1379. Determination of the Arbekacin Exposure Required to Prevent Amplification of Resistant Subpopulations Using Patient Pharmacokinetics Simulated in a Hollow-Fiber Infection Model (HFIM)

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Background. ME1100 (arbekacin inhalational solution) is an aminoglycoside in clinical development for the treatment of patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP and VABP, respectively). Due to the increase in resistance of *Staphylococcus aureus* and *Pseudomonas aeruginosa* to many antimicrobial agents, it is important to understand the relationships between amplification of drug resistance and each of drug exposure and therapy duration. The objective of the studies described herein was to utilize the HFIM to determine the arbekacin exposure after ME1100 administration required to prevent the emergence of drug-resistant subpopulations.

Methods. Duplicate 10-day HFIM assays were completed in which arbekacin total-drug epithelial lining fluid (ELF) concentration–time profiles following inhalational administration of ME1100 every 12 hours were simulated. Four isolates, two methicillin-resistant *S. aureus* (Arbekacin MIC = 1 mg/L), and two *P. aeruginosa* (Arbekacin MIC = 4 mg/L), were exposed to total-drug ELF area under the concentration–time curve (AUC) values ranging from 217 to 25,053 mg hour/L, which were simulated using two different half-lives, 1 hour (α) and 6.93 hours (β). The initial bacterial burden was 1.0×10^8 CFU/mL. Samples were collected for enumeration of both the total and drug-resistant bacterial burdens and evaluation of pharmacokinetic samples using LC/MS–MS.

Results. Total-drug ELF AUC:MIC ratios required to prevent amplification of MRSA and *P. aeruginosa* resistance in the HFIM over 10 days were 1,512 and 2,942, respectively. The higher AUC:MIC ratio required to prevent resistance for *P. aeruginosa* was most likely due to the presence of a small colony variant population. The relationship between total-drug ELF AUC:MIC ratio and change in $\log_{10}$ CFU from baseline of the drug-resistant sub-populations found on agar plates on Day 10 took the form of an inverted-U for three pathogens and a step-function for one (Figure 1).

Conclusion. These data, which address the goal of considering arbekacin exposures that prevent the development of on-therapy resistance in a clinical setting, will help to provide guidance for future ME1100 dose selection for the treatment of patients with HABP/VABP.

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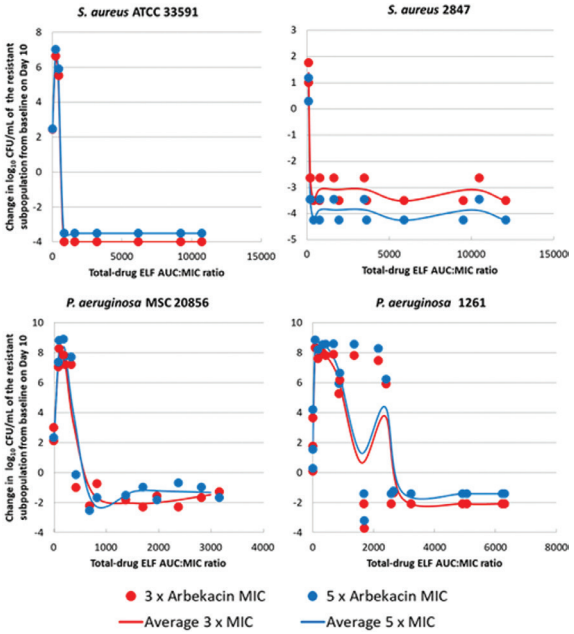
Figure 1 . Relationship between arbekacin total-drug ELF AUC:MIC ratio and change in $\log_{10}$ CFU/mL from baseline of the drug-resistant subpopulations found on agar plates supplemented with three- and five-times the arbekacin MIC on Day 10



1380. Effect of Absolute Body Weight on Clinical Outcomes of Obese Patients Treated with Cefepime

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Background. Differences in pharmacokinetic and pharmacodynamic parameters for obese (OB) patients compared with nonobese (NOB) patients are well known, but drug safety and efficacy when using package insert dosing remain unclear. The purpose of this study was to evaluate the clinical outcomes of cefepime (FEP) for OB patients vs. NOB patients.

