30 days and resolution of AKI at discharge were similar in all groups.

Table.Comparison of various antibiotic combinations causing AKI

Variable	Combinations		Unadjusted OR (95% CI)	*P*Value	Adjusted OR (95 % CI)	*P*Value
	TZP-VAN (n=50)	TZP-TEI (n=85)				
AKI	20 (40.0)	17 (20.0)	**2.66** (1.22-5.79)	**.012**	**3.21** (1.36-7.57)	**.008**
Risk	13 (26.0)	12 (14.1)				
Injury	4 (8.0)	3 (3.5)				
Failure	3 (6.0)	2 (2.4)				
	MER-VAN (n=104)	MER-TEI (n=140)				
AKI	25 (24.0)	34 (24.3)	**0.98** (0.54-1.78)	**.96**	**1.20** (0.62-2.32)	**.574**
Risk	13 (12.5)	17 (12.1)				
Injury	8 (7.7)	12 (8.6)				
Failure	4 (3.8)	5 (3.6)				
	TZP-VAN (n=50)	MER-VAN (n=104)				
AKI	20 (40.0)	25 (24.0)	**2.10** (1.02-4.34)	**.041**	**2.28** (1.008-5.18)*	**.048**
Risk	13 (26.0)	13 (12.5)				
Injury	4 (8.0)	8 (7.7)				
Failure	3 (6.0)	4 (3.8)				

Conclusion. TZP causes increased nephrotoxicity when combined with VAN. Combination with TEI may offset this side effect. Additionally, the higher AKI incidence with TZP-VAN than MER-VAN may suggest a particular nephrotoxic synergy between TZP and VAN. Randomized controlled trials should confirm this observation.

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

1412. Caspofungin and Anidulafungin Behave as Fungistatic Agents Against *Candida auris*

Catiana Dudiuk, PhD[1,2]; Indira Berrio, MD, MSc[3,4]; Laura Theill, PhD[1,2]; Soraya Morales-Lopez, PhD[5,6]; Soraya Salcedo, MD, MSc[7]; Jose Rodriguez, MD[8,9]; Soledad Gamarra, PhD[1,2] and Guillermo Garcia-Effron, PhD[1,2]; [1]Laboratorio de Micología y Diagnóstico Molecular–Cátedra de Parasitología y Micología–Facultad de Bioquímica y Ciencias Biológicas–Universidad Nacional del Litoral, Santa Fe, Argentina, Santa Fe, Argentina, [2]Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET), CCT-Santa Fe, Argentina, Santa Fe, Argentina, [3]Medical and Experimental Mycology Group, Corporación para Investigaciones Biológicas (CIB), Medellin, Colombia, [4]Hospital general de Medellin "Luz Castro de Gutiérrez" ESE, Medellín, Colombia, [5]Universidad Popular del Cesar, Valledupar, Colombia, Valledupar, Colombia, [6]Laboratorios Nancy Flórez García S.A.S, Valledupar, Colombia, Valledupar, Colombia, [7]Clínica General del Norte, Barranquilla, Colombia, [8]Hospital Rosario Pumarejo Lopez, Valledupar, Colombia, [9]Centro de Investigaciones Microbiológicas del Cesar–CIMCE Ltda, Valledupar, Colombia, Valledupar, Colombia

Session: 145. PK/PD Studies

Friday, October 5, 2018: 12:30 PM

Background. *Candida auris* is an emerging multiresistant nosocomial pathogen responsible for outbreaks around the world. It is associated with therapeutic failure and high mortality rates. Echinocandins are the empiric treatment choice for *C. auris* infections. However, clinical reports show that some patients respond poorly to this therapy. The aim of this study was to determine the in vitro activity of Caspofungin and Anidulafungin against *C. auris* by time–kill curves method.

Methods. Twenty *C. auris* strains were studied. They were isolated from patients with proven invasive fungal infection. Susceptibility testing was performed following the Clinical and Laboratory Standards Institute (CLSI) M27-A3 and S4 documents. Time-killing experiments were conducted for 10 of the 20 isolates (in duplicate on 2 separate days) using RPMI-1640 buffered with MOPS. Caspofungin and anidulafungin tested concentrations were 0.12, 0.25, 0.50, 1.00 and 8.00 µg/mL. The inoculum was adjusted to 1×10^5 CFU/mL using a Neubauer chamber. A 0.05 mL aliquot of each dilution was taken at different time points (0, 2, 4, 6, 8, 10, 24 and 48 hours). These aliquots were serially diluted in sterile water, spread onto Sabouraud plates and incubated at 35°C to determine the numbers of CFU per milliliter. The killing kinetics and the fungicidal activity were analyzed by fitting the mean data at each time point to an exponential equation: $N_t = N_0 \times e^{-}kt$ (N_t viable yeasts at time t; N_0 starting inoculum; K killing rate; t incubation time).

Results. Anidulafungin and caspofungin MICs geometric means were 1.68 µg/mL (range: 0.5–8.0 µg/mL) and 2.55 µg/mL (range 0.25–8.0 µg/mL), respectively. None of the drugs were able to reach fungicidal activity (no 99.9% inhibition). The mean time to reach 50% growth reduction were 1.74 ± 0.45 hours and 5.30 ± 2.81 hours for the MIC values of each strain for anidulafungin and caspofungin, respectively

Conclusion. The tested echinocandins showed no in vitro fungicidal activity against *C. auris* at concentrations reached in serum despite strain's MICs. Caspofungin exhibited a significant lowest killing rate.

