800. Improving Definitive Therapy Among Patients with Methicillin-resistant Staphylococcus aureus Bloodstream Infections: Predictors of Early Therapeutic Switch to Linezolid or Daptomycin

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Session: 76. Treatment of Resistant Infections - Clinical Analyses
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Background. Vancomycin is a first-line antibiotic for treating methicillin-resistant S. aureus bloodstream infections (MRSA BSI), due to its activity against MRSA and low cost. If vancomycin fails, patients are often switched to daptomycin or linezolid. We aimed to determine predictors for switching from vancomycin to daptomycin or linezolid. Close follow-up and early identification of patients who may benefit from these newer antibiotics could improve outcomes.

Methods. Retrospective cohort study of all Veteran patients with MRSA BSI who began therapy on vancomycin from 2007 to 2014. Patients were followed for 30 days. Potential predictors of switching measured at the time of admission included demographic, diagnoses, and comorbidities. Co-infections were defined using ICD-9 codes. Additional predictors were time-varying during index admission, including; therapeutic level of vancomycin (defined as 24-hour area under concentration-time-curve to minimum inhibitory concentration [AUC/MIC] > 400), duration of neutropenia prior to the diagnosis of bacteremia (< vs. > 10 days), severity of illness (ICU vs. < ICU), initial isolation of potential resistant organisms (≤ 0.5 = none).

Results. 34 cases of DNSE and 65 cases of VRE were identified. There were no cases of VRE BSI. The DNSE cohort had longer periods of neutropenia prior to the diagnosis of bacteremia (median 32.1 days vs. 19.3 days, OR 1.85 95% CI (0.75-1.60)). Patients with DNSE had a longer time interval to initiation of appropriate antibiotics (median 3.5 days vs. 2.0 days, P = 0.01). There were similar rates of bone marrow transplantation (53% of DNSE vs. 51% of VRE), however, DNSE cases were more likely to develop graft vs. host disease [OR 3.65% 95% CI (1.07-12.38)]. In the 90-day period prior to bacteremia, daptomycin exposure occurred in only 12 (35.3%) of DNSE cases vs. 1 (1.5%) VRE case [OR 34.8% 95% CI (4.3-284.1)]. Median lengths of stay (LOS) were similarly high in both groups, however, DNSE patients were more likely to have a LOS over 50 days as compared with VRE (P = 0.048). 30-day mortality in the DNSE cohort was 50% compared with 38% in the VRE group (P = 0.12).

Conclusion. In a retrospective study, the 30-day mortality associated with DNSE bacteremia was 50%. Infection prevention interventions targeting this particular multi-drug-resistant organism are warranted in this vulnerable population.

Disclosures. All authors: No reported disclosures.

802. Evaluation of telavancin dose capping in a large community hospital
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Background. Telavancin is a bactericidal lipoglycopeptide treat susceptible Gram-positive pathogens including Methicillin-resistant Staphylococcus aureus. Pharmacokinetic studies have shown that obese patients have increased exposure to telavancin compared with non-obese patients. Dose capping of 750 mg was utilized in selected patients with the purpose of minimizing toxicity and decreasing costs without compromising efficacy.

Methods. Retrospective case series includes adult patients admitted from 2010-2016 who were admitted with at least three doses of telavancin. Data collection includes patient demographics, telavancin dosing, antibiotic indication, length of stay, laboratory and microbiological data, and risk factor index (CMI). The primary outcome is to assess the efficacy of capping telavancin doses at 750 mg with non-capped doses. Secondary outcomes include safety and financial outcomes, as well as readmission rates.

Results. 333 patients were evaluated with 164 meeting the inclusion criteria. Seventy-five patients were in the capped group and 91 in the non-capped group. Most common infections included ABSSSI, pneumococcal and bacteraemia. Mean weight 110 kg in capped vs. 108 kg in non-capped, mean age 52 vs. 58, male 63% vs. 70%, fever resolution 83% vs. 60%, CMI 3.19 vs. 3.43 Six patients (8.2%) in the capped group were readmitted with antibiotics compared with 12 (13.2%) in the non-capped group. The non-capped group experienced nephrotoxicity compared with 21 (23.1%) in the non-capped group (P = 0.04). The capped group experienced 9 (6.6%) incidents of mortality vs. 28 (30.8%) in the non-capped group (P < 0.001). When doses were capped, approximately $1,400 was saved per patient.

Conclusion. The use of a capped 750 mg telavancin dose in adult patients appears to be an alternative dosing scheme that maintains efficacy and safety as well as being associated with reduced cost. Further studies with pharmacokinetic and clinical studies are needed to further investigate the use of capped dosing of telavancin to support the findings of this retrospective case series.

Disclosures. All authors: No reported disclosures.

803. Impact of minocycline, polymyxin B, meropenem, and amikacin on growth prevention of Acinetobacter baumannii with various biofilm-forming capabilities
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Background. Acinetobacter baumannii is a clinically challenging pathogen with biofilm (BF) forming capabilities, making eradication difficult. The objective of this study was to compare in vitro activity of minocycline, polymyxin B, meropenem, and amikacin and evaluate the effectiveness in preventing BF formation utilizing various validated methodology.

