Fellowship Forum 2018

Infectious Diseases Fellowship Forum: Together we can do great things

Buffalo, New York

June 21 – 23, 2018
Timothy F. Murphy, MD, Professor and Senior Associate Dean for Clinical and Translational Research, Jacobs School of Medicine, University at Buffalo

Timothy Murphy, MD, is Professor and Senior Associate Dean for clinical and translational research. He also directs the school's Clinical and Translational Science Institute, a facility that includes a nine-bed Clinical Research Center with support services for clinical research. An internationally recognized expert in respiratory tract bacterial infections, Murphy is a SUNY Distinguished Professor of medicine and microbiology and immunology.

Murphy holds more than a dozen patents related to vaccine development and is co-principal investigator on the longest-standing study of COPD, which he is conducting at the Buffalo Veterans Affairs Medical Center. His work is funded by grants from the National Institutes of Health. A graduate of New York University, Murphy received his medical degree from Tufts University School of Medicine and completed a fellowship in infectious diseases at Tufts before coming to UB in 1981. He has published more than 150 articles in peer-reviewed journals, including the New England Journal of Medicine.

Eric Wenzler, PharmD, BCPS, AAHIVP, Assistant Professor in the Department of Pharmacy Practice at the University of Illinois at Chicago College of Pharmacy

Eric Wenzler, PharmD, is an Assistant Professor in the Department of Pharmacy Practice at the University of Illinois at Chicago College of Pharmacy. He recently completed a 3-year Infectious Diseases Pharmacotherapy Fellowship at the University of Illinois at Chicago in June 2017.

He graduated from Ohio Northern University Raabe College of Pharmacy in 2012 and completed his Postgraduate Year 1 training in 2013 and Postgraduate Year 2 in Infectious Diseases in 2014 at The Ohio State University Wexner Medical Center in Columbus, Ohio. Dr. Wenzler’s research interests include pharmacokinetics, pharmacodynamics, antimicrobial stewardship, and clinical microbiology.
Zack Bulman, PharmD, Assistant Professor in the Department of Pharmacy Practice at the UIC College of Pharmacy.

Dr. Bulman graduated from the University at Buffalo School of Pharmacy and Pharmaceutical Sciences in June 2015 and completed his Infectious Diseases Fellowship at the University at Buffalo in July 2017.

Dr. Bulman’s research aims to devise novel therapeutic approaches that are capable of successfully treating infectious diseases while also suppressing the evolution or perpetuation of new resistance mechanisms. Ongoing projects in Dr. Bulman’s laboratory are exploring patient specific treatment strategies for bacteria with genetically defined resistance mechanisms.

Justin Lenhard, Pharm.D., Assistant Professor, California Northstate University, College of Pharmacy

Dr. Lenhard graduated from the University at Buffalo School of Pharmacy and Pharmaceutical Sciences in 2014 and then completed a fellowship in infectious diseases pharmacology with Brian Tsuji from 2014 to 2016. In 2016,

Dr. Lenhard joined the California Northstate University College of Pharmacy as an Assistant Professor and also currently serves as an antimicrobial stewardship pharmacist at Lodi Memorial Hospital. Dr. Lenhard’s research focuses on strategies to overcome multidrug resistance and also the co-culture of clinically relevant pathogens.
ORGANIZING COMMITTEE

Brian T. Tsuji, Pharm.D., Chair
Professor and Director of Clinical Research
School of Pharmacy and Pharmaceutical Sciences
University at Buffalo, State University of New York
President, International Society for Anti-Infective Pharmacology

Michael J. Rybak, Pharm.D., M.P.H., Ph.D., Deputy Chair
Professor and Director of the Anti-Infective Research Laboratory
Eugene Applebaum College of Pharmacy and Health Sciences
Wayne State University
Chair, Scientific Committee, MAD-ID

Kerry Laplante, Pharm.D., Deputy Chair
Professor and Director of the Infectious Diseases Research Program. Infectious Diseases Pharmacotherapy Specialist
College of Pharmacy
University at Rhode Island
President-Elect, Society of Infectious Diseases Pharmacists

Eric Wenzler, Pharm.D., Organizing Committee
Assistant Professor
College of Pharmacy
University of Illinois Chicago

Zackery Bulman, Pharm.D., Organizing Committee
Assistant Professor
College of Pharmacy
University of Illinois Chicago
KL2 Scholar

Justin Lenhard, Pharm.D., Organizing Committee
Assistant Professor
School of Pharmacy
California Northstate University

Nicholas Smith, Pharm.D., M.S., Organizing Committee
Ph.D Candidate
School of Pharmacy and Pharmaceutical Sciences
University at Buffalo
Thursday, June 21
4:30pm to 7:00pm
Opening Reception
Sponsored by Making a Difference in Infectious Diseases - MAD-ID
Westin, 250 Delaware Ave, Buffalo, NY 14202, USA.

