Support)**Hoffmann-La Roche** (Grant/Research Support)**Horizon Orphan LLC** (Grant/Research Support)**ICPD Biosciences, LLC** (Grant/Research Support, Other Financial or Material Support, member/owner)**Indalo Therapeutics** (Grant/Research Support)**Insmed Inc.** (Grant/Research Support)**Institute for Clinical Pharmacodynamics** (Employee)**Iterum** (Grant/Research Support)**KBP Biosciences USA** (Grant/Research Support)**Kyoto Biopharma, Inc.** (Grant/Research Support)**Matinas** (Grant/Research Support)**Meiji Seika Pharma Co., Ltd.** (Grant/Research Support)**Melinta Therapeutics** (Grant/Research Support)**Menarini Ricerche S.p.A.** (Grant/Research Support)**Merck & Co., Inc** (Grant/Research Support)**Mutabilis** (Grant/Research Support)**Nabriva Therapeutics AG** (Grant/Research Support)**Naeja-RGM Pharmaceuticals** (Grant/Research Support)**Nosopharm SAS** (Grant/Research Support)**Novartis Pharmaceuticals Corp.** (Grant/Research Support)**NuCana Biomed** (Grant/Research Support)**Paratek Pharmaceuticals, Inc.** (Grant/Research Support)**Polyphor, Ltd.** (Grant/Research Support)**Prothena Corporation** (Grant/Research Support)**PTC Therapeutics** (Grant/Research Support)**Rempex Pharmaceuticals** (Grant/Research Support)**Roche TCRC** (Grant/Research Support)**Sagimet** (Grant/Research Support)**scPharmaceuticals Inc.** (Grant/Research Support)**Scynexis** (Grant/Research Support)**Spero Therapeutics** (Grant/Research Support)**TauRx Therapeutics** (Grant/Research Support)**Tetraphase Pharmaceuticals** (Grant/Research Support)**Theravance Biopharma Pharmaceutica** (Grant/Research Support)**USCAST** (Grant/Research Support)**VenatoRx** (Grant/Research Support)**Vical Incorporated** (Grant/Research Support)**Wockhardt Bio AG** (Grant/Research Support)**Zavante Therapeutics** (Grant/Research Support)**Zogenix International** (Grant/Research Support)

1106. Evaluation of Penetration of Cefiderocol into Cerebrospinal Fluid Using a Rat Meningitis Model

Miki Takemura, MS[1]; Sachi Kanazawa, PhD[1]; Naoki Kohira, PhD[1]; Yuki Aoe, BS[2]; Atsushi Morimoto, n/a[2]; Kana Horiuchi, MPharm[1]; Yuji Inoue, MPharm[1]; Yoshinori Yamano, PhD[1]; [1]Shionogi & Co., Ltd., Osaka, Osaka, Japan; [2]Shionogi TechnoAdvance Research Co., Ltd., Toyonaka, Osaka, Japan

Session: P-62. PK/PD Studies

Background. Central nervous system (CNS) infections caused by Gram-negative bacteria (GNB) are sometimes hard to treat due to antibiotic resistance and difficulty with penetration into cerebrospinal fluid (CSF). Cefiderocol (CFDC) which was approved by the FDA and the EMA in 2019 to 2020 is a siderophore cephalosporin with potent activity against various GNB including carbapenem-resistant strains. In this study, we evaluated the penetration of CFDC into CSF using a rat meningitis model.

Methods. To induce meningitis, the anesthetized immunocompetent rats were infected by intracisternal inoculation of a bacterial suspension of 8.7×10^1 CFU of *E. coli* SR200138. 200 mg/kg or 50 mg/kg of CFDC was administered via tail vein bolus injection to uninfected rats (n=4/sampling point) and rats with meningitis (n=4/sampling point) 24 hours after infection. CSF was collected by cisternal puncture and blood was collected from heart. The samplings were performed 0.25, 0.5, 1, 3, and 5 hours after dosing. The concentrations of CFDC in plasma and CSF for individuals were determined by LC/MS/MS. PK parameters for the average values in plasma and CSF were calculated.

