be critical to prevent attachment of pathogen. BF production increased or remained unchanged in the presence of amikacin. Due to toxicity concerns and variation in resistance patterns, minocycline is a viable treatment option against A. baumannii.

**Disclosures.** Multidrug-resistant A. baumannii, S. maltophilia, and B. cepacia have been identified as priority organisms of infectious diseases and as important causes of refractory pneumonia. These three pathogens require urgent attention for development of new therapeutic options. However, few if any novel antibacterial antibiotics against these organisms are available. In order to understand the impact of minocycline dose on plasma and tissue distribution, we conducted a detailed pharmacokinetic study in rabbits.

**Methods.** NZW rabbits received a single dose of minocycline as an IV infusion with serial plasma sampling over 24 hours. During the second stage, minocycline was administered Q12h for 6 days at 6, 12, 24, 48, or 96 mg/kg with serial plasma sampling and tissue recovery on day 7. Plasma and tissue concentrations were determined by LC/MS/MS. Minocycline pharmacokinetic parameters were estimated using standard non-compartmental methods.

**Results.**

| Minocycline dose (mg/kg) | Cmax (ug/mL) | CL (L/hour/kg) | Vss (L/kg) |
|-------------------------|--------------|----------------|-----------|
| 6                       | 26.9 ± 2.0   | 20.9 ± 2.1     | 226.3 ± 19.2 |
| 12                      | 64.5 ± 5.2   | 44.2 ± 7.3     | 197.8 ± 16.1 |
| 24                      | 211.0 ± 21.7 | 119.7 ± 15.5   | 116.4 ± 10.8 |
| 48                      | 660.7 ± 59.5 | 296.0 ± 33.9   | 74.2 ± 6.4   |
| 96                      | 1228.2 ± 106.1 | 369.7 ± 75.6 | 78.7 ± 6.6   |

The data show that minocycline tissue exposures increased with increasing minocycline doses and minocycline plasma levels increased in a dose-proportional manner. Minocycline was highly distributed in tissues and body fluids including choroid, epithelial lining fluid, alveolar macrophages, vitreous and aqueous humor, and CSF.

**Conclusion.** These data suggest that administration of minocycline in rabbits should produce levels of drug that would be active against target organisms in plasma, tissues, and other body fluids.

**Disclosures.** T. G. Nolan, The Medicines Company: Employee, Salary. D. C. Griffith, The Medicines Company: Employee, Salary. M. N. Dudley, The Medicines Company: Employee, Salary. T. J. Walsh, Astellas, Actavis, Contrafect, Drais, iCo Novartis, Methylene, Pfizer, Sigma-Tau: Consultant, Consulting fee. Astellas, Actavis, Merck, Novartis, Pfizer, Schreiner, Tetraphase, The Medicines Company: Theravance Grant Investigator, Research grant.

805. Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of Dalbavancin Alone and in Combination with Ceftriaxone against Methicillin-Resistant Strains (MRSA) of Staphylococcus aureus Razieh Kebrizai, PhD1 and Michael J. Rybak, PharmD, MPH, PhD2; 1Antiinfective Research Laboratory, Department of Pharmacy Practice, Wayne State University, Eugene Applebaum College of Pharmacy & Health Sciences, Detroit, Michigan; 2Anti-Infective Research Laboratory, Department of Pharmacy Practice, Wayne State University, Eugene Applebaum College of Pharmacy & Health Sciences, Detroit, Michigan.

**Session.** Use of PK/PD to optimize existing antibiotics and antifungals Thursday, October 5, 2017: 12:30 PM

**Background.** Glycopeptide antibiotics, principally vancomycin, have been the first armamentarium against MRSA. However, Staphylococcus aureus strains have now developed reduced susceptibility to common glycopeptides. (DAL) is a novel, 2nd generation lipoglycopeptide antibiotic with reported activity against Gram-positive bacterial pathogens, including MRSA. The long bioplateau lateral chain in DALs structure extends its half-life and promotes its anchoring to the cell membrane (vancomycin lacks this side chain). While a considerable amount of data is available on susceptibility testing for this agent, information regarding the potential for synergy with β-lactams with newer lipoglycopeptides, including dalbavancin, is lacking. Our objective was to evaluate the impact of DAL or vancomycin (VAN) in combination with ceftriaxone (CPT) against MRSA.