Friday 6/22
All talks to be held in the 2nd Floor Bruce Holm Commons
Location: 701 Ellicott Street, Buffalo, NY, 14203, NYS Center of Excellence
Phone. 17168818900. https://goo.gl/maps/8sHrfVJi85L2

7:30am  Light Breakfast

8:45am  Welcome
Brian T. Tsuji, Pharm.D.
Professor and Director of Clinical Research
University at Buffalo

8:55am  Welcome from the School of Pharmacy and Pharmaceutical Sciences
James O’Donnell, Ph.D.
Dean and Professor
University at Buffalo

9:05am  A History of Fellow Forum
Michael J. Rybak, Pharm.D., M.P.H., Ph.D.
Professor and Director of Anti-Infective Research Lab
Wayne State University

9:15am  Decades of NIH Funding: Lessons Learned
Timothy F. Murphy, M.D.
SUNY Distinguished Professor
Senior Associate Dean for Clinical and Translational Research, University at Buffalo
Friday 6/22

10:00am  **Group Photo**  
*3rd Floor Stairwell, Center of Excellence*

10:30am  **Fellow Presentations**

**Session A. The Pesky Gram-Positives: Pharmacodynamics and In vivo Pharmacology**  
Chairs: Brian Tsuji, Pharm.D. and Kerry Laplante, Pharm.D.

10:30am  **A1. Pharmacodynamic Analysis of Daptomycin-Treated Enterococcal Bacteremia**  
Lindsay M. Avery, Pharm.D.  
Hartford Hospital

10:45am  **A2. Liposomal Vancomycin and Cefazolin Combinations for S. aureus Biofilms**  
Razieh Kebriaei, Ph.D.  
Wayne State University

11:00am  **A3. Pharmacodynamics of Daptomycin Against Enterococcus faecium and Enterococcus faecalis in the Murine Thigh Infection Model**  
James Kidd, Pharm.D.  
Hartford Hospital

11:15am  **A4. Adjuvant Azithromycin for Bacteremic Pneumonia due to Methicillin-resistant Staphylococcus aureus**  
Sarah Jorgensen, Pharm.D.  
Wayne State University

11:30am  **A5. Prevalence of Multidrug Resistant Organisms Infections in Patients with Clostridioides difficile Infection**  
Kierra M. Dotson, Pharm.D.  
University of Houston
Friday 6/22

11:45pm  Boxed Lunches

12:15pm  Session B. Collateral Damage and Stewardship: Toward Optimal Antibiotic Use
Chairs: Eric Wenzler, Pharm.D.
        Marc Scheetz, Pharm.D.

12:15pm  B1. A National Comparison of Antibiograms Between Veterans Affairs Long-Term Care Facilities and Affiliated Hospitals
Maria-Stephanie A. Tolg, Pharm.D.
University of Rhode Island

12:30pm  B2. Estimated clinical and economic impact of routine use of SteriPath to reduce false-positive blood cultures in the emergency department
Erik Skoglund, Pharm.D.
University of Houston

12:45pm  B3. Leveraging appropriate antimicrobial prescribing on a family medicine ward by reporting unit-specific metrics and antibiotic-related harms
Nicholas J Mercuro, Pharm.D.
Wayne State University

1:00pm   B4. Identifying time periods of high and low vancomycin use
Jiajun Liu, Pharm.D.
Midwestern University

1:15pm   B5. Microbial Economics: The Cost-Benefit of Polymyxin Resistance Amplification and Virulence in Acinetobacter baumannii
Tyler Bedard, Pharm.D. and Pharmaceutical Sciences Graduate Student
University at Buffalo
Friday 6/22

4:30pm  Reception and Dinner  
Sponsored by Achoagen  
Kelly Wright, Pharm.D.  
Senior Medical Scientist  

7:05pm  Friday Night Events Chairs: Kerry Laplante, Pharm.D. and Michael Rybak, Pharm.D., M.P.H., Ph.D.  

Buffalo Bisons Game, Location: 1 James D Griffin Plaza, Buffalo, NY 14203, USA
Saturday 6/22

All talks to be held in the 2nd Floor Bruce Holm Commons
Location: 701 Ellicott Street, Buffalo, NY, 14203, NYS Center of Excellence, Phone. 17168818900. https://goo.gl/maps/8sHrfVJi85L2.

7:30am  Breakfast

8:30am  Welcome to Day 2
        Brian T. Tsuji, Pharm.D.
        Professor and Director of Clinical Research
        University at Buffalo

8:45am  Trade Secrets: What you Absolutely Need to Know Starting Out as Faculty
        Eric Wenzler, Pharm.D.
        Assistant Professor, University of Illinois at Chicago

        Zack Bulman, Pharm.D.
        Assistant Professor, University of Illinois at Chicago

        Justin Lenhard, Pharm.D.
        Assistant Professor, California North State University

9:45am  Session C. Resistant Gram-Negatives: Raising Lazarus from the Dead
        Chairs: Zackery Bulman, Pharm.D.
        Justin Lenhard, Pharm.D.

9:45am  C1. Optimizing Aminoglycoside Selection for KPC-Producing Klebsiella pneumoniae with Aminoglycoside Modifying Enzyme AAC(6’)-Ib
        David A. Butler, Pharm.D.
        University of Illinois at Chicago

10:00am  C2. Carbapenem resistant Klebsiella pneumoniae have low potential to form biofilm
         Jaclyn A. Cusumano, Pharm.D.
         University of Rhode Island
Saturday 6/22

10:15am  C3. Assessment of the In Vivo Efficacy of Human-simulated Epithelial Lining Fluid (ELF) Exposure of Meropenem/Nacubactam Combination against serine carbapenemase-producing Enterobacteriaceae in Neutropenic Lung Infection Model
Tomefa E. Asempa, Pharm.D.
Hartford Hospital

10:30am  Break

10:30am  C4. Activity of minocycline, polymyxin B, sulbactam and meropenem against multi-drug resistant and non-multi drug resistant Acinetobacter baumannii in a 72-hour in vitro pharmacodynamic model
Maya Beganovic, Pharm.D.
University of Rhode Island