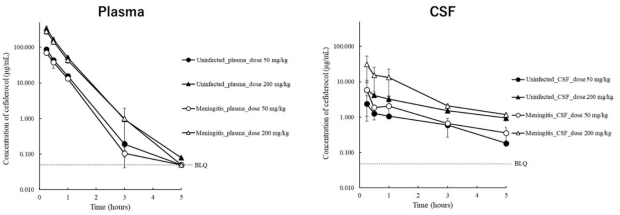
Results. CFDC concentration and the PK parameters are shown in Figure and Table, respectively. The penetration of CFDC from plasma to CSF was observed in both uninfected and meningitis groups, and the penetration rates increased in the rats withs meningitis (AUC_{CSF}/AUC_{plasma}: 0.149-0.183) compared with the uninfected rats (AUC_{CSF}/AUC_{plasma}: 0.0508-0.0588). The penetration rates of CFDC in the meningitis were comparable to those of piperacillin, cefepime, and meropenem in human (0.32, 0.103, and 0.39 in strongly inflamed meninges, respectively) [1]. In both groups, elimination of CFDC from CSF was slower compared with that from plasma as seen with other β-lactam antibiotics such as meropenem, suggesting that $T_{>MIC}$, an indicator that correlates with the efficacy of β-lactams, may be higher in CSF [2].

Table. PK Parameters of Cefiderocol after Intravenous Bolus Administration in Uninfected Rats and Rats with Meningitis

Pharmacokinetic parameters	Sample	Uninfected		Meningitis	
		50 mg/kg[a]	200 mg/kg[a]	50 mg/kg[a]	200 mg/kg[a]
C_{max} (μg/mL)	Plasma	88.0	339	70.3	280
$t_{1/2,z}$ (hr)		0.317	0.427	0.292	0.353
$AUC_{0\text{-}inf}$ (hr·μg/mL)		80.4	301	64.9	248
C_{max} (μg/mL)	CSF	2.36	6.09	5.97	31.2
$t_{1/2,z}$ (hr)		1.57	2.24	1.58	1.14
$AUC_{0\text{-}inf}$ (hr·μg/mL)		4.73	15.3	9.66	45.4
AUC ratio		0.0588	0.0508	0.149	0.183

Animal: Crl:CD(SD) rat, male; n = 3 or 4 for each sampling point in each treatment group
Infection: intracisternal inoculation (challenge dose: 8.7×10^1 CFU/rat)
Dose: bolus administration into tail vein; 24 hours after infection for meningitis group
Sampling point after dosing: 0.25, 0.5, 1, 3, and 5 hours
a: Dose of cefiderocol as free base

Figure. Concentrations of Cefiderocol after Intravenous Bolus Administration in Uninfected Rats and Rats with Meningitis



Animal: Crl:CD(SD) rat, male; n = 3 or 4 for each sampling point in each treatment group
Infection: intracisternal inoculation (challenge dose: 8.7×10^1 CFU/rat)
Dose: bolus administration into tail vein; 24 hours after infection for meningitis group
Sampling point after dosing: 0.25, 0.5, 1, 3, and 5 hours
Concentrations of cefiderocol were represented as mean ± standard deviation concentrations
BLQ means below the lower limit of quantification

Conclusion. It was confirmed that CFDC penetrates into CSF from plasma in a rat model and the penetration rate was increased 3-fold in meningitis.

References.

1. Nau, R. et al. Clin Microbiol Rev. 2010 Oct;23(4):858–883.
2. Nau, R. et al. Antimicrob Agents Chemother. 1998 Aug;42(8):2012–2016.