**Methods.** MRSA 494 was studied in six different regimens independently. All the experiments were performed in one-compartment PK/PD models in duplicate during 7 days. DAL 1.500 mg day one Cmax = 30.1 µg/mL, VAN 2 q12h Cmax = 36 µg/mL. CPT 600 mg every 12 hours Cmax = 17.04 µg/mL. DAL 1.500 mg day 1 plus CPT 400 mg q12h, VAN 2 q 12h plus Cefalotin 600 mg q12h and Growth Control. Antibiotic carry over was accounted for by washing and centrifugation of the samples. Model samples were plated and counted using an automated colony counter and differences in log10 CFU/mL between regimens was evaluated.

**Results.** Combination of DAL + CPT offered a significant reduction in log10 CFU/mL amounts (more than 5 log10 CFU/mL and up to detection limits) in 24 hours compared with CPT alone. CPT alone demonstrated bactericidal activity with a reduction in log10 CFU/mL, 32 hours although regrowth with resistance was observed 36-72 hours. Mean CFU/mL for DAL models reached detection limits in 72 hours and no regrowth was detected after this time.

**Conclusion.** Combination of DAL + ceftriaxone offers encouraging results for MRSA strain 494. This combination therapy can potentially lead to optimizing patient outcomes and preserving dalbavancin therapy for serious MRSA infections through utilization of ideal combinations and dose exposures.

**Disclosures.** J. M. Rybak, Allergen: Scientific Advisor, Consulting fee.
6.6 hours

Statistic

2.00 (1.00 – 2.00)

6835 (1330)

-1034 (456)

32.62 (1.439)

Allergan: Employee, Salary.

13149 (3252)

2.00 (1.00 – 4.00)

576 (151)

Background. While well-recognized that clearance of bacterial infections occurs through a collaboration between antibiotics and the immune system, existing strategies for evaluating optimal antibiotic treatment regimens, including pharmacodynamic/pharmacokinetic assessments and mathematical/computer simulation models, have been limited in their consideration of the immune response and variations therein.

Methods. This study develops a within-host mathematical model of an acute, potentially self-limiting bacterial infection and utilizes it to explore antibiotic dose regimens under conditions of varying immune response efficacy by comparing a normal response that would clear the infection to: (i) a hypoactive/suppressed, and (ii) a hyperactive/dysfunctional immune response, to examine how different regimens affect time to clearance of the infection, as well as de novo generation of antibiotic-resistant populations. Simulations of existing antibiotic regimens and new regimens are then performed.

Results. Numerical analyses of the model demonstrate that there are threshold antibiotic doses required to mitigate the immunologic deficits of the abnormally immune responses to allow for clearance of the infection and decrease the likelihood of resistance evolving. Treating with low doses fosters the generation of high-level antibiotic-resistant populations at all levels of immune efficacy. However, more moderate dosing regimens can slow the rate of ascent of pre-existing-resistant populations, particularly when immune responses are suboptimal.

Conclusion. This study demonstrates the effect of variations in immune response on optimal antibiotic treatment regimens that maximize rate of infection clearance and minimize the likelihood of resistance evolution in acute, potentially self-limiting infections. It illustrates the importance of incorporating quantitative immunological assessments into evaluations of antibiotic treatment regimens.

Disclosures. All authors: No reported disclosures.

808. Multiple Ascending Dose Safety, Tolerability, and Pharmacokinetics of KBP-7072, a Novel Third-generation Tetracycline

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Session: 77. Use of PK/PD to optimize existing antibiotics and antifungals

Background. KBP-7072 is a novel aminomethylcycline exhibiting broad-spectrum antibiotic activity against Gram- and Gram- resistant bacterial isolates and strains. KBP-7072 has previously been studied in a single ascending dose study up to 300 mg in healthy adults.

Methods. This was a randomized, single-blind, placebo-controlled, sequential parallel-group study. Multiple ascending dose study to evaluate the safety, tolerability, and pharmacokinetics (PK) of KBP-7072 in healthy adults. Four cohorts were planned with 8 subjects (6 KBP-7072, 2 placebo) in each cohort to evaluate KBP-7072 100 mg QD, 200 mg QD, 300 mg QD, and 200 mg BID for 10 days. Dose escalation stopped following completion of the 200 mg QD cohort. Safety, tolerability, and PK were evaluated for each cohort.

