

and no accumulation was observed. The data support evaluation of repeat dose administration in virally infected patients.

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1422. Comparative Monte-Carlo Analysis of Aztreonam-Avibactam vs. Ceftazidime-Avibactam Against Carbapenem-Resistant Gram-Negative Pathogens

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Background. The new β -lactamase inhibitor, avibactam (AVI), has recently been combined with ceftazidime (CAZ) as CAZ-AVI. AVI is also in Phase 3 clinical trials combined with aztreonam as ATM-AVI. Both drug combinations have similar *in vitro* activity against some organisms, but ATM-AVI is more potent against metallo- β -lactamase (MBL) producing organisms. However, against *P. aeruginosa* (PA), CAZ-AVI is more potent. Since these compounds have similar pharmacokinetic (PK)/pharmacodynamic (PD) profiles, and there is a need for drugs for the treatment of resistant microorganisms, a Monte-Carlo analysis (MCA) was used to assess their potential efficacy against carbapenem-resistant pathogens.

Methods. MCA ($n = 10,000$) was performed for ATM-AVI and CAZ-AVI using PK parameters, CrCl vs. CL regression, PD targets, and recent MICs from peer-reviewed literature against five carbapenem-resistant (CR) organisms: *P. aeruginosa* (CR-PA), *E. cloacae* (CR-EC), *K. pneumoniae* (CR-KP), Enterobacteriaceae (CR-ENT), and MBL producing Enterobacteriaceae (MBL-ENT). Only MIC studies that directly evaluated both combinations were utilized. Our institution's inpatient CrCl distribution (range: 10–120 mL/minute) was used to assess drug clearance. The ATM-AVI regimen was 1.5 g q6h with a 3 hours infusion and adjusted for renal function) and the CAZ-AVI regimen was 2 g q8h with a 2-hour infusion and adjusted for renal function). PD targets (% $_{FT}$ >MIC) for ATM-AVI were 40 and 60% and for CAZ-AVI were 40 and 70%.

Results. Target attainment (TA%) for each regimen and organism was:

Drug	ATM-AVI		CAZ-AVI	
	1.5 g q6h (3h infusion)		2 g q8h (2h infusion)	
Regimen				
$_{FT}$ >MIC (% of interval)	40	60	40	70
CR-PA	48	43	93	87
CR-EC	100	100	100	100
CR-KP	100	100	100	100
CR-ENT	100	100	96	96
MBL-ENT	100	99	2	2

Conclusion. Both ATM-AVI and CAZ-AVI displayed very high TA% (>95%) for CR-EC, CR-KP, and CR-ENT at both PD targets. However, TA% for MBL-ENT was very low for CAZ-AVI and $\geq 99\%$ for ATM-AVI. Against CR-PA, CAZ-AVI was had much higher TA% than ATM-AVI (87–93% vs. 43–48%). These differences suggest different roles for each drug combination in clinical practice.

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1423. Plasma and Intrapulmonary Pharmacokinetics of Sitafloxacin in Thai Critically Ill Patients With Pneumonia

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Background. Pneumonia is a major cause of mortality in critically ill patients. Sitafloxacin, broad-spectrum fluoroquinolone, has an *in vitro* activity against many drug-resistant pathogens causing pneumonia. The objectives of this study were to determine epithelial lining fluid (ELF) concentrations of sitafloxacin and compare those with plasma, including pharmacokinetic (PK) parameters in Thai critically ill patients.

Methods. Sitafloxacin concentrations were determined using LC-MS/MS assay. Twelve critically ill patients with pneumonia were enrolled to receive oral sitafloxacin 200 mg single dose. Serial blood samples were collected in each patient (seven time points) prior to dose and over 12-hour interval. BAL samples were collected once in each patient simultaneously with plasma sampling. Intrapulmonary penetration was evaluated as the ELF to unbound plasma concentration ratio calculated by fraction unbound related to albumin concentration in each patient. A compartment model was applied to describe plasma PK parameters using WinNonLin software.