10:45am  C5. Searching for the Optimal Treatment Regimen for Metallo-ß-Lactamase Producing Enterobacteriaceae: Aztreonam and Ceftazidime/Avibactam vs. Aztreonam and Meropenem/Vaborbactam
Mark Biagi, Pharm.D.
University of Illinois at Chicago

11:00am  Session D. Next Gen Pharmacometrics: To Infinity and Beyond
Chairs: Nicholas Onufрак, Pharm.D.
Institute for Clinical Pharmacodynamics
Elizabeth Lakota, Pharm.D., M.S.
Institute for Clinical Pharmacodynamics

11:15am  D1. 24-Hour Pharmacokinetic Relationships for Intravenous Vancomycin and Novel Urinary Biomarkers of Acute Kidney Injury
Sean N. Avedissian, Pharm.D.
University of Illinois Chicago
11:30am  D2. Through the Looking-Glass of Resistance: Polymyxin Exposure and the Differentiation of MCR-1 populations  
Nicholas M. Smith, Pharm.D., M.S., Ph.D Candidate  
University at Buffalo

11:45am  Working Lunch

12:00pm  D3. Dosing Vancomycin in the Super Obese: Less is More  
Ryan L. Crass, Pharm.D.  
University of Michigan

12:15pm  D4. Cloud-Based Monte Carlo Simulation Platform to Provide Robust Anti-infective Dose Assessment  
Courtney Safir, Pharm.D.  
Institute for Clinical Pharmacodynamics

12:30pm  D5. Increased Clinical Failure Rates Associated with Reduced Metronidazole Susceptibility in Clostridioides difficile  
Anne Gonzales-Luna, PharmD  
University of Houston

12:45PM  Fellow Forum 2019

1:00pm  Closure of Lectures

Evening  Saturday Events Chairs: Zackery Bulman, Eric Wenzler  
Justin Lenhard, and Nicholas Smith.

Buffalo River Works  
https://buffaloriverworks.com/sports/

Anchor Bar  
https://www.anchorbar.com/

Niagara Falls  
https://www.niagarafallsusa.com/

Fellowship Forum 2018  
Infectious Diseases Fellowship Forum  
Buffalo, New York  
June 21 – 23, 2018
Abstract A1

Pharmacodynamic Analysis of Daptomycin-Treated Enterococcal Bacteremia

Lindsay M. Avery1, Joseph L. Kuti1, Maja Weisser3, Adrian Egli4,5, Michael J. Rybak6, Evan J. Zasowski6,7, Cesar A. Arias8,9,10, German A. Contreras8, Pearlie P. Chong11, Samuel L. Aitken12, Adam J. DiPippo12, Jann-Tay Wang13, Nicholas S. Britt14,15, David P. Nicolau1,2

1 Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, USA; 2 Division of Infectious Diseases, Hartford Hospital, Hartford, CT, USA; 3 Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland; 4 Division of Clinical Microbiology, University Hospital Basel, Basel, Switzerland; 5 Applied Microbiology Research, University of Basel, Basel, Switzerland; 6 Anti-Infective Research Laboratory, College of Pharmacy, School of Medicine, Division of Infectious Diseases, Wayne State University, Detroit, MI, USA; 7 Department of Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, TX, USA; 8 Center for Antimicrobial Resistance and Microbial Genomics and Division of Infectious Diseases, University of Texas Health Science Center, McGovern Medical School at Houston, Houston, TX, USA; 9 Center for Infectious Diseases, University of Texas Health Science Center, School of Public Health, Houston, TX, USA; 10 Molecular Genetics and Antimicrobial Resistance Unit – International Center for Microbial Genomics, Universidad El Bosque, Colombia. 11 Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, TX, USA; 12 Division of Pharmacy, University of Texas MD Anderson Cancer Center, Houston, USA; 13 Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; 14 Research Department, Dwight D. Eisenhower Veterans Affairs Medical Center, Leavenworth, KS, USA; 15 Department of Pharmacy Practice, University of Kansas School of Pharmacy, Kansas City, KS, USA

Background: DAP is commonly dosed at 8-12 mg/kg daily for enterococcal BSIs, particularly for vancomycin-resistant isolates (VRE). Although emerging data support these higher doses (≥8 mg/kg), PD targets associated with positive outcomes have not been established. Moreover, clinical failures have been reported for DAP-susceptible enterococcal infections (MIC ≤4 µg/mL), calling into question the appropriateness of DAP breakpoints and driving the need to establish optimal PD targets for enterococcal BSIs.

Methods: This study pooled data from 7 published observational studies assessing patient outcomes in DAP-treated enterococcal BSIs. The fAUC/MIC was calculated using a published population pharmacokinetic model based on creatinine clearance, 90% protein binding, and baseline MIC for each patient that received ≥72 hours of DAP monotherapy. The fAUC/MIC threshold predictive of 30-day survival was determined by classification and regression tree (CART) analysis and confirmed with multivariable logistic regression. Monte Carlo simulation was performed to determine the probability of target attainment (PTA) at each MIC in doubling dilutions between 0.25-8 µg/mL. Males and females were simulated separately as DAP clearance is lower in females.

