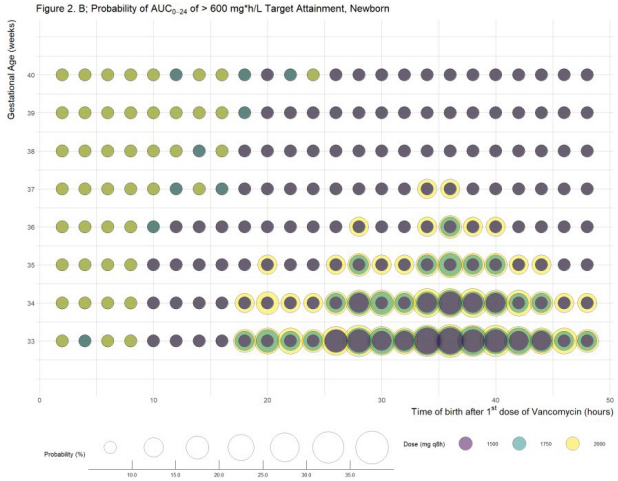
Figure 2.B



Conclusion: Current recommendations by #797 for dosing of vancomycin pose significant risk to mother and newborn alike, especially in cases with lengthy duration of labor. Based on our results, maternal therapeutic drug monitoring for all cases requiring more than two doses should be considered. With the proposed dosing regimen going un-adjusted, 1 out of 4 newborns and 4 out of 5 mothers may be subjected to nephrotoxic exposures in prolonged labor.

Table 1.

Parameter	Population mean	BSV (%)
V, maternal (L)	39.66	49.40
V, fetal (L)	2.07	39.53
CL, maternal (L/h)	4.78	43.64
$K_{m->f}$ (h^{-1})	0.51	31.68
$K_{f->m}$ (h^{-1})	0.36	34.13

V, volume of distribution; CL, clearance; $K_{m->f}$ –$K_{f->m}$, transfer rate constants from mother to fetus and back

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

1301. Breakthrough Invasive Fungal Infections based on CYP2C19 Levels in Patients Who were on Voriconazole as Primary Antifungal Prophylaxis in Acute Myeloid Leukemia (AML) undergoing Induction Chemotherapy

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Session: P-59. PK/PD studies

Background. Voriconazole (Vori) is often used for prophylactic anti-fungal therapy in induction chemotherapy for Acute Myeloid Leukemia (AML) patients due to predictable absorption and an extended spectrum antifungal activity. Vori is metabolized predominately by CYP2C19 to metabolites with less antifungal activity. There has been a great interest in understanding CYP2C19 as it significantly affects drug metabolism and pharmacokinetics of numerous drugs including voriconazole.

Approximately 39% of patients are genetically predicted to be CYP2C19 ultra-rapid or rapid metabolizers and thus are at an increased risk of breakthrough fungal infection. This study assesses the incidence of breakthrough invasive fungal infections (bIFI) at Moffitt Cancer Center based on CYP2C19 activity. bIFI is defined as new fungal infection while on vori, leading to treatment with liposomal amphotericin B, echinocandin, and/or different triazole.

Methods. This is a single-center retrospective analysis of patients who underwent induction chemotherapy for newly diagnosed AML and received voriconazole as the primary antifungal prophylaxis between July 2017 and June 2019. The patients enrolled were over 18 years old and did not have a history of stem cell transplant or solid organ transplant, Human Immunodeficiency Virus, relapsed AML or received systematic antifungal therapy 30 days prior. CYP2C19 were checked for each of the patients between July 2017 to June 2019 who were undergoing induction chemotherapy for newly diagnosed AML. It was checked within one week of admission. The patients were categorized as rapid metabolizers, intermediate metabolizers, normal metabolizers, and unknown CYP2C19.