Results. The median age was 57 years with median weight was 52 kg. The highest penetration ratio of ELF to unbound plasma concentrations based on median value

was 1.3, observed during 5–6 hours (Table 1). The data fitted to one-compartment model that described absorption, distribution and elimination. PK parameters are presented in Table 2.

Conclusion. Oral sitafloxacin well penetrate into ELF at a penetration ratio of 130% related to unbound plasma in Thai critically ill patients. Sitafloxacin is a promising agent for treatment of lower respiratory tract infections caused by susceptible pathogens in intensive care unit.

Table 1: Penetration Ratio Based on Median of Sitafloxacin Concentrations in Each Sampling Time

BAL Fluid Sampling Time (hour)	Sample (n)	ELF Conc. (μ g/mL)	Unbound Plasma Conc. (μ g/mL)	Ratio ELF: Unbound Plasma	Penetration (%)
0.5 - 2	3	0.09	0.29	0.3	30
3 - 4	3	0.50	0.91	0.5	50
5-6	3	0.84	0.64	1.3	130
7-9	3	0.22	0.42	0.5	50

Table 2: PK parameters of sitafloxacin 200 mg single dose based on the median values (min–max).

PK Parameters	Plasma	ELF
$T_{1/2}$ (h)	3.7 (1–8)	5.5
C_{max} (μ g/mL)	1.5 (0.48–1.82)	0.84
K_{el} (h^{-1})	10.84 (3.64–48.49)	NA
CL/F (mL/minute)	221.62 (45.13–533.22)	NA
V/F (L)	148.92 (100.88–361.81)	NA
AUC ₀₋₁₂ (μ g-hour/mL)	10.84 (3.64–48.49)	NA

K_{el} , absorption rate constant; NA, not applicable.

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1424. Examining the Relationship Between Vancomycin Area Under the Concentration–Time Curve and Serum Trough Levels in Adults with Presumed or Documented Staphylococcal Infections

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Background. Recent studies evaluating area under the concentration–time curve (AUC)-guided vancomycin dosing have reported reduced drug exposure and nephrotoxicity as compared with traditional trough-guided (target 15–20 mg/L) dosing for invasive infections, but studies exploring the relationship between vancomycin trough concentration and AUC remain limited.

Methods. This was a retrospective observational study performed at two hospitals within a large health system. Patients receiving AUC-guided vancomycin dosing for a presumed or confirmed invasive staphylococcal infection between December 1, 2016 and July 31, 2017 were evaluated. Two steady-state serum vancomycin levels were obtained in each patient and used to determine the 24-hour AUC/MIC ratio; the AUC/MIC target was >600 mg/L hour for endocarditis and >400 mg/L hour for all other sources. The relationship between trough and AUC was explored using the Pearson product-moment correlation coefficient. Patient demographics and dosing details were also collected.

Results. Thirty-four patients were included in the study, with two patients having vancomycin levels drawn twice (36 sets of levels). Most patients were located in an ICU (91.2%) and 85.3% of patients had bacteremia, pneumonia or endocarditis. An organism was recovered from 28 patients (82.3%) of which 21 (75%) had a vancomycin MIC of 1 mg/L and 25 were *S. aureus* (89.3%). The mean vancomycin trough was 16.6 ± 6.1 mg/L and the mean AUC/MIC was 588 ± 156 mg/L hour. There was a strong correlation between vancomycin trough and 24-hour AUC ($R^2 = 0.731$; $P < 0.001$; Figure 1). The rate of 24-hour vancomycin AUC/MIC target attainment was 91.2% ($n = 31/34$). Among patients with a trough >9 mg/L, 100% ($n = 33$) achieved AUC/MIC values >400 mg/L hour and 94% were >500 mg/L hour.

Conclusion. Targeting a vancomycin trough between 15 and 20 mg/L frequently results in an AUC/MIC in excess of the target identified for efficacy. Considering the strong correlation observed between trough and AUC alongside practical challenges associated with wide-scale implementation of AUC monitoring, a reduced target trough in conjunction with targeted application of AUC-guided dosing warrants further evaluation.