Results: Of 114 total patients included, 72 (63.2%) were alive at 30 days. E. faecium was responsible for the BSI in 103 (90.4%) patients (~85.6% were VRE). The median fAUC/MIC was 29.9 (range: 10.1 – 134.5). CART identified a fAUC/MIC >27.4 to be associated with survival (66.2 versus 47.8%), though the difference was not significant (p=0.051). When the cohort was categorized according to severity of illness, CART identified the same threshold (fAUC/MIC >27.4) to be significantly associated with survival in low-acuity (n=77) patients (68.9 versus 37.5%, p=0.006). This threshold remained statistically significant (p=0.026) after adjusting for BSI source and immunosuppression. The table displays PTA at 1, 2, and 4 µg/mL for daily doses of 6, 8, 10, and 12 mg/kg (upper range denotes female PTA).
<table>
<thead>
<tr>
<th>Daily dose (mg/kg)</th>
<th>MIC 1 µg/mL</th>
<th>MIC 2 µg/mL</th>
<th>MIC 4 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>91.0 – 97.9%</td>
<td>32.4 – 54.4%</td>
<td>1.5 – 5.5%</td>
</tr>
<tr>
<td>8</td>
<td>98.7 – 99.9%</td>
<td>60.7 – 80.4%</td>
<td>7.3 – 18.1%</td>
</tr>
<tr>
<td>10</td>
<td>99.9 – 100.0%</td>
<td>80.4 – 92.9%</td>
<td>18.1 – 36.2%</td>
</tr>
<tr>
<td>12</td>
<td>100.0%</td>
<td>91.0 – 97.9%</td>
<td>32.4 – 54.4%</td>
</tr>
</tbody>
</table>

**Conclusions:** For DAP monotherapy of enterococcal BSI, a fAUC/MIC >27.4 was associated with survival at 30 days. Based on this PD threshold, DAP 6 mg/kg daily is optimal for treatment of enterococci with MICs ≤1 µg/mL, while a 12 mg/kg daily dose is required for MICs up to 2 µg/mL.
Abstract A2

Liposomal Vancomycin and Cefazolin Combinations for S. aureus Biofilms

Razieh Kebriaei¹, Seth A. Rice¹, Ketki Bhise², Samaresh Sau², Kyle C. Stamper¹, Arun K. Iyer²,³, Michael J. Rybak¹,⁴,⁵,

¹. Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum college of pharmacy, Wayne State University, Detroit, Michigan USA 2. Use-inspired Biomaterials & Integrated Nano Delivery (U-BiND) Systems Laboratory, 3. Molecular Therapeutics Program, Karmanos Cancer Institute, Detroit, Michigan, USA 4. Department of Pharmacy Services, Detroit Medical Center, Detroit, Michigan, USA 5 Department of Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit, Michigan, USA

Background: Biofilms are sophisticated communities of matrix-encased and surface-attached bacteria that exhibit a distinct and specific resistant/tolerant phenotype to almost all antibacterial agents, with activity reduced 10-1000-fold. This augmented resistance rapidly reverts when bacteria detach from the biofilm and return to a planktonic state. However, in this in-vitro pharmacokinetic and pharmacodynamic (PK/PD) model we can expose biofilms to shear rates that are consistent with human interface and mimic antibiotic penetration and diffusion pathways from serum antibiotic concentration in humans.

Methods: Methicillin-susceptible ATCC 29213 and MRSA 494 strains were evaluated. Initial susceptibility tests were performed by broth microdilution method. Time kill studies were performed to identify synergy patterns for liposomal and commercial antibiotics. Biofilm eradication was investigated using antibiotics vancomycin (VAN) (commercial) vs. liposomal VAN (VAN-L) (Patent#17-1460) and combination of VAN- cefazolin (commercial) vs. liposomal vancomycin and liposomal cefazolin (CFZ-L) (Patent# 17-1460) in biofilms for strain MRSA 494. Biofilms were generated overnight using the BioFlux Microfluidic system (Fluxion BioSciences) at constant and continuous shear rates to optimize biofilm attachment and creation. Perfusion of antibiotic solutions (free peak concentration) was applied over a 24h period. Time lapse pictures were recorded to determine antibiotic biofilm eradication rates over 18h of incubation and pictures were analyzed using Bioflux Montage software.

Results: MIC values demonstrated a 2-fold reduction for liposomal vancomycin vs. commercial vancomycin. Also, combination of liposomal VAN MIC in presence of CFZ-L showed a 15.87-fold reduction in comparison to commercial VAN for 494. Overall, our biofilm results demonstrated a 43.6% improved eradication using VAN-L and CFZ-L combination in comparison to commercial VAN-CFZ combination. We also observed 5.7% improved eradication using VAN-L vs. commercial VAN.

Conclusions: Liposomal form of VAN and CFZ combinations are a promising approach to improved efficacy and reduced VAN resistance in S. aureus biofilms.
Abstract A3

Pharmacodynamics of Daptomycin Against *Enterococcus faecium* and *Enterococcus faecalis* in the Murine Thigh Infection Model

James M. Kidd¹, Kamilia Abdelraouf¹, Tomefa E. Asempa¹, Romney M. Humphries²,³, David P. Nicolau¹

¹Center for Anti-Infective Research and Development, Hartford Hospital, Harford, Connecticut, USA, ²UCLA Pathology & Laboratory Medicine, Los Angeles, CA, USA, ³Current Address: Accelerate Diagnostics, Tucson, AZ, USA

The Clinical Laboratory Standards Institute (CLSI) daptomycin MIC susceptibility breakpoint for the treatment of enterococcal infections is ≤4 µg/mL. However, patients receiving daptomycin for enterococci with MICs ≤4 µg/mL may experience treatment failures. We assessed the pharmacodynamics of daptomycin against enterococci in a neutropenic murine thigh infection model and determined exposures necessary for bacteriostasis and 1 log₁₀ CFU reduction against *Enterococcus faecalis* and *Enterococcus faecium*. We further characterized daptomycin efficacy at clinically achievable exposures.