Disclosures. **Miki Takemura, MS**, **SHIONOGI & CO., LTD.** (Employee) **Sachi Kanazawa, PhD**, **Shionogi & Co., Ltd.** (Employee) **Naoki Kohira, PhD**, **Shionogi & Co., Ltd.** (Employee) **Yuki Aoe, BS**, **Shionogi TechnoAdvance Research Co., Ltd.** (Employee) **Atsushi Morimoto, n/a**, **Shionogi TechnoAdvance Research Co., Ltd.** (Employee) **Kana Horiuchi, MPharm**, **Shionogi & Co., Ltd.** (Employee) **Yuji Inoue, MPharm**, **Shionogi & Co., Ltd.** (Employee) **Yoshinori Yamano, PhD**, **Shionogi** (Employee)

1107. Vancomycin AUC Dosing: Is One Concentration in the Hand Worth Two in the Bush?

Justin Spivey, PharmD, BCPS, BCIDP[1]; Jenny Shroba, PharmD[2]; Connor Deri, PharmD[3]; Cara Nys, PharmD[3]; Rebekah Wrenn, PharmD, BCPS[4]; Michael E. Yarrington, MD[5]; [1]Duke University Medical Center, Durham, North Carolina; [2]Duke Raleigh Hospital, Raleigh, North Carolina; [3]Duke University Hospital, Durham, North Carolina; [4]Duke University, Durham, North Carolina; [5]Duke Center for Antimicrobial Stewardship and Infection Prevention, Durham, North Carolina

Session: P-62. PK/PD Studies

Background. Recent guidelines recommend a transition from trough-based to area-under the curve-based (AUC) monitoring for vancomycin for serious invasive methicillin-resistant *Staphylococcus aureus* infections. Due to the challenges of performing AUC monitoring in clinical practice, this study sought to compare the accuracy of an AUC calculated from two points using trapezoidal calculations and from a single steady-state trough combined with population assumptions.

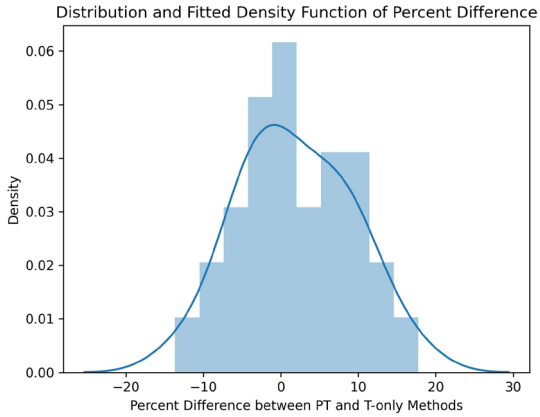
Methods. This prospective cohort analysis included hospitalized patients with stable renal function from 10.2020 to 12.2020 with two vancomycin concentrations obtained at steady-state during a single dosing interval. For each patient, AUC was calculated via trapezoidal equations utilizing peak and trough concentrations (P/T) and using the trough concentration (T) combined with population volume of distribution. Appropriate concentrations were defined as a peak at least 2 hours after the end of the infusion and a trough within one hour of the next dose. The percent and actual differences were calculated between the P/T and T AUC assessments for each patient. A patient level review was independently conducted by two clinical pharmacists to evaluate if a change in dosing would have been made according to AUC estimation methodology.

Results. Thirty-one patients had appropriate steady-state P/T obtained. Baseline demographics are shown in Table 1 with the majority of patients being overweight with normal renal function. The mean calculated AUC for both groups was similar, P/T 544.8 and T 549.8. The mean and median percent differences were 1.85% and 0.65%, with a standard deviation of 7.3% and an apparent normal distribution (Figure 1, p = 0.94 by Shapiro's test). The median absolute difference in AUC was 25.82 mg*h/L between methodologies. Both methods would have resulted in the same modification to the vancomycin regimen based on patient level chart review.