Results. There was an incidence of 20.2% (18/89) bIFI in patients who were on Vori in this study. Of these patients with bIFI infections, 15.7% (3/19) of patients were rapid metabolizers, 14.7% (5/34) were normal metabolizers, 28.5% (4/14) were intermediate metabolizers and 0% (0/3) were poor metabolizers. There were 31% (6/19) breakthrough infections in patients with unknown CYP2C19 characteristics.

Conclusion. There is no significant statistical difference (p=0.6) among CYP2C19 categories with respect to breakthrough of invasive fungal infections at Moffitt Cancer Center between July 2017 - June 2019.

Disclosures. **Rod Quilitz, Pharm D.**, **Astellas** (Advisor or Review Panel member)

1302. Cefiderocol Population Pharmacokinetics and Probability of Target Attainment in Plasma and Epithelial Lining Fluid in Patients with Pneumonia, Bloodstream Infection/Sepsis, or Complicated Urinary Tract Infections

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Session: P-59. PK/PD studies

Background. Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against a broad range of Gram-negative bacteria. The aim of this study was to perform population pharmacokinetic (PopPK) analysis and evaluate probability of target attainment (PTA) in plasma and epithelial lining fluid (ELF) based on a modeling and simulation approach.

Methods. PopPK analysis in plasma was conducted using 3427 concentration data from 425 patients with pneumonia, bloodstream infection/sepsis (BSI/sepsis), complicated urinary tract infection (cUTI), or acute uncomplicated pyelonephritis in 3 Phase 2 or 3 studies (NCT03032380, NCT02714595, and NCT02321800), and 91 subjects without any infection in Phase 1 studies. In addition, intrapulmonary modeling was conducted using ELF concentration data from 7 pneumonia patients (NCT03862040) and 20 healthy subjects. Monte-Carlo simulations were performed by generating 1000 virtual patients for each infection site (pneumonia, BSI/sepsis, or cUTI) to predict PTA for 75% of time for which free drug concentration in plasma or ELF (only pneumonia patients) exceeds the minimum inhibitory concentration (MIC; 0.25–16 μg/mL) over dosing interval following CFDC 2 g q8h infused over 3 hours with dose adjustment based on renal function, including augmented renal clearance.

Results. The developed PopPK model described the plasma and ELF CFDC concentrations. Creatinine clearance, body weight, infection site, and albumin concentration were statistically significant covariates on CFDC PK in plasma. There were no clinically significant differences in CFDC plasma exposure based on infection site or with/without ventilation. The penetration ratio of ELF to free plasma in pneumonia patients (0.340) was 1.3-fold higher than that in healthy subjects (0.263). As shown in the table below, plasma PTA was >90% against MICs ≤4 μg/mL, regardless of infection site and renal function. ELF PTA in pneumonia patients was >90% against MICs ≤2 μg/mL and >85% against MICs ≤4 μg/mL, regardless of renal function.

