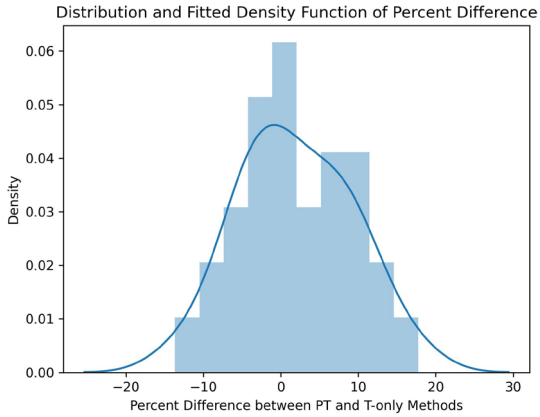

Conclusion. The single-trough method performed similarly to the more laborious P/T method. No patient would have received a dose adjustment based on the two different AUC estimation methods. The single-trough method may represent a resource and workflow conscious AUC estimation method for patients meeting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

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

1108. Evaluation of Vancomycin Dosing in Adolescents

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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.

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

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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

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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.

Methods. Retrospective data were collected for infants aged 0-90 days with methicillin-resistant *Staphylococcus aureus* (MRSA or coagulase-negative staphylococci (CoNS) bacteraemia over a 4-year period at the Royal Children's Hospital Melbourne, Australia. Vancomycin broth microdilution minimum inhibitory concentrations (MIC) were determined. A published pharmacokinetic model was externally validated using the study dataset and a time-to-event pharmacodynamic model developed using non-linear mixed effects modelling, with the event being the first negative blood culture. Simulations were performed to determine the 24-hour trough vancomycin concentration correlating with a 90% probability target attainment (PTA) of the area under the curve in the first 24-hours (AUC_{0-24}) exceeding the identified target.

Results. Thirty infants, 28 with CoNS and two with MRSA bacteraemia, who had 165 vancomycin concentrations determined were included. The vancomycin broth microdilution MIC was determined for 24 CoNS and one MRSA isolate, both with a median MIC of 1 mg/L (CoNS range 0.5 to 4). An AUC_{0-24} ≥3 00 mg/L·h was associated with a 7.8-fold increase in the chance of bacteriological cure for all staphylococci at any time point compared to an AUC_{0-24} < 300 mg/L·h (hazard ratio 95% CI: 3.21-18.8). The 24-hour trough concentrations associated with a 90% PTA of achieving this target were > 13-16 mg/L and > 8-12 mg/L for 6 and 12-hourly dosing, respectively.

Conclusion. Our study found that an AUC_{0-24} ≥ 300 mg/L·h was associated with a 7.8-fold increase in bacteriological cure in young infants with staphylococcal bloodstream infections.

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

1111. Therapeutic Drug Monitoring of Colistin in Cerebrospinal Fluid in the Treatment of Neurosurgical Meningitis caused by *Pseudomonas aeruginosa* and KPC-producing *Enterobacterales*

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Session: P-62. PK/PD Studies

Background. Central nervous system (CNS) infections caused by carbapenem-resistant *Enterobacterales* (CRE) and Difficult-to-treat resistant (DTR)-*P. aeruginosa* (PA) present a therapeutic dilemma. Therapies are limited due to antibiotic resistance and inadequate CNS diffusion. Intraventricular polymyxins are utilized in this setting despite a lack in pharmacokinetic data after CNS injection. We describe the utilization of intravenous and intrathecal polymyxin E [colistimethate (CMS)] therapeutic drug monitoring (TDM) in 3 cases of post-neurosurgical meningitis.

Methods. Bacterial identification and susceptibility testing were performed using MicroScan. TDM was employed by dosing CMS at 125,000 IU (i.e., 4.1 mg CBA or 10 mg) administered via external ventricular drain twice daily and 4.5 MIU (133.2 CBA or 360 mg) CMS administered over 30 minutes IV twice daily. Four pairs of CSF and blood samples were collected for each patient (Table 1). Samples were placed on ice to minimize in-vitro conversion of CMS to Colistin. Colistin binding in plasma and CSF was measured using ultracentrifugation. Concentrations of CMS and Colistin in CSF and human plasma were determined by liquid chromatography/mass spectrometry. Patients A, B and C received 20, 15, and 12 doses of CMS, respectively, prior to TDM.

Results. Bacterial cultures revealed DTR *PA*, bla_{KPC} *E. cloacae* and bla_{OXA-48} *K. pneumoniae* for patients A, B and C, respectively. Colistin minimum inhibitory concentrations (MIC) were 0.5 µg/ml, 0.125 µg/ml, and 0.125 µg/ml, respectively. The measured CSF and plasma concentrations of CMS, Colistin, and binding are shown in Table 1. Clinical resolution and microbiological cure were attained in all patients.