Twelve *E. faecium* and 6 *E. faecalis* isolates (daptomycin MIC, 0.5-32 µg/mL) were studied. Daptomycin was administered at various doses over 24 h to achieve area under the free drug concentration–time curve to MIC ratios (fAUC₀-2₄/MIC) from 1-148. Daptomycin regimens that simulate mean human exposures following doses of 6, 8, and 10 mg/kg/day were also studied. Efficacy was assessed by differences in log₁₀ CFU/thigh at 24 h. The Hill equation was used to estimate fAUC₀-2₄/MIC required to achieve bacteriostasis and 1 log₁₀ CFU reduction.

For *E. faecium*, 1 log₁₀ CFU reduction required a fAUC₀-2₄/MIC of 9.8 (R²=0.69). For *E. faecalis*, 1 log₁₀ CFU reduction was not achieved, while the fAUC₀-2₄/MIC required for stasis was 7.2 (R²=0.8). With a human-simulated regimen of 6 mg/kg/day, 1 log₁₀ CFU reduction was observed in *E. faecium* in 6/7 isolates with MIC ≤4 µg/mL and 1/5 isolates with MIC >4 µg/mL; however, 1 log₁₀ CFU reduction was not achieved against any of the 6 *E. faecalis*. These results, alongside clinical data, prompt a re-evaluation of the current breakpoint.
Abstract

Adjuvant Azithromycin for Bacteremic Pneumonia due to Methicillin-resistant Staphylococcus aureus

Jorgensen S.C.J.1, Trinh T.D.1,2 Zasowski E.J.1,3, Lagnf A.M.1, Bhatia S.1, Rybak M.J.1,4,5

1. Anti-Infective Research Laboratory, College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI
2. University of California San Francisco, School of Pharmacy, San Francisco, CA
3. University of Houston, College of Pharmacy, Houston, TX
4. Detroit Medical Center, Detroit, MI
5. School of Medicine, Wayne State University, Detroit, MI

Background: Bloodstream infection (BSI) secondary to methicillin-resistant Staphylococcus aureus pneumonia (MRSA PNA) complicates 5% to 20% of cases with associated mortality rates up to 6-fold higher than for MRSA PNA without BSI. Macrolides have demonstrated favorable immunomodulatory effects in experimental models and have been associated with improved clinical outcomes in a number of inflammatory and infectious lung conditions. Furthermore, sub-inhibitory macrolide concentrations exhibit anti-virulence affects against S. aureus.

Objective: To investigate clinical outcomes associated with early azithromycin (AZM) use in patients with MRSA PNA + BSI

Methods: Retrospective, observational, cohort study in adults (≥ 18 y) with MRSA PNA + BSI admitted to the Detroit Medical Center between 2008 and 2017. Patients with a positive Legionella pneumophila urinary antigen or isolation of an atypical pathogen from a respiratory or blood specimen were excluded. The primary outcome was 90-day mortality among patients who received at least 1 dose of AZM within 48 hours of blood culture collection compared to those who received no AZM. Multivariable logistic regression was conducted to examined the independent association of AZM and 90-day mortality.

Results: A total of 87 patients were included (AZM 27 vs. no AZM 60). The majority were male (62.1%) with a mean age of 63.2 (± 14) y. A lower proportion of patients in the AZM group were admitted from a skilled-nursing facility / outside hospital (29.6% vs. 55.0%; P = 0.028) or met criteria for hospital-acquired/ventilator-associated PNA (11.1% vs. 43.3%; P = 0.003). However, there were no differences in the median Charlson Comorbidity Index (3 [2 - 6] vs. 3 [1 - 5]; P = 0.498) or APACHE II score (28 [22 - 32] vs. 25 [19 - 33]; P = 0.762). Ninety-day mortality was significantly lower among patients in the AZM group by univariate analysis (25.5% vs. 48.3%; P = 0.050). On multivariable analysis, age ≥ 62 years and APACHE II score ≥ 22 were independently associated with increased 90-day mortality (aOR 5.512, 95% CI 1.836 – 16.547; aOR 3.847, 95% CI 1.009 – 14.665, respectively), while receipt of AZM was independently associated with decreased 90-day mortality (aOR 0.272, 95% CI 0.80 – 0.921)

Conclusions: The early use of AZM among patients with MRSA PNA + BSI was independently associated with decreased 90-mortality. Future studies, including a larger number of patients, are needed to confirm these preliminary findings.
Abstract A5

Prevalence of Multidrug Resistant Organisms Infections in Patients with Clostridioides difficile Infection

Kierra M Dotson, PharmD, Chris Lancaster, MS, Feroz Hossain, Farnoosh Haghighi, Bradley T Endres, PhD, Evan J Zasowski, PharmD, Jahangir Alam, PhD and Kevin W Garey, PharmD, MS

University of Houston College of Pharmacy, Houston, TX

Background: Broad spectrum antibiotic use associated with C. difficile infection kills host microbiota leading to MDRO colonization in the gut. However, the clinical importance of MDRO colonization is unknown. The purpose of this study was to assess MDRO colonization and infection rates in CDI patients.