Table. Probability of Target Attainment for 75% fT>MIC or 75% fT>MIC,ELF

Probability of target attainment for 75% $fT_{>MIC}$ or 75% $fT_{>MIC,ELF}$									
Target	Renal function group	Dose regimens with 3-hr infusion	MIC (μg/mL)						
			0.25	0.5	1	2	4	8	16
Pneumonia patients									
75% $fT_{>MIC}$ Plasma	Augmented	2 g q6h	100	100	100	100	99.7	94.5	60.4
	Normal	2 g q8h	100	100	100	99.9	98.9	87.1	43.4
	Mild	2 g q8h	100	100	100	100	99.8	97.0	69.7
	Moderate	1.5 g q8h	100	100	100	100	99.9	98.7	83.3
	Severe	1 g q8h	100	100	100	100	100	99.9	90.7
	ESRD	0.75 g q12h	100	100	100	100	100	99.6	86.3
75% $fT_{>MIC,ELF}$ ELF	Augmented	2 g q6h	100	100	100	99.8	91.8	54	10.2
	Normal	2 g q8h	100	100	100	99.6	87.7	42.9	6.2
	Mild	2 g q8h	100	100	100	99.8	93.8	59.8	14.9
	Moderate	1.5 g q8h	100	100	100	100	95.9	66	17.5
	Severe	1 g q8h	100	100	100	99.9	97.7	74.6	24.8
	ESRD	0.75 g q12h	100	100	100	99.9	94.3	63.1	20.8
BSI/sepsis patients									
75% $fT_{>MIC}$ Plasma	Augmented	2 g q6h	100	100	100	100	99.4	91.3	49.6
	Normal	2 g q8h	100	100	100	99.9	97.3	80.6	32.6
	Mild	2 g q8h	100	100	100	99.9	99.6	94.4	57.7
	Moderate	1.5 g q8h	100	100	100	100	99.9	98.0	74.8
	Severe	1 g q8h	100	100	100	100	100	99.8	84.8
	ESRD	0.75 g q12h	100	100	100	100	100	99.2	79.2
cUTI patients									
75% $fT_{>MIC}$ Plasma	Augmented	2 g q6h	100	100	100	100	99.9	96.9	73.3
	Normal	2 g q8h	100	100	100	100	99.6	93.6	56.3
	Mild	2 g q8h	100	100	100	100	99.8	98.4	81.2
	Moderate	1.5 g q8h	100	100	100	100	100	99.6	90.4
	Severe	1 g q8h	100	100	100	100	100	100	95.9
	ESRD	0.75 g q12h	100	100	100	100	100	100	91.6

Conclusion. The recommended dosing regimen (2 g, q8h, 3-hr infusion) adjusted by renal function provided adequate exposure to CFDC in patients with infections caused by Gram-negative pathogens, irrespective of infection site and renal function.

Disclosures. Takayuki Katsube, PhD, Shionogi & Co., Ltd. (Employee) Nao Kawaguchi, BPharm, Shionogi & Co., Ltd. (Employee) Roger Echols, MD, Shionogi Inc. (Consultant) Toshihiro Wajima, PhD, Shionogi & Co., Ltd. (Employee) David P. Nicolau, PharmD, Cepheid (Other Financial or Material Support, Consultant, speaker bureau member or has received research support.)Merck & Co., Inc. (Consultant, Grant/Research Support, Speaker's Bureau)Wockhardt (Grant/Research Support)

1303. Characterization of Isavuconazole Serum Concentrations with Various Administration Routes in a Hospitalized Cohort

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Session: P-59. PK/PD studies

Background. Patients with invasive fungal infections are often critically ill and immunosuppressed with multiple comorbidities that may impact drug absorption and exposure. This study sought to characterize isavuconazole serum concentrations (ISCs) in a cohort of real-world hospitalized patients when administered by intravenous solution (IV), enteral as intact capsules, or tube as opened capsule contents.

Methods. This retrospective cohort analysis included all hospitalized patients who received isavuconazole as prophylaxis or treatment between September 2017 and September 2018 and had therapeutic drug monitoring performed. For patients receiving isavuconazole by tube, the capsules were opened and contents were diluted with 10-30 mL of sterile water. Administration was per package insert for intact capsules and IV solution. ISCs were obtained as part of routine care and were quantified by high-performance liquid chromatography. An appropriate trough was defined as within 4 hours of the next scheduled dose. Currently, there is a lack of correlation between isavuconazole exposure and efficacy or toxicity; thus, ISCs were compared between administration routes.

Results. 93 ISCs were obtained during 65 encounters from 55 unique patients. The majority of patients were post-transplant (69.1%) and death occurred during 12 (18.5%) encounters. ISCs based on different characteristics of the cohort are shown in Table 1. All ISC assessments were detectable, median 2.3 mg/dL (Q1: 1.5 mg/dL, Q3: 3.3 mg/dL). Administration via tube achieved similar ISCs compared with IV therapy (1.6 mg/dL vs. 1.9 mg/dL, respectively). However, administration of intact capsules resulted in higher median ISCs, 3 mg/dL (Q1: 1.9 mg/dL, Q3: 4.1 mg/dL). All 14 patients with administration via tube were post-transplant, which was not shown to have a significant impact on ISCs (median, transplant 2.2 mg/dL vs. non-transplant 2.7 mg/dL).

