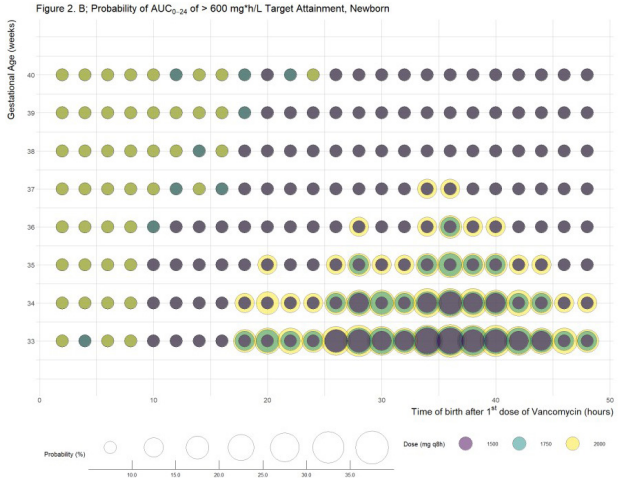
Figure 2.B



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.

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

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