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

Disclosures. **O. Naderer**, Chimerix: Employee, Salary. **V. Schuck**, Chimerix: Research Contractor, Consulting fee. **M. Morrison**, Chimerix: Employee, Salary. **M. Anderson**, Chimerix: Employee, Salary. **T. Arumugham**, Chimerix: Employee, Salary. **J. Dunn**, Chimerix: Employee, Salary.

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	
Regimen	1.5 g q6h (3h infusion)		2 g q8h (2h infusion)	
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 ≥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.

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

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

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Session: 145. PK/PD Studies

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Background. Pneumonia is a major cause of mortality in critically ill patients. Sitafloxacin, broad-spectrum fluoroquuinolone, 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. (μg/mL)	Unbound Plasma Conc. (μg/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_{max} (h)	3.7 (1–8)	5.5
C_{max} (μg/mL)	1.5 (0.48–1.82)	0.84
K_a (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} (μg·hour/mL)	10.84 (3.64–48.49)	NA

K_a, absorption rate constant; NA, not applicable.

Disclosures. **T. Paiboonvong**, Daiichi Sankyo (Thailand) LTD.: Grant support, Research support. **V. Tangsujaritvijit**, Ramathibodi Hospital: Grant support, Research support.

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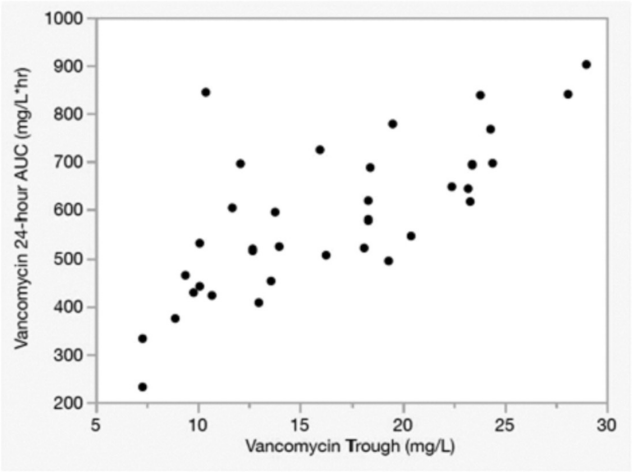
Background. Recent studies evaluating area under the concentration–time curve (AUC)-guided vancomycin dosing have reported reduced drug exposure and nephrotoxicity as compared with traditional trough-guided (target 15–20 mg/L) dosing for invasive infections, but studies exploring the relationship between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

Figure 1. Relationship between 24-hour vancomycin AUC and serum trough.



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

1425. Population Pharmacokinetic Analysis of Ciprofloxacin and Levofloxacin in Critically Ill Trauma, Surgical, and Burn Patients

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Background. Antibiotic pharmacokinetics (PK) differ between critically ill and noncritically ill patients, as do the bacteria causing infection, yet dosing regimens are derived from noncritically ill populations. The purpose of this study was to examine the adequacy of ciprofloxacin and levofloxacin dosing in critically ill trauma, surgery, and burn patients for treating common nosocomial pathogens.

Methods. Time–concentration curves derived from plasma samples in critically ill patients receiving ciprofloxacin 400 mg IV q12h ($N = 11$) or q8h ($N = 5$) or levofloxacin 750 mg IV q24h ($N = 9$) were used to calculate individual PK parameters and create population PK models. Monte-Carlo simulations were performed to assess the cumulative fraction of response (CFR) to achieve the target pharmacodynamic index (PDI) of AUC:MIC ≥ 125, using Gram-negative MIC distributions from the European Committee on Antimicrobial Susceptibility Testing.

Results. The fit of both the ciprofloxacin and levofloxacin population models was improved with the addition of CrCl as a covariate. Despite simulating higher dosing regimens, such as ciprofloxacin 600 mg q8h and 800 mg q8h and levofloxacin 1,125 mg q24h and 1,500 mg q24h, only a single dosing regimen/Gram-negative species combination demonstrated a CFR ≥90%. This result was consistent with the finding that the maximum MICs at which individual patients achieved the target PDI were well below the CLSI breakpoints of ciprofloxacin and levofloxacin for *Enterobacteriaceae*, *Pseudomonas*, and *Acinetobacter* of ≤1 and ≤2 mg/mL, respectively.

Conclusion. In critically ill trauma, surgical, and burn patients, standard dosing regimens of ciprofloxacin and levofloxacin failed to achieve PDIs sufficient to treat optimally *Enterobacteriaceae*, *Pseudomonas*, and *Acinetobacter* isolates with MICs up to the CLSI breakpoints. When increased doses were simulated, the CFR of all but one dose/species combination remained suboptimal. Individualized dosing guided by therapeutic drug monitoring may be an appropriate next step to improve fluoroquinolone efficacy in these critically ill patients.