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

1413. A Phase IIa Efficacy, Safety, Tolerability and Pharmacokinetic (PK) Study of Encochleated Amphotericin B in Patients with Mucocutaneous (Esophogeal, Oropharyngeal, Vulvovaginal) Candidiasis Who are Refractory or Intolerant to Standard Non-Intravenous Therapies

Lilian Kibathi, PharmD[1]; Parag Kumar, PharmD[1]; Michail Lionakis, MD, Sc.D.[2]; Amanda Urban, CRNP[2]; Elise Ferre, PA-C, MPH[2]; Maryellen McManus, RN, MPH[3]; Benjamin Colton, PharmD[1]; Chris Lambros, PhD[2]; Ruying Lu, BS[4]; Raphael Mannino, PhD[4]; Edmund Tramont, MD, FIDSA [2] and Alexandra F. Freeman, MD[2]; [1]Clinical Center, Pharmacy Department, National Institutes of Health, Bethesda, Maryland, [2]National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, [3]Medical Science & Computing, Bethesda, Maryland, [4]Matinas BioPharma, Inc., Bedminster, New Jersey

Session: 145. PK/PD Studies

Friday, October 5, 2018: 12:30 PM

Background. Current oral therapeutic options for chronic mucocutaneous candidiasis (CMC) are often associated with resistance and toxicity. Amphotericin B (AMB) has broad fungicidal activity and markedly resists emergence of resistance but requires parenteral administration and monitoring for significant nephrotoxicity, which worsens with chronic treatment. Encochleated amphotericin B (CAMB) is a novel oral formulation of AMB. In animal models, CAMB demonstrates antifungal activity with similar efficacy as intraperitoneal AMB deoxycholate, but without the associated toxicity. This on-going patient volunteer study assesses the efficacy, safety, tolerability and PK of CAMB in patients with CMC who are refractory or intolerant to standard oral azole antifungals.

Methods. Four patients have completed the clinical protocol treatment period: 3 patients with STAT3 deficient Hyper IgE syndrome and CMC, and one patient with chronic esophageal candidiasis. Eligible patients were dose escalated (Figure 1), with option of enrolling in an extension phase. Serial plasma PK samples were collected over 24 hours over the study period, with data available from two patients (Figure 2).

Figure 3: Clinical Response (%) in Oropharyngeal Candidiasis over treatment period (days)

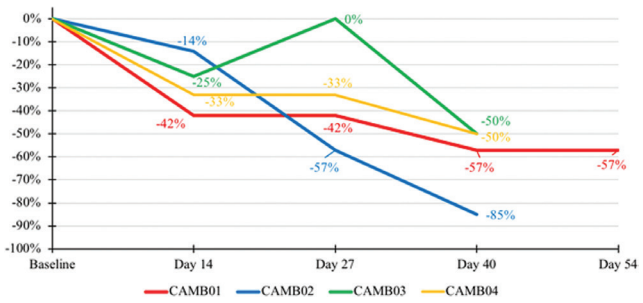
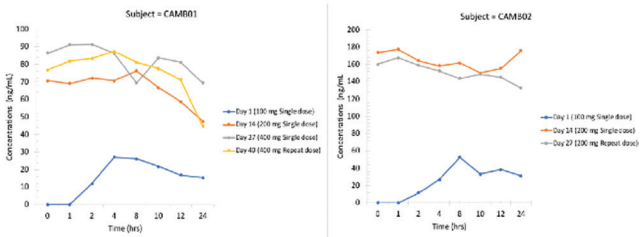


Figure 2: Plasma AMB Concentrations (ng/mL) vs. Time (h)



Results. CAMB was well tolerated by all four patients, and all are currently on the extension phase (Figure 3). There was significant improvement in clinical severity symptom scores of esophageal and oropharyngeal symptoms; CAMB01 achieved reduction in clinical symptoms by 57% (800 mg/day), CAMB02 by 85% (400 mg/day), CAMB03 50% (800 mg/day) and CAMB04 50% (800 mg/day). CAMB02 maintained higher plasma PK exposure throughout the study compared with CAMB01, a possible explanation for clinical response at a lower 400 mg/day dose. Reported adverse events were grade 1, mostly nausea and dizziness. There were no signs of liver, kidney or hematologic toxicity in any of the patients, with CAMB01 and CAMB02 receiving study drug for ~1 year.

Conclusion. CAMB was well tolerated in patient volunteers with long-standing symptomatic azole-resistant CMC. All four patients have met the primary endpoint of achieving ^{3} 50% clinical response. CAMB is a promising oral therapy for patients with history of CMC, with potential use in treatment and prophylaxis of invasive fungal infections.

Disclosures. **M. Lionakis**, Matinas BioPharma Inc: Research Support, Research support. **R. Lu**, Matinas BioPharma Inc: Employee and Shareholder, Salary. **R. Mannino**, Matinas BioPharma Inc: Employee and Shareholder, Salary.

1414. Inoculum Effect of Piperacillin/Tazobactam Concentration on Emergence of Resistance in *Klebsiella aerogenes*

Marco Custodio, PharmD[1]; Beverly Anderson, BA[1]; Daniel Sanchez, BS[1]; Keenan Ryan, PharmD, PhC[2]; Carla Walraven, PharmD, MS[2] and Renee-Claude Mercier, PharmD[3]; [1]University of New Mexico, Albquerque, New Mexico, [2]University of New Mexico Health Sciences Center, Albuquerque, New Mexico, [3]University of New Mexico College of Pharmacy, University of New Mexico College of Pharmacy, Albquerque, New Mexico

Session: 145. PK/PD Studies

Friday, October 5, 2018: 12:30 PM