Therapeutic Drug Monitoring of Unchanged CMS and Formed Colistin in CSF samples for patient A, B, and C

Cerebrospinal fluid (CSF)							
Patient ID	**Time of CMS dose**	**Collection Time**	**Time elapsed from last IV dose (h)**	**Time elapsed from last IT dose (h)**	**Formed Colistin (µg/ml)**	**Unchanged CMS (µg/ml)**	**Colistin binding**
Patient A	IV dosing at 10:16	10:00	13.8 *	10.1 *	1.31	59.2	
		12:10	1.9	0.2	3.15	314	25.7%
	IT dosing at 12:00	14:05	3.8	2.1	5.39	45.1	
		16:15	6	4.3	6.56	10.6	10.4%
			Time elapsed from last IT dose (h)	**Time relative to 2nd IT dose (h)**			
Patient B	First IT dosing at 00:43	9:43	9 *	-0.3	4.36	0.67	
	Second IT dosing at 10:00	11:00	11.3	1.0	3.58	487	11.4%
		13:55	13.2	3.9	5.62	58.4	12.0%
		16:10	15.5	6.2	5.27	3.19	
			Time elapsed from last IT dose (h)	**Time relative to 2nd IT dose (h)**			
Patient C	IV dosing at 10:00; IT dosing at 10:00	10:00	0	0	5.64	2.95	
		12:00	2	2	5.22	92.9	20.5%
		14:15	4.25	4.25	8.71	26.3	
		16:40	6.67	6.67	14.5	31.6	25.6%

Therapeutic Drug Monitoring of Unchanged CMS and Formed Colistin in Plasma Samples for patient A, B, and C

Human plasma (HP)							
Patient ID	**Time of CMS dose**	**Collection Time**	**Time elapsed from last IV dose (h)**	**Time elapsed from last IT dose (h)**	**Formed Colistin (µg/ml)**	**Unchanged CMS (µg/ml)**	
Patient A	IV dosing at 10:16	10:00	13.8 *	10.1 *	9.50	2.68	
		12:10	1.9	0.2	13.4	35.9	78.8%
	IT dosing at 12:00	14:05	3.8	2.1	12.1	43.7	
		16:15	6.25	4.3	12.7	16.7	79.7%
			Time elapsed from last IV dose (h)	**Time relative to 2nd IT dose (h)**			
Patient B	First IT dosing 0:43	9:43	9 *	-0.3	0.78	0.30	
	Second dosing at 10:00	11:00	11.3	1.0	0.67	2.87	79.6%
		13:55	13.2	3.9	0.66	2.05	77.1%
		16:10	15.5	6.2	0.64	1.71	
			Time elapsed from last IV dose (h)	**Time relative to 2nd IT dose (h)**			
Patient C	IV dosing at 10:00; IT dosing at 10:00	10:00	0	0	1.63	2.50	
		12:00	2	2	1.75	44.7	64.8%
		14:15	4.25	4.25	2.80	22.0	
		16:40	6.67	6.67	3.04	7.37	63.8%

*: Trough value estimates

Conclusion. Favorable concentrations of formed Colistin and CMS in CSF were achieved in 3 patients with complicated CNS infection. To the best of our knowledge, this is the first study to report the binding of Colistin in CSF in humans. A TDM method was effectively applied to demonstrate that Colistin achieves and maintains the PK/PD target (fAUC/MIC) [ratio of area under the plasma concentration curve of unbound drug to MIC] that best correlates with killing activity. Overall, our results support intraventricular polymyxins for treating DTR Gram-negative CNS infections.

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1112. Vancomycin Nephrotoxicity Relative to Alternative Antibiotic Treatments: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Session: P-62. PK/PD Studies

Background. Vancomycin is one of the most frequently prescribed antibiotics. Existing clinical evidence on vancomycin nephrotoxicity is limited to observational studies which are prone to confounding and bias. The purpose of this systematic review and meta-analysis is to compare acute kidney injury between vancomycin and comparator anti-methicillin resistant *Staphylococcus aureus* (MRSA) antibiotics using randomized controlled trial (RCT) data.

Methods. PubMed and Embase were searched for RCTs comparing intravenous vancomycin to other anti-MRSA antibiotics in adult patients, published from 1990 to January 2021. Studies were included if they reported comparative data on renal outcomes. The primary outcome was change in renal function, referred to as 'nephrotoxicity' in this study. Studies where another known nephrotoxic medication was part of study therapy in any treatment group were excluded. Eighteen studies met the inclusion criteria, and two independent reviewers assessed the risk of bias. Data on nephrotoxicity definition, comparator drug, infection type, vancomycin dosing strategy, duration of treatment, and concurrent gram-negative coverage were extracted. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

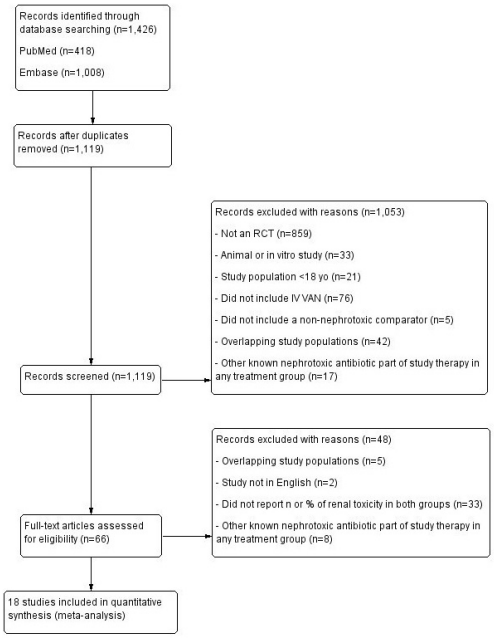

Figure 1. Flow chart of article selection.