Table 1. Characterization of Isavuconazole Concentrations

Table 1. Characterization of Isavuconazole Concentrations[a]

Characteristic	Frequency (n=93 serum concentrations)	Isavuconazole Serum Concentration (mg/dL)
Concentration:		
< 4 hours of next dose	80 (86)	2.3 (1.5-3.4)
≥ 4 hours of next dose	13 (14)	3.0 (1.9-3.3)
Duration of therapy at assessment		
Day 5 or less	3 (3.2)	3.3 (3.2-4.5)
Day 6-10	25 (26.9)	2.0 (1.3-2.7)
Day 10-30	35 (37.6)	1.9 (1.4-3)
Primary route of administration		
Intravenous	34 (36.6)	1.9 (1.3-2.8)
By mouth	45 (48.4)	3.0 (1.9-4.1)
Via tube	14 (15.1)	1.6 (1.3-2.5)
Transplant status		
Yes	71 (76.3)	2.2 (1.5-3.5)
No	22 (23.7)	2.7 (1.5-3.3)
Treatment purpose:		
Prophylaxis	26 (28)	3.0 (2.0-5.2)
Treatment	67 (72)	2.0 (1.4-3.2)
Location during assessment:		
Floor	65 (69.9)	2.7 (1.8-3.7)
Intensive care unit	28 (30.1)	1.9 (1.3-2.5)

[a]Data are reported in n (%) or median (IQR)

Conclusion. ISCs were detectable in all patients regardless of transplant status or location at the time of assessment. Administration of isavuconazole via an enteral feeding tube achieved comparable serum concentrations compared with FDA-approved routes of administration and may represent an important alternative for select patients.

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

1304. Characterization of Tebipenem Pivoxil Hydrobromide Pharmacokinetics-Pharmacodynamics (PK-PD) in a Neutropenic Murine Acute Pyelonephritis (AP) Model

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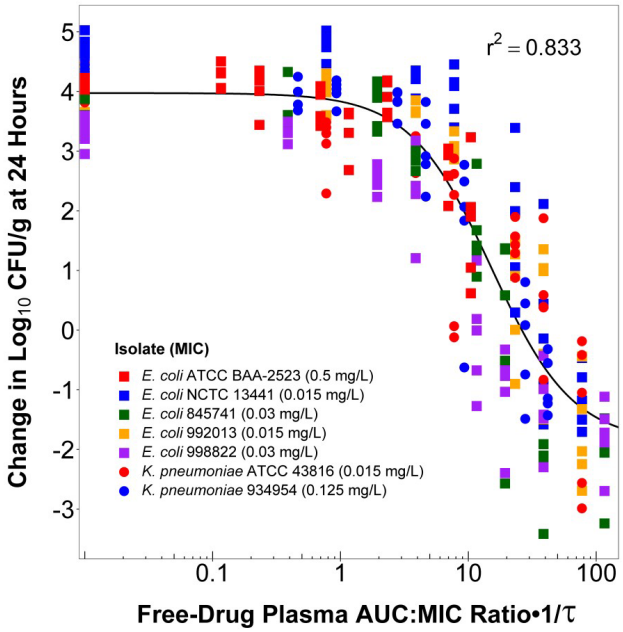
Session: P-59. PK/PD studies

Background. Tebipenem pivoxil hydrobromide (tebipenem HBr), an orally (PO) bioavailable prodrug of tebipenem, is a carbapenem with broad-spectrum activity against Gram-positive and -negative bacteria that is being developed for the treatment of patients with complicated urinary tract infections, including AP. Data from a one-compartment *in vitro* infection model demonstrated that the ratio of free-drug plasma area under the curve (AUC) to MIC with adjustment for dosing interval (τ) (AUC:MIC ratio•1/τ) was the PK-PD index most associated with tebipenem HBr efficacy [VanScoy BD *et al.*, IDWeek 2019, Poster 1565]. Studies were undertaken to characterize the magnitude of tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ associated with efficacy for Enterobacteriaceae using a neutropenic murine AP model.

