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*

Mohamad Yasmin, MD[1]; Amir nutman, MD[2]; Steven Marshall, MS[3]; Lu Wang, PhD[4]; Ke Chen, Lab[4]; Dafna Yahav[5]; Jiping Wang, PhD[4]; Jian Li, PhD[4]; Robert A. Bonomo, MD[6]; [1]Case Western Reserve University, Cleveland, Ohio; [2]Beilinson Hospital, Tel aviv, Tel Aviv, Israel; [3]Louis Stokes Cleveland Medical Center, Cleveland, OH; [4]Monash University, Melbourne, Victoria, Australia; [5]Tel Aviv University, Rabin Medical Center; [6]Louis Stokes Cleveland VA Medical Center, Cleveland, OH

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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

Nayle Ibragimova, n/a[1]; Katherine Huynh, n/a[2]; Vanessa Ng, n/a[1]; Vionna Wong, n/a[1]; Evan J. Zasowski, PharmD, MPH[3]; [1]Touro University California, Stockton, California; [2]Touro University CA, San Jose, California; [3]Tuoro University California, Vallejo, CA

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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.

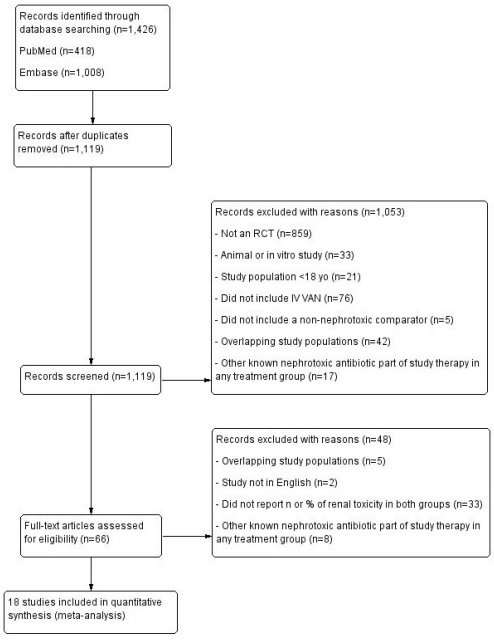

Figure 1. Flow chart of article selection.