Table 1. Vancomycin AUC Demographics

Parameter (n=31)	Value
Age, median	59 years
Scr, median (IQR)	1 mg/dL (1.75 to 1.07)
CrCl, median (IQR)	83 mL/min (69.5 to 120)
BMI, median (IQR)	28.16 kg/m² (25.3 to 34.5)
Mean % difference in AUC* (SD)	1.85% (7.3)
Median % difference in AUC*(IQR)	0.65% (-3.8 to 8.2)
Mean absolute difference in AUC* (SD)	30.85 mg*h/L (24.4)
Median absolute difference in AUC* (IQR)	25.82 mg*h/L (16.7 to 42.2)
Trough values, mean (SD)	14.3 mg/L (5.9)

* Trough-only vs. two level
AUC: area under the curve, BMI: body mass index, CrCl: creatinine clearance, IQR: interquartile range, Scr: serum creatinine, SD: standard deviation



Conclusion. The single-trough method performed similarly to the more laborious P/T method. No patient would have received a dose adjustment based on the two different AUC estimation methods. The single-trough method may represent a resource and workflow conscious AUC estimation method for patients meeting population assumptions.

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

1108. Evaluation of Vancomycin Dosing in Adolescents

Ashley I. Weaver, PharmD[1]; Genene A. Wilson, PharmD[2]; Emily Belarski, PharmD, BCPPS[3]; Allison Nelson, PharmD[4]; Madan Kumar, DO[5]; Palak Bhagat, PharmD, BCPS[3]; [1]University of Chicago Medicine/, Indianapolis, Indiana; [2]Dell Children's Medical Center, Austin, Texas; [3]University of Chicago Medicine, Chicago, Illinois; [4]University of Chicago Medicine Comer Children's Hospital, Geneva, IL; [5]University of Chicago, Chicago, IL

Session: P-62. PK/PD Studies

Background. Pediatric vancomycin dosing varies based on age and renal function. Recent literature suggests previously recommended doses of 45-60 mg/kg/day may be insufficient to achieve an AUC:MIC ratio of 400-600 mg-hr/L and higher doses of at least 60 mg/kg/day may be required. However, data to guide dosing in adolescents is limited.

Methods. A single-center, retrospective chart review of patients aged 12 to 18 years who received vancomycin and had therapeutic drug monitoring (TDM) performed between July 2017 to June 2020 were included. The primary endpoint was the median total daily dose (TDD) of vancomycin required to achieve therapeutic serum concentrations. Secondary endpoints were to characterize how factors such as age, weight, trough versus AUC monitoring, malignancy, and trauma may influence dosing. The safety endpoint was the development of acute kidney injury (AKI).

Results. 130 vancomycin courses in 86 patients were included. Baseline characteristics are presented in Table 1. Of the 130 vancomycin courses, 50 courses (38%) achieved therapeutic serum concentrations at a median TDD of 49.8 mg/kg/day (IQR 42 – 59.4). This was not statistically different from the sub- or supra-therapeutic groups (p=0.22). Based on age, the median TDD for 12-14 year olds was higher at 60 mg/kg/day (IQR 45-78.8; n=14) than for 15-16 and 17-18 year olds [45.3 mg/kg/day (IQR 41.1-51; n=15), 48 mg/kg/day (IQR 42-52; n=21), respectively]. Obese patients needed a median TDD of 43.5 mg/kg/day vs at least 51 mg/kg/day in healthy and overweight patients. Finally, AUC guided dosing resulted in a slightly lower overall median TDD vs trough guided dosing (45.8 mg/kg/day vs 50.5 mg/kg/day). Additional dose requirements based on age, weight, TDM and other characteristics are presented in Table 2. Of the 15 patients who developed AKI per pRIFILE criteria, 2 were classified as injury and 3 as failure.