Methods. This retrospective cohort included inpatient adults ≥18 years treated with FEP monotherapy for ≥72 hours between July 2015 and July 2017. Exclusion criteria were source control not achieved within 72 hours and polymicrobial infections requiring > 1 antibiotic for definitive therapy. Additional data collected were demographics, comorbid conditions, laboratory markers, site of infection, and microbiology. The primary endpoint was clinical treatment failure, defined as change in definitive therapy at >72 hours due to clinical worsening, leukocytosis (WBC > 10×10^9/L) for >72 hours after treatment initiation, fever (single temperature >100.9°F) after >72 hours of treatment initiation, or readmission within 30 days due to re-infection. Secondary outcomes were 30-day inpatient all-cause mortality and 30-day readmission.

Results. One hundred fourteen subjects were included (58 OB; 56 NOB). Median (IQR) age 58[46–66] years; 66(58%) males. Median [IQR] weight 107[95–124] kg OB patients; 75[63–84] kg NOB patients. Median Charlson score was 3[2–5] ($P = 0.478$). Sixty-two percent OB patients vs. 46% NOB patients experienced a respiratory infection ($P = 0.094$); 28% OB patients vs. 39% NOB patients experienced a urinary tract infection ($P = 0.185$). 62% OB patients and 59% NOB patients received FEP 1g q8h ($P = 0.732$). Most common minimum inhibitory concentration (MIC) in both groups was 1 mg/L (74% OB vs. 83% NOB; $P = 0.289$). Clinical failure occurred in 52% (67% OB vs. 36% NOB; $P = 0.001$). OB patients more likely to need a second antibiotic (31% vs. 14%; $P = 0.033$) and have persistent leukocytosis (50% vs. 30%; $P = 0.033$). Inpatient all-cause mortality occurred in 17% (22% OB vs. 12% NOB; $P = 0.164$). 72% of patients were not readmitted within 30 days of discharge.

Conclusion. OB patients experienced higher treatment failure than NOB patients. Further examination is needed to assess impact of FEP dose and organism MIC on clinical failure in OB patients.

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1381. Impact of Total Body Weight on Efficacy of Ceftriaxone in Obese Patients

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Background. Ceftriaxone (CRO), while highly protein bound, retains a small volume of distribution. Obese patients have larger volumes of distributions and higher clearance than nonobese patients. The effect of these differences on the pharmacokinetics and efficacy of CRO remain unclear.

Methods. This retrospective cohort study included adult in-patients who received CRO for ≥72 hours as definitive monotherapy from July 2015 to July 2017. Patients were excluded if there was a lack of adequate source control at 72 hours or if there was a polymicrobial infection requiring multiple antibiotics. Obesity was defined as BMI ≥30 kg/m^2. The primary outcome was clinical treatment failure, defined as changing therapy at >72 hours due to clinical worsening, leukocytosis (WBC > 10×10^9/L), fever (single temperature >100.9°F) for >72 hours, or readmission to the hospital within 30 days for re-infection. Secondary outcomes included discharge disposition and 30-day readmission.

Results. One hundred one patients were included: 39 obese patients and 62 nonobese patients. Median [IQR] age was 62 [51–70] years; 55% males. Median weight was 103 [95–120] kg in obese patients vs. 66 [58–77] kg in nonobese patients ($P < 0.001$). There were no differences in comorbidities (Charlson 3[1–5] obese vs. 2[1–4] nonobese; $P = 0.293$). Infection sources were similar: urinary tract (54% obese vs. 52% nonobese; $P = 0.827$), respiratory (28% obese vs. 23% nonobese; $P = 0.524$), bloodstream (20% obese vs. 23% nonobese; $P = 0.806$). The most common causative organism was *E. coli* (48%). There were no differences in CRO regimen between groups (1g q24h: obese 54% vs. nonobese 69%; $P = 0.115$). Treatment failure occurred in 24 (61%) obese patients compared with 25(40%) nonobese patients ($P = 0.038$). Obese patients had delayed resolution of leukocytosis (54% vs. 29%, $P = 0.013$). Eight patients died (13% obese vs. 5% nonobese; $P = 0.255$); 82% of patients were not readmitted within 30 days.