Methods. Minimum inhibitory concentrations (MICs) were performed on all isolates in duplicate using CLSI standards. Tryptic soy broth plus 1% dextrose (TSB-D1%) was used to quantify BF formation of 12 clinically unique and diverse strain A. baumannii. Biofilm formation was defined as the formation of BF at concentrations where no biofilm attachment was observed, as determined by optical density (OD). BFPC was determined by evaluating increasing concentrations of antibiotic in TSB-D1% for 48 hours. BF was quantified by measuring OD of each well at 570nm via spectrophotometer. Previously described BF adherence categories were utilized to define BF strength (OD < 1s) > 2 strong; OD 1-2 = moderate; OD >5 >0.5 = weak; OD 0.5 = none.

Results. Twelve clinical isolates were evaluated with a full range of BF formation capabilities. Prevention of BF formation was observed at concentrations below the MIC by 2.57 to 4.12-fold for minocycline, 5.57 to 8.97-fold for polymyxin B, 5.77 to 17.56-fold for meropenem, and 0.72 to 0.35-fold for amikacin. Minocycline prevented BF formation at or below the MIC for 75% of isolates tested vs. 67% for polymyxin B, 33% for meropenem, and 33% for amikacin. Free drug concentrations at the end of a dosing interval, derived from pharmacokinetic data, imply that BF would be prevented for 75% of minocycline-exposed isolates vs. 58.3% polymyxin B, 8.3% meropenem-, and 8.3% amikacin- exposed isolates.

Conclusion. Minocycline, polymyxin B and meropenem prevented BF formation at clinically relevant concentrations. Prompt antimicrobial administration may
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. Additional studies are warranted.

Disclosures. K. LaPlante, Merck: Grant Investigator, Grant recipient, Pfizer: Grant Investigator, Grant recipient, Cephalon: Scientific Advisor, Consulting fee. The Medicines Company: Grant Investigator, Grant recipient. Allergen: Scientific Advisor, Consulting fee. Bard/Davol: Scientific Advisor, Consulting fee. Ocean Spray: Grant Investigator and Scientific Advisor, Consulting fee and Grant recipient. Zavante: Scientific Advisor, Consulting fee. Achagen: Scientific Advisor, Consulting fee.

804. Pharmacokinetics and Tissue Distribution of Minocycline following Intravenous Administration in Rabbits

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Background. 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 (µg/mL) | AUC 0-24h (µg h/mL) | CL (L/hour/kg) | Vss (L/kg) |
|-------------------------|--------------|---------------------|----------------|-----------|
| 6                       | 22.9 ± 2.0   | 20.9 ± 2.1          | 226.3 ± 19.2   | 378.1 ± 47.3 |
| 12                      | 64.5 ± 5.2   | 44.2 ± 7.3          | 197.8 ± 16.1   | 358.6 ± 41.2 |
| 24                      | 211.0 ± 21.7 | 119.7 ± 15.5        | 116.4 ± 10.8   | 226.6 ± 27.3 |
| 48                      | 660.7 ± 55.9 | 296.0 ± 33.9        | 74.2 ± 6.4     | 170.7 ± 15.4 |
| 96                      | 1228.2 ± 106.9 | 369.7 ± 75.6    | 78.7 ± 6.6     | 246.9 ± 33.6 |

Minocycline tissue concentrations 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, Contralabs, Dracis, iCo Novartis, Methylene, Pfizer, Sigma-Tau: Consultant, Consulting fee. Altellas, Actavis, Merck, Novartis, Pfizer, Schinzen, Tetraphase, The Medicines Company, Theravance: Grant Investigator, Research grant.

805. Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of Dalbavancin Alone and in Combination with Ceftaroline against Methicillin-Resistant Strains (MRSA) of Staphylococcus aureus

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Background. Glycopeptide antibiotics, principally vancomycin, have been the first antarmament 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 biophilic 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 on vancomycin (VAN) in combination with ceftaroline (CTF) 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 (fCmax = 30.1 µg/mL, VAN 2 q12h fCmax = 36 µg/mL, CPT 600 mg every 12 hours fCmax = 17.04 µg/mL, DAL 1,500 mg day 1 plus CPT 400 mg q12h, VAN 2 q 12h plus Cefaloridine 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 log$_{10}$ CFU/mL between regimens was evaluated.

Results. Combination of DAL + CPT offered a significant reduction in log$_{10}$ CFU/mL amounts (more than 5 log$_{10}$ CFU/mL and up to detection limits) in 24 hours compared with CPT alone. CPT alone demonstrated bactericidal activity with a reduction in log$_{10}$ CFU/mL by 32 hours although regrowth was observed in 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+ ceftaroline 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 evaluation.

Disclosures. M. J. Rybak, Allergan: Scientific Advisor, Consulting fee.