Table 2. Total Daily Dose Course Analysis

Category		Total Daily Dose (mg/kg/day)			p-value
		Therapeutic	Sub-therapeutic	Supra-therapeutic	
Primary Outcome		49.8 (42 - 59.4) n=50	47.5 (45 - 60) n=42	57 (45 - 60) n=38	0.22
Age (n=130)					
	Age 12 - 14 n =41	60 (45 - 78.8) n=14	56.8 (45 - 60) n=13	57.7 (45 - 60) n=14	0.32
	Age 15 - 16 n =33	45.3 (41.1 - 51) n=15	46.6 (45 - 60) n=14	67.5 (56 - 75) n=4	0.05
	Age 17 - 18 n =56	48 (42 - 52) n=21	47.6 (37.6 - 51) n=15	50.8 (44.8 - 61.2) n=20	0.26
	Age 15 - 18 n =89	46.6 (41.8 - 51.7) n=36	47 (45 - 56) n=29	54.5 (45 - 63.1) n=24	0.088
Weight (n=129)					
	Underweight n = 7	n=0	47 (45 - 84) n=7	n=0	-
	Healthy n = 73	51 (45 - 60) n=29	50.7 (45 - 60) n=21	58.4 (48.2 - 62.4) n=23	0.46
	Overweight n =19	51.2 (43.8 - 58.3) n=8	45.7 (43.2 - 51.8) n=8	75 (57 - 75) =3	0.078
	Obese n = 30	43.5 (33.6 - 50.5) n=12	45 (27.8 - 60) n=6	45 (33.6 - 60) n=12	0.51
Trough based dosing (n=85)					
	All patients	50.5 (43.2 - 56.7) n=30	47.2 (44.5 - 56.4) n=28	58.4 (45 - 60.1) n=27	0.17
	Median Trough Level	12.9	8.0	20.2	-
	Age 12 - 14 n= 22	60 (45 - 79) n=7	56.8 (45 - 63.2) n=7	60 (57.6 - 60.1) n=8	0.84
	Age 15 - 16 n= 20	46.8 (38 - 51) n=7	45 (45 - 47) n=9	67.5 (56 - 75) n=4	0.03
	Age 17 - 18 n=43	50.5 (42.6 - 53.2) n= 16	48.5 (39.8 - 51.8) n=12	48.2 (44.6 - 60) =15	0.72
AUC based dosing (n=45)					
	All patients	45.8 (39.3 - 60) n=20	55.2 (45 - 60) n=14	57 (40.5 - 59.7) n=11	0.78
	Median AUC Level	470.4	341.5	762	-
	Age 12 - 14 n= 19	60 (37.5 - 78.8) n=7	52.2 (27.8 - 60) n=6	48.3 (39.5 - 57) n=6	0.20
	Age 15 - 16 n= 13	45.2 (43 - 50.7) n=8	60 (60 - 84) n=5	n=0	0.057
	Age 17 - 18 n= 13	41.6 (37.2 - 46.3) n=5	46.2 (28.8 - 51) n=3	59.7 (57 - 62.4) n=5	0.09
Active Malignancy n = 32		46.8 (45.3 - 59.4) n=15	60 (47.5 - 63.2) n=9	54.3 (48.3 - 58.5) n=8	0.18
Trauma n = 25		50 (42 - 52) n=9	47.6 (42 - 51) n=11	59.7 (57 - 62.4) n=5	0.046

All data presented as median (IQR)

Table 1. Patient Characteristics

Category	
Age (years), mean (SD)	15.7 (2.0)
Male, n (%)	63 (73)
Weight (kg), median (IQR)	68.5 (51.8 - 81)
Height (cm), median (IQR)	170.2 (160.7 - 175.3)
BMI, median (IQR)	23 (19 - 30)
Underweight, n (%)	6 (7)
Healthy, n (%)	44 (51)
Overweight, n (%)	12 (14)
Obese, n (%)	24 (28)
Active Malignancy, n (%)	20 (23)
Trauma, n (%)	16 (18.6)
Length of stay (days), median (IQR)	17 (8 - 35)
Baseline SCr (mg/dL), mean (SD)	0.63 (0.21)
Nephrotoxic Medication, n (%)	57 (66.3)
Nephrotoxic Medications per patient, mean (SD)	1.65 (1.7)

Conclusion. To achieve therapeutic levels, adolescents 12 to14 years old need higher empiric doses of 60 mg/kg/day compared to 45 mg/kg/day in 15 to 18 year olds. Obese patients, however, may require lower TDD than underweight, healthy, and overweight patients. Patients that receive AUC versus trough monitoring may also require lower TDD to achieve therapeutic concentrations. More data is needed to further evaluate our findings.