Conclusion. Obese patients treated with ceftriaxone had higher rates of treatment failure compared with nonobese patients. While not statistically significant, there was numerically higher mortality in obese patients compared with nonobese patients. Obese patients may be slow to recover from infection when treated with CRO.

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1382. Acute Kidney Injury with Piperacillin–tazobactam and Vancomycin in the Intensive Care Unit

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Background. Several recent retrospective studies have suggested that the combination of vancomycin (V) with piperacillin–tazobactam (PTZ) is associated with increased nephrotoxicity. We prospectively evaluated the outcomes of patients admitted to all of our medical and surgical intensive care units (ICU) with a normal baseline creatinine clearance (CrCl) that received vancomycin in combination with either cefepime (CEF) or PTZ to determine whether kidney injury occurs using RIFLE criteria.

Methods. ICU patients who received combinations of V with either PTZ or CEF were prospectively evaluated from June 1, 2017 to April 28, 2018 using Theradoc. V and PTZ dosing were standardized per ICU policy and monitored by clinical pharmacists. We included patients between ages 18 and 90, and receipt of >72 hours of combination antibiotic therapy. We excluded patients that were pregnant, had a hematologic malignancy, chronic kidney disease, or neuromuscular disease. Data collected included, CrCl, V troughs, dosage and length of all antibiotics used, ICU length of stay (LOS), and co-administered nephrotoxic medications (e.g., NSAIDs and IV contrast). The primary objective was to compare the incidence of AKI in these study groups, as defined by the RIFLE criteria.

Results. Of 233 patients evaluated, 58 (25%) met inclusion criteria, 45 received PTZ-V and 13 CEF-V. Only eight of 58 (14%) MRSA-positive culture.

Table 1: Data Summary

	PTZ-V	CEF-V	*P*-value
Age (median, range)	58 (35–84)	64 (18–79)	0.54
Gender (male)	30 (67%)	7 (54%)	0.51
Median weight (kg)	86 (54–136)	82.4 (51–156)	0.6
No > 100 kg	11 (24%)	3 (23%)	1
No V trough >20	2 (4%)	1 (8%)	0.6
Median V trough(range)	11.4 (5.4–32.7)	10.6 (6.4–29.5)	0.695
Median V days (range)	5 (3–16)	4 (3–13)	0.99
Co-admin nephrotoxic agent	41 (91%)	11 (85%)	0.61
ICU LOS	11 (4–36)	14 (3–32)	0.35
Hospital LOS	15 (4–36)	20 (6–72)	0.037
No. AKI by RIFLE	13	0	0.028

We found no correlation with co-administered nephrotoxic agents, vancomycin troughs, or body weight and AKI.

Conclusion. Our prospective observational study data revealed significant AKI with PTZ-V compared with CEF-V but it did not impact patient long-term outcomes. Caution with PTZ-V may be required when used in ICU settings even in patients with normal baseline CrCl.

Disclosures. **J. S. Lewis II**, Merck: Consultant, Consulting fee.

1383. *In vivo* Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of NOSO-502, a First-in-Class Odilorhabdin Antibiotic, Against *E. coli* (EC) and *K. pneumoniae* (KPN) in the Murine Neutropenic Thigh Model

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Background. NOSO-502 is a novel, first-in-class Odilorhabdin antibiotic targeting bacterial protein translation, with potent *in vitro* activity against *Enterobacteriaceae* including strains with MDR or CRE-phenotype. The goal of this study was to determine the PK/PD characteristics of NOSO-502 using the murine thigh infection model against a diverse group of EC and KPN strains.

Methods. Twelve strains (6 EC, 6 KPN) were utilized, including those with tetracycline or β-lactam resistance. MICs were determined by CLSI Methods. Single dose murine plasma PK of NOSO-502 was determined after administration of 7.81, 31.25, 125 and 500 mg/kg by SC route. Dose fractionation (DF) study was used to determine which PK/PD index was associated with efficacy. The relationship between each PK/PD indices and CFU outcome data were analyzed using the sigmoid Emax (Hill) model with nonlinear regression. Treatment studies were then performed with the remaining 11 strains. Four-fold increasing NOSO-502 doses (3.91–1,000 mg/kg/6 hours SC route) were administered. Treatment data and AUC/MIC was analyzed to determine AUC/MIC targets associated with net stasis and 1-log kill (when achieved) for all strains.