Methods. A single dose pharmacokinetic study was completed in neutropenic mice infected via intra-renal injection with 10^4 CFU/kidney of *Escherichia coli* NCTC 13441. Following PO administration of 4 tebipenem HBr doses (1, 15, 45 and 100 mg/kg), plasma samples were collected at 0.25, 0.5, 1, 2, 4, 6 and 8 hours post-treatment initiation and drug concentrations were determined using LC/MS/MS. Dose-ranging studies were completed using a panel of 7 Enterobacteriaceae isolates (tebipenem HBr MIC values of 0.015 to 0.5 mg/L). Mice were infected with 10^4 CFU/kidney via intra-renal injection. Two hours post-incubation, 8 total daily tebipenem HBr doses (0.3 to 135 mg/kg) were fractionated into regimens given every 8 hours. The relationship between change in $\log_{10}$ CFU/g from baseline at 24 hours and free-drug plasma AUC:MIC ratio•1/τ was fit using a Hill-type model. Free-drug plasma AUC:MIC ratio•1/τ values associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU/g reductions from baseline at 24 hours were determined.

Results. The relationship between change in $\log_{10}$ CFU/g from baseline at 24 hours and tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ described the data well ($r^2 = 0.833$). Free-drug plasma AUC:MIC ratio•1/τ values associated with net bacterial stasis and a 1-$\log_{10}$ CFU/g reduction from baseline were 26.2 and 54.1, respectively. A 2-$\log_{10}$ CFU/g reduction was not achieved.

Relationship between change in log10 CFU/g from baseline at 24 hours and tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ based on data for a panel of Enterobacteriaceae isolates evaluated in the dose-ranging studies conducted using a neutropenic murine acute pyelonephritis model



Conclusion: These data will be useful to support tebipenem HBr dose selection for clinical studies in patients with AP.

Disclosures. Brian D. VanScoy, B.S., Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Steven Fikes, BA, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Christopher M. Rubino, PharMD, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Sujata M. Bhavnani, PharMD, MS, FIDSA, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Nicole S. Cotroneo, BS, Spero Therapeutics (Employee, Shareholder) Ian A. Critchley, PhD, Spero Therapeutics (Employee, Shareholder) Thomas R. Parr, PhD, Spero Therapeutics (Employee, Shareholder) Paul G. Ambrose, PharMD, FIDSA, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support)

1305. Comparison of Pharmacokinetics of DSTA4637S, a novel THIOMAB™ Antibody-Antibiotic Conjugate, in Patients with Staphylococcus aureus Bacteremia Receiving Standard-of-Care Antibiotics with Pharmacokinetics in Healthy Volunteers

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Session: P-59. PK/PD studies

Background. DSTA4637S, a THIOMAB™ antibody-antibiotic conjugate against *Staphylococcus aureus,* is a potential therapy for complicated *S. aureus* bacteremia. Single doses showed favorable safety and pharmacokinetics (PK) in healthy volunteers (HVs). This study compares HV PK results to PK from a Phase 1b study evaluating multiple doses in patients with bacteremia.

Methods. In a Phase 1a study, HVs received single intravenous (IV) doses (5, 15, 50, 100, or 150 mg/kg) of DSTA4637S. The Phase 1b, randomized, double-blind, placebo-controlled, multiple ascending-dose study enrolled patients with MRSA or MSSA bacteremia receiving ≥ 4 weeks of standard-of-care (SOC) antibiotics in combination with IV DSTA4637S (15, 45, or 100 mg/kg) weekly (4-6 doses). Intensive PK serum and plasma sampling was performed after first and last doses of DSTA4637S. Total antibody (TAb) was measured in serum by ELISA. DSTA4637S conjugate (ac-dmDNA31)