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

1109. Pharmacokinetics and Exposure of Cefepime in Critically Ill Patients Receiving Extracorporeal Membrane Oxygenation (ECMO)

Abigail K. Kois, PharmD[1]; Jason A. Gluck, DO[2]; David P. Nicolau, PharmD[1]; Joseph L. Kuti, PharmD[3]; [1]Hartford Hospital, Hartford, Connecticut; [2]Hartford Healthcare, Hartford, Connecticut; [3]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut

Session: P-62. PK/PD Studies

Background. ECMO is a life-saving tool utilized in critically ill patients that require respiratory and/or cardiac support. ECMO may also affect the pharmacokinetics (PK) of certain medications, including some antibiotics. Cefepime is a widely used antibiotic in this population due to its broad spectrum activity but limited data are available to guide dosing in patients requiring ECMO.

Methods. This was a prospective, single-center study of 6 critically ill adult patients requiring ECMO and receiving cefepime 2g q8h as a 3h infusion. After obtaining informed consent, 4-6 blood samples within the dosing interval were collected to determine cefepime concentrations. Population PK was conducted in Pmetrics using R. Final MAP Bayesian parameter estimates were used to simulate free time above MIC (%fT >MIC) for various cefepime dosing regimens. The target pharmacodynamic exposure was 70% fT >MIC.

Results. Patients were between 31-62 years old; 4/6 (66.7%) were on veno-venous (VV) ECMO and 2 veno-arterial (VA) ECMO. Two patients required continuous venovenous hemodiafiltration (CVVHDF) while the other 4 had a CrCL between 92-199 ml/min. A two compartment model fitted the data better than a one compartment model. Median (range) final population PK parameters were: clearance (CL), 9.8 L/h (7.6-33.1); volume of central compartment (V_C), 6.9 L (4.7-49.8); and intercompartment transfer constants (k_{12}), 2.04 h^{-1} (1.48-2.29); and k_{21}, 1.49 h^{-1} (0.75-1.71). The 2g q8h (3h infusion) regimen resulted in target exposure in all patients up to an MIC of 8 mg/L (the susceptibility breakpoint for *Pseudomonas*), with 5/6 patients achieving this at 16 mg/L. A standard 2g q12h (0.5h infusion) regimen would have resulted in 5/6 patients achieving 70% fT >MIC at 8 mg/L and 1/6 at 16 mg/L.

Conclusion. These are the first data describing cefepime PK and exposure attainment in critically ill patients receiving ECMO. Cefepime 2g q8h (3h infusion) achieved target pharmacodynamic exposure up to the susceptibility breakpoint of 8 mg/L in all 6 patients, including 2 with concomitant CVVHDF. Additional studies are warranted to define cefepime PK in patients on ECMO across a robust range of CrCL to guide dosing.

Disclosures. **David P. Nicolau, PharmD**, **Abbvie, Cepheid, Merck, Paratek, Pfizer, Wockhardt, Shionogi, Tetraphase** (Other Financial or Material Support, I have been a consultant, speakers bureau member, or have received research funding from the above listed companies.) **Joseph L. Kuti, PharmD**, **Allergan** (Speaker's Bureau)**BioMérieux** (Consultant, Research Grant or Support, Speaker's Bureau)**Contrafect** (Scientific Research Study Investigator)**GSK** (Consultant)**Merck** (Research Grant or Support)**Paratek** (Speaker's Bureau)**Roche Diagnostics** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Summit** (Scientific Research Study Investigator)

1110. *In Vivo* Pharmacodynamics of Vancomycin Against Staphylococci in Young Infants

Amanda Gwee, MBBS, FRACP, DTMH, PhD[1]; Stephen Duffull, PHD[2]; Derek Zhu, PhD[2]; [1]The Royal Children's Hospital, Melbourne, Victoria, Parkville, Victoria, Australia; [2]University of Otago, Dunedin, Otago, New Zealand

Session: P-62. PK/PD Studies

Background. Coagulase-negative staphylococci are the predominant pathogen causing late onset sepsis in young infants, however, the pharmacodynamic target for vancomycin therapy is unknown. This study aimed to determine the pharmacodynamic target of vancomycin in young infants with staphylococcal infections.