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

1426. Impact of Routine Pediatric PCV13 on the Incidence and Severity of Invasive Pneumococcal Disease in Adults in Ontario, Canada

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Session: 146. Pneumococcal Vaccines
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Background. Monitoring the incidence and severity of disease due to varied pneumococcal (Pn) serotypes (STs) over time is important in assessing the benefit of Pn vaccines. We describe changes in adult IPD after the 2010 introduction of routine infant PCV13 in Ontario, Canada (PCV13 is funded only for immunocompromised adults ≥50 years as of 2015).

Methods. TIBDN has conducted population-based surveillance for IPD in Toronto/Peel, Canada (pop 4.3M) since 1995. Cases are reported to a central office; one isolate/case is serotyped. Demographic and clinical data are collected by chart review and patient/family physician interview.

Results. Of 6,275 episodes of adult IPD, 5,674 (90%) have STs and 6,007 (96%) detailed clinical data. Incidence of IPD decreased from 14.2/100,000/year in 1995 to 6.0/100,000/year in 2013–2017). One thousand two hundred and three (19%) adults with IPD were 15–44 years, 1,889 (30%) were 45–64 years, 3,182 (51%) ≥65 years. Figures 1 and 2 show rates over time by ST group and age. In multivariable analyses, there was no difference across vaccine ST groups (nonvaccine type (NVT) vs. PPV23 not PCV vs. PCV13) in patient age, proportion with ICU admission, requirement for mechanical ventilation (MV), death, length of stay (LOS) or diagnosis of meningitis, except that patients with NVT isolates were more likely to require ICU admission (OR 1.5, 95% CI 1.2,2.0), and to have meningitis (OR 1.9, 95% CI 1.1,3.3). Case fatality declined from 25% (480/1,949) 1995–2001 to 19% (148/763) in 2012–2017 (multivariable OR/year 0.98 95% CI 0.97,0.99); requirements for ICU admission (26–31%; OR/year 1.02, 95% CI 1.01,1.03) and MV (OR/year 18–22%; 1.02, 95% CI 1.01–1.03) increased, LOS did not change. From 2013 to 2017, the distribution of vaccine group STs has not changed: 37% PCV13 (383/1,031); 20% PCV20not13 (205); 9% PPV23not 20 (94), 34% NVT (349). NVT strains include over 23 ST, most commonly 23A (72, 21%), 15A (46, 13%), 35B (37,11%), 6C (36, 10%), 23B (20, 8%).

Conclusion. In our population, with infant but no routine adult PCV13, the incidence of adult IPD appears to have stabilized, with PCV13 ST strains contributing 37% of IPD. Case fatality has decreased; ICU admission increased. Adult vaccination may be required to further reduce PCV13 ST infections.

Figure 1: IPD incidence, adults 15–65 years, by ST group, 2006–2017. Infant PCV7 started 2005 and PCV13 in 2010.

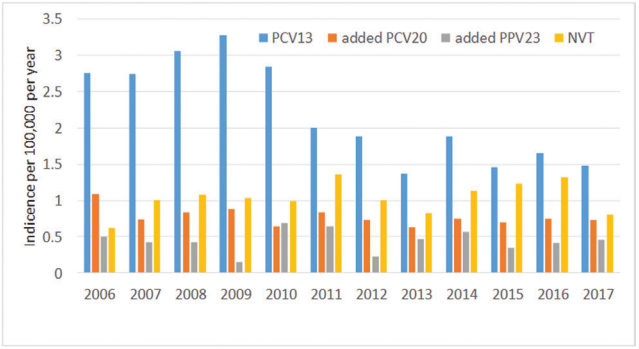
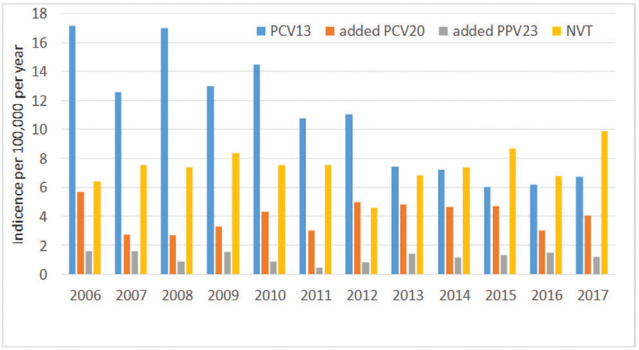


Figure 1. IPD incidence, adults ≥65 years, by ST group, 2006–2017. Infant PCV7 started 2005 and PCV13 in 2010.



Disclosures. **A. McGeer**, Pfizer: Grant Investigator and Scientific Advisor, Research grant and Research support; Merck: Scientific Advisor, Research support; GlaxoSmithKline: Grant Investigator and Scientific Advisor, Research support.

1427. A Dynamic Modeling Study of the Effect of Introducing a New Higher Valent Pneumococcal Conjugate Vaccine in a Paediatric Population in the United States

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Session: 146. Pneumococcal Vaccines
Friday, October 5, 2018: 12:30 PM

Background. Routine use of pneumococcal conjugate vaccines (PCVs) in young children has substantially reduced vaccine-type invasive pneumococcal disease (IPD) in the United States and Europe. However, increases in disease and colonization caused by nonvaccine serotypes have been observed, suggesting the need for new PCVs with