Results. MICs ranged from 1 to 4 mg/L. PK ranges for doses included: Cmax 1.5–85 mg/L, $AUC_{0-\infty}$ 1.9–352 mg hour/L, T1/2 0.4–1.1 hour. DF regression analysis: AUC/MIC R^2 0.86, Cmax/MIC R^2 0.70, $T >$ MIC R^2 0.77. Against each of the 12 strains there was dose-dependent activity and net stasis was achieved against all strains, with maximal activity of 1–2 log killing in EC and almost 3 log killing in KPN. The 24 hours stasis total and free drug PD targets are shown (table). 1-log kill targets were determined for KPN and noted at a median 24 hours fAUC/MIC of 11.

		24 hours Static Dose (mg/kg)	Stasis tAUC/MIC	Stasis fAUC/MIC
EC	Mean	374	53	10
	Median	409	59	12
	SD	182	32	6.3
KPN	Mean	81	21	4.2
	Median	56	9.1	1.8
	SD	56	24	4.7

Conclusion. NOSO-502 demonstrated in vivo potency against a diverse group of EC and KPN strains including those with resistance to tetracycline and β-lactams. The PK/PD index predictive of efficacy is AUC/MIC. Stasis 24 hours AUC/MIC targets were numerically low for KPN and EC. This data suggest that NOSO-502 is a promising novel agent and these targets will provide a basis for developing human dosing regimens to optimize efficacy.

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1384. RSV Monoclonal Antibody (MK-1654) Phase 1 Pharmacokinetics (PK) in Healthy Adults and Population PK Modeling to Support Pediatric Development

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Background. Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection and hospitalization in infants. MK-1654 is a monoclonal antibody (mAb) being developed to prevent RSV infection in infants and is undergoing evaluation in a Phase 1 study. Incorporation of YTE mutations extend its half-life to allow for dosing once every RSV season. Preliminary Phase 1 PK results and the development of a population PK model that characterizes adult PK to predict pediatric exposures are presented here.

Methods. In this double-blinded Phase 1 study, 152 healthy males and females of nonchildbearing potential aged 19–59 years were randomized in a 3:1 ratio to receive a single dose of MK-1654 or placebo as a bolus intramuscular injection (IM) or in an intravenous infusion (IV) over 2.5 hours. Dose levels included 100 mg IM, 300 mg IM, 300 mg IV, 1,000 mg IV and 3,000 mg IV. Serial serum samples were collected to measure MK-1654 PK via a validated LC/MS assay. A noncompartmental PK analysis was conducted using preliminary data from 60 subjects up to Day 150 (900 observations). A population PK model was developed to simultaneously characterize the IM and IV adult PK data and to predict pediatric PK through allometric scaling. Pediatric MK-1654 PK was predicted for several IM doses for a typical sized infant (35 weeks gestational age at birth; 4 months chronological age at dosing; 50th percentile weight).

Results. In adults, the median time to maximum concentration observed was ~6–10 days following IM injection. The apparent half-life of MK-1654 ranged from ~70–85 days after either IM or IV doses. The estimated IM bioavailability was ~71%. C_{max} and $AUC_{0\text{-}90\ days}$ increased dose proportionally following IV administration. MK-1654 adult PK was best characterized using a two-compartment model with first-order elimination. IM absorption was described using a first-order rate constant with lag time. Inter-individual variability was included for clearance (CL and Q), central volume (V2), and absorption rate (Ka). The pediatric model suggested apparent terminal half-life in a typical infant is shorter than adults, likely being driven by infant growth during treatment.

Conclusion. Predicted infant PK profiles support further development of MK-1654 in children.

Figure 1: Mean ± Standard Deviation Serum Concentration-Time Profiles in Healthy Adults (n=12/panel) Following a Single Dose of MK-1654