Methods: This was a prospective, observational study of adult hospitalized CDI patients without a history of MDRO infections at a large, university-affiliated tertiary care hospital. Leftover stool samples were collected from patients with positive C. difficile toxin test. Stool was cultured for C. difficile growth and MDROs including methicillin resistant S. aureus (MRSA), vancomycin-resistant Enterococci (VRE), CRE and Candida spp. Patients were followed for 30-days after positive CDI toxin test and all MDRO cultures from systemic, normally sterile sites (i.e.: blood, urine, cerebrospinal fluid) ordered as part of clinical care were collected. Clinical data collected included patient demographics, CDI disease severity, and clinical outcomes.

Results: A total of 188 CDI patients were assessed of which 177 patients aged 62±18.5 years (female gender: 55%) were eligible for inclusion. MDRO present in stool (n=110) included VRE (50%), MRSA (11%), and CRE (1.8%). Overall, 35 patients (19.8%) of CDI patients developed a systemic infection in the subsequent 30 days. The most common cause of systemic MDRO infection included Candida spp. (34.2%), VRE (13.2%), and MRSA (9.2%). The urinary tract was the most common site of infection (46%) followed by respiratory tract infections (19.7%) or bacteremia (15.8%). Five (17.2%) in-hospital deaths occurred among patients with systemic MDRO infections.

Conclusion: MDRO gut colonization and systemic MDRO infections are common in patients with CDI.
Abstract B1

A National Comparison of Antibiograms Between Veterans Affairs Long-Term Care Facilities and Affiliated Hospitals

Maria-Stephanie A. Tolg, PharmD1,2; Aisling R. Caffrey, PhD1,2; Robin L. P. Jump, MD, PhD3,4; Vrishali Lopes, MS1; Haley J. Appaneal, PharmD1,3; Stefanie I. Gidmark, MPH1; David M. Dosa, MD, MPH1,5; Kerry L. LaPlante, PharmD, FCCP, FIDSA1,3

Affiliations:

1. Providence Veterans Affairs Medical Center, Infectious Diseases Research Program, Providence, RI
2. University of Rhode Island, College of Pharmacy, Kingston, RI
3. Geriatric Research Education and Clinical Center (GRECC) and the Specialty Care Center of Innovation at the Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH
4. Division of Infectious Diseases and HIV Medicine, Department of Medicine and Department of Population & Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH
5. Warren Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, RI

Background: Long-term care facilities (LTCFs) face several barriers to creating antibiograms. Here, we evaluate if LTCFs can use antibiograms from affiliated hospitals as their own antibiogram.

Methods: Facility-specific antibiograms were created for all Veterans Affairs (VA) LTCFs and VA Medical Centers (VAMCs) for 2017. LTCFs and affiliated VAMCs were paired and classified as being on the same campus or geographically distinct campuses based on self-report. For each pair, Escherichia coli susceptibility rates (%S) to cefazolin, ceftriaxone, cefepime, ciprofloxacin, nitrofurantoin, sulfamethoxazole/trimethoprim, ampicillin/sulbactam, piperacillin/tazobactam, and imipenem were compared. As guidelines discourage empiric use of antibiotics if susceptibility rates are <80%, we assessed clinical discordance between each LTCF and affiliated VAMC antibiogram at a threshold of 80% susceptible. The proportion of concordant susceptibilities between LTCFs and VAMCs on the same versus geographically distinct campuses was compared using Chi-square tests.

Results: A total of 119 LTCFs and their affiliated VAMCs were included in this analysis, with 70.6% (n=84) of facilities located on the same campus and 29.4% (n=35) on different campuses. The table below shows the overall clinical concordance (agreement) of LTCFs with their affiliated VAMC in regards to E. coli %S to the compared antibiotics. No significant differences were found comparing LTCFs on the same campus versus geographically distinct campuses.
Agreement Rates between LTCFs and Affiliated VAMCs

<table>
<thead>
<tr>
<th>Agreement Rates</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-100%</td>
<td>Ampicillin/sulbactam</td>
</tr>
<tr>
<td></td>
<td>Imipenem</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>80-89%</td>
<td>Cefepime</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
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<tr>
<td></td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>70-79%</td>
<td>Sulfamethoxazole/trimethoprim</td>
</tr>
<tr>
<td>60-69%</td>
<td>Cefazolin</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
</tr>
</tbody>
</table>

**Conclusions**: Antibiograms between LTCFs and affiliated VAMCs had a high concordance except for sulfamethoxazole/trimethoprim, cefazolin and ceftriaxone in regards to susceptibility rates of *E. coli*. Facilities on the same campus were found to have similar concordance rates to geographically distinct facilities. Future studies are needed to investigate how the various approaches to creating LTCF-specific antibiograms are associated with clinical outcomes.
Abstract B2

Estimated clinical and economic impact of routine use of SteriPath to reduce false-positive blood cultures in the emergency department

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2. Department of Pharmacy, CHI Baylor St. Luke’s Medical Center, Houston, TX
3. Department of Pharmaceutical Health Outcomes and Policy, University of Houston College of Pharmacy, Houston, TX

Background: Blood culture contamination results in increased hospital costs and unnecessary patient-exposure to antimicrobials. We sought to evaluate the potential clinical and economic benefits of a novel blood culture diversion device when routinely utilized for blood culture collection in the emergency department (ED) of a quaternary care medical center.

Methods: A decision analysis model was created. Probabilistic costs were determined from published literature and direct observation of pharmacy/microbiology staff. The primary outcome was the expected per-patient cost savings (microbiology, pharmacy, and indirect hospital costs) after initial specimen diversion device (e.g. SteriPath) implementation in the ED using a hospital perspective. Indirect hospital costs included increased hospital length of stay, additional procedures, adverse drug reactions, and hospital-acquired infections. Models were created for hospitals that routinely or do not routinely use rapid diagnostic tests (RDT) on positive blood cultures.

Results: The routine implementation of an initial specimen diversion device for blood culture collection in the ED was cost-beneficial compared to conventional blood culture collection methods and was also associated with a reduction in antibiotic usage, adverse drug reactions and hospital-acquired infections. When implemented in a hospital utilizing RDT with a baseline contamination rate of 6%, initial specimen diversion device use was associated with a cost-savings of $272 (3%) per blood culture in terms of overall hospital costs and $28 (5.4%) in direct-only costs. Main drivers of cost included the baseline rate of contamination in the ED and the duration of antibiotics given to patients with negative blood cultures.

Conclusion: Implementation of an initial specimen diversion device is estimated to be a cost-beneficial strategy to reduce the clinical and economic impact of blood culture contamination in terms of microbiology, pharmacy and wider indirect hospital costs.
Abstract B3

Leveraging appropriate antimicrobial prescribing on a family medicine ward by reporting unit-specific metrics and antibiotic-related harms

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2. Wayne State University, Eugene Applebaum College of Pharmacy, Detroit MI
3. Henry Ford Hospital, Department of Family Medicine, Detroit MI

Background: Approximately 30-50% of inpatient antibiotics are inappropriate, and 1 in 5 hospitalized adults develop an antimicrobial-related harm. Antimicrobial stewardship (AS) initiatives targeting safety may reduce unnecessary drug exposures. The objective of this study was to evaluate the impact of a customized antibiotic use and outcome report for family medicine (FAM) providers, and critically assess potential adverse drug events (ADEs).

Methods: This was a single-center quasiexperiment before and after AS/FAM collaborative intervention. Jan-Mar 2017: routine audit and feedback. Jan-Mar 2018: monthly interventions with routine audit and feedback. Interventions included: reports of antimicrobial use, appropriateness, and harms; positive-deviance cases; education and survey of rotating FAM providers; and handheld prescribing tools and guidelines. Adults admitted to the FAM ward with respiratory, urinary, and skin infections were evaluated. Primary endpoint: duration of optimal prescribing. Each day of therapy (DOT) was classified as optimal, suboptimal, unnecessary, or inappropriate. Antimicrobials were stratified by spectrum and propensity to cause harm. Potential antibiotic ADEs were evaluated with Naranjo scoring up to 30-days post-therapy.

Results: 1499 total antibiotic days were assessed among 150 adults (76 pre, 74 post). There were no differences in age, comorbid conditions, and antimicrobial indications (Figure 1). Following intervention, unnecessary DOTs decreased from 2 to 0 days (p<0.001) and optimal definitive therapy selection increased from 25% to 58% (p<0.001). Total optimal DOTs did not significantly change (4.5 vs 5 days, p=0.055) and guideline-concordant duration improved (37% vs 57%, p=0.015). Narrow-spectrum agent utilization increased (41% vs 59%) while use of broader (52% vs 48%) and extended spectrum agents (57% vs 44%) were not significantly different. Sixty-eight potential ADEs were identified among 54 patients and 13 were considered serious. Patients with ADEs were more likely to have unplanned healthcare revisits (OR=2.42 [1.16—5.05]) and more antimicrobial days (11 vs 8 days, p= 0.036).

Conclusion: Reporting unit-specific antimicrobial use, harms and successes, improved antimicrobial prescribing and quality of care. One in four hospitalized patients developed antimicrobial-related harms and ADEs were associated with more total antimicrobial days.
<table>
<thead>
<tr>
<th></th>
<th>Pre n=76</th>
<th>Post n=74</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age, years ±SD</td>
<td>60.9 ± 19.4</td>
<td>61.4 ± 18.7</td>
<td>0.937</td>
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<tr>
<td>Charlson score, median (IQR)</td>
<td>2 (1—4)</td>
<td>2 (1—4)</td>
<td>0.537</td>
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<tr>
<td>Unit census, median (IQR)</td>
<td>77.9 (72.1—85.5)</td>
<td>81.4 (77.7—90.7)</td>
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<td>Length of stay, median (IQR)</td>
<td>2 (2—4)</td>
<td>3 (2—4)</td>
<td>0.142</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Urinary tract</td>
<td>31 (40.8)</td>
<td>22 (29.7)</td>
<td>0.157</td>
</tr>
<tr>
<td>• Skin/soft tissue</td>
<td>10 (13.2)</td>
<td>13 (17.6)</td>
<td>0.454</td>
</tr>
<tr>
<td>• COPD exacerbation</td>
<td>9 (11.8)</td>
<td>14 (18.9)</td>
<td>0.229</td>
</tr>
<tr>
<td>• Community-acquired pneumonia</td>
<td>29 (38.2)</td>
<td>28 (37.8)</td>
<td>0.968</td>
</tr>
<tr>
<td>• CURB-65, score (IQR)</td>
<td>2 (0—2.5)</td>
<td>2 (1—3)</td>
<td>0.437</td>
</tr>
<tr>
<td>Duration of therapy, days (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Optimal</td>
<td>8 (6—10.75)</td>
<td>6 (5—8)</td>
<td>0.001</td>
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<tr>
<td>• Unnecessary</td>
<td>4.5 (1—7)</td>
<td>5 (4—7)</td>
<td>0.055</td>
</tr>
<tr>
<td>• Inappropriate</td>
<td>2 (0—6)</td>
<td>0 (0—1)</td>
<td>&lt;0.001</td>
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<td>Optimal empiric selection, n (%)</td>
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<tr>
<td>Optimal definitive selection, n (%)</td>
<td>52 (68.4)</td>
<td>59 (79.7)</td>
<td>0.114</td>
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<td>Guideline concordant duration, n (%)</td>
<td>19 (25)</td>
<td>43 (58.1)</td>
<td>&lt;0.001</td>
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<tr>
<td>• Prolonged</td>
<td>28 (36.8)</td>
<td>42 (56.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>• Short</td>
<td>42 (55.3)</td>
<td>23 (31.1)</td>
<td>0.003</td>
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<td>C. difficile, n (%)</td>
<td>6 (7.9)</td>
<td>9 (12.2)</td>
<td>0.384</td>
</tr>
<tr>
<td>• Tested</td>
<td>1 (1.3)</td>
<td>0 (0)</td>
<td>---</td>
</tr>
<tr>
<td>30-day readmission, n (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Infection related</td>
<td>18 (23.7)</td>
<td>13 (17.6)</td>
<td>0.355</td>
</tr>
<tr>
<td>Clinical resolution at follow-up (when follow-up available), n (%)</td>
<td>49/61 (80.3)</td>
<td>51/55 (92.7)</td>
<td>0.053</td>
</tr>
</tbody>
</table>
Abstract B4

Identifying time periods of high and low vancomycin use

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1Department of Pharmacy Practice, Chicago College of Pharmacy, Midwestern University, Downers Grove, IL, USA; 2Midwestern University, Chicago College of Pharmacy Center of Pharmacometric Excellence; 3Henry Ford Hospital, Detroit, MI; 4Wayne State University, Detroit, MI; 5Optimal Data Analysis, LLC, Chicago, IL; 6Michigan Medicine University of Michigan, Ann Arbor, MI

Background: A national goal has been set to decrease inappropriate antibiotic use by 2020. To quantify decreases in use, consumption metrics and benchmarking strategies are implicit. However, while tracking and reporting antimicrobial use is widely recommended, these data do not address appropriateness. Accordingly, we developed a methodology to identify and report high and low vancomycin use periods which may represent inappropriate or unsafe antimicrobial use.

Methods: This is an observational, retrospective study of facility-wide vancomycin consumption data, aggregated and examined on a hospital level from three academic medical centers: Northwestern Medicine (NM), Michigan Medicine (UM) and Henry Ford (HF) Hospital. Utilization was quantified as antimicrobial days (AD) per 1000 days present (DP) on a monthly basis, recorded over 46 consecutive months (January 2014 through October 2017) for NM and HF, and 40 consecutive months (July 2014 through October 2017) for UM. Linear regression models and prediction intervals were generated to identify high-usage months. Use exceeding the upper bound of a prediction interval of 80 percent in a given month was used to define increased use, and the lower bound was used to define decreased use.

Results: Vancomycin use averaged 70.3 AD per 1000 DP at NM, 89 at UM, and 153.8 at HF. Regression models indicated HF and UM consumption decreased at a monthly rate of 1.2 AD per 1000 DP and 0.1 AD per 1000 DP, respectively, whereas NM use increased at a rate of 0.1 AD per 1000 DP over the study period. Overall, we identified n=6, n=5 and n=6 vancomycin increased use months and n=7, n=6 and n=5 decreased use months at NM, UM and HF, respectively.

Conclusions: Our methodology identified a total of 17 potential instances of increased and 18 decreased use periods for vancomycin. Patient-specific and/or hospital-level factors may contribute to inappropriate vancomycin use and requires further study. The relationship between increased or decreased antibiotic use and appropriateness should be a focus in future efforts. Once the link between use and appropriateness is known, interventions can target specific use periods to maximize benefit of the intervention.
Abstract B5

Microbial Economics: The Cost-Benefit of Polymyxin Resistance Amplification and Virulence in *Acinetobacter baumannii*

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¹State University of New York at Buffalo, Buffalo, NY, USA, ²California Northstate University, College of Pharmacy, Elk Grove, CA, USA, ³Monash University, Melbourne, Australia, ⁴Buffalo Veteran Affairs Medical Center, Buffalo, New York, USA, *Joint 1st Authors

**Background:** Given a prodigious level of carbapenem resistance, *Acinetobacter baumannii* (AB) can lead to severe infections. The objective of this study is to quantify the changes in resistance, as a response to treatment by front-loaded polymyxin B (PB) in a hollow fiber infection model (HFIM), changes in virulence, as described by a Galleria *mellonella* waxworm model, and the interplay between the two models systems.

**Methods:** AB strain 149.01 (MIC₉₀ₐ₅=1.0 mg/L and MIC₉₀مرةن=64 mg/L) was exposed to Front-Loading PB (3.33 mg/kg q12h for 1 dose followed by 1.43 mg/kg q12h) in the HFIM. Quantification of resistant subpopulations was performed via population analysis profiles (PAPs) on plates containing PB 0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 10.0 mg/L. To access virulence, 10⁵ CFU/mL of bacteria from each HFIM sample was injected into the right pro-leg of 20 wax worms. Controls included 20 waxworms a) with phosphate-buffer-saline and b) with no injection. The waxworms were incubated at 37°C and mortality was tracked every 24 h over a 6 day period.

**Results:** PB Front-Loading achieved a nadir of 10⁷ CFU/mL, with rapid regrowth to 10