Results. 16 subjects (male: 87.5%; 18–55 years of age) were enrolled including 8 KBP-7072, 2 placebo) in each cohort to evaluate KBP-7072 100 mg QD, 200 mg QD, 300 mg QD, and 200 mg BID for 10 days. Dose escalation stopped following completion of the 200 mg QD cohort. Safety, tolerability, and PK were evaluated for each cohort.

Conclusion. This study demonstrated that KBP-7072 was safe and generally well-tolerated at doses up to and including 200 mg QD.

Disclosures. F. Yang, KBP Biosciences Co., Ltd.: Employee, Salary. Y. Wang, KBP Biosciences USA Inc.: Employee, Salary. P. Wang, KBP Biosciences Co., Ltd.: Employee, Salary. M. Hong, KBP Biosciences: Employee, Salary. Y. Bern, KBP Biosciences USA Inc.: Employee, Salary.

809. Evaluation of Vancomycin Dosing in Intravenous Drug Users Admitted to an Internal Medicine Service

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Session: 77. Use of PK/PD to optimize existing antibiotics and antifungals

Background. Vancomycin clearance can be enhanced in intravenous drug users (IVDUs) with otherwise normal renal function, creating the potential for subtherapeutic exposure with standard dosing schemes. The aim of this project was to describe vancomycin target trough attainment rates in non-critically ill IVDUs.

Methods. This was a retrospective chart review of adult IVDUs admitted to the internal medicine service at University of Utah Health from July 1, 2014 to November 30, 2016. Included patients had an estimated creatinine clearance (CrCl) >60 mL/minute (Cockcroft-Gault), and had at least one steady-state vancomycin trough concentration obtained on a consistent dosing regimen. A target vancomycin trough concentration was defined as 15–20 mg/L. Nephrotoxic events were defined as an increase in serum creatinine by 0.5 mg/dL or 25% or ≥3 days of therapy. For patients with multiple vancomycin concentrations obtained within a dosing interval, concentrations were fit to a one-compartment open model to estimate pharmacokinetic (PK) parameters.

Results. Forty-seven patients were included. The median (IQR) age was 40 years (32–50). The median (IQR) estimated CrCl was 112 mL/minute (90–141 mL/minute). Heroin (88%) and methamphetamine (43%) were the most commonly reported drugs of abuse, and 37 (79%) patients were treated for skin and soft-tissue infections. Forty-five patients (96%) received vancomycin loading doses. The median (IQR) vancomycin loading dose and maintenance regimen was 20.7 mg/kg (19.5–22.4 mg/kg) and 15.2 mg/kg (14.8–17.1 mg/kg) every 12 hours. Forty-four patients (94%) had vancomycin trough concentrations <15 mg/L with their initial regimens. The median (IQR) initial trough concentration was 7.1 mg/L (5.5–10.7 mg/L). No nephrotoxic events were observed. Vancomycin PK parameters were able to be estimated for one patient and are reported in Table 1.

Table 1: Estimated Vancomycin Pharmacokinetic Parameters

| Parameter | Value |
|-----------|-------|
| Clearance | 75 L/hours |
| Volume of Distribution | 715 L |
| Half-life | 6.6 hours |

Conclusion. Vancomycin trough concentrations were frequently below guideline-based effectiveness targets in this cohort of IVDUs. Additional studies assessing alternative dosing or monitoring schemes for vancomycin in this population are warranted.

Disclosures. R. Benefield, Merck: Grant Investigator, Research grant

810. Pharmacokinetics of Daptomycin in Pediatric Intensive Care Patients

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Session: 77. Use of PK/PD to optimize existing antibiotics and antifungals

Background. Daptomycin is a lipopeptide agent active against Gram-positive microorganisms, including methillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. To date, only single dose pharmacokinetics (PK) has been studied in children. We studied multiple dose PK of daptomycin administered as salvage therapy in critically ill pediatric patients.

Methods. Patients hospitalized in 2 pediatric intensive care units from June 2014 to December 2016, who received daptomycin for infections caused by Gram-positive organisms not responding or intolerant to conventional antimicrobial agents and had normal renal function, were eligible for the study. Daptomycin was administered as 30-minute infusion dissolved in 50 mL normal saline at doses decided by the treating physicians. Blood samples were collected immediately before and 30, 60, 90, 120, 240, and 360 minutes after the end of First and Fifth dose. Plasma concentrations of daptomycin were determined with ultra performance liquid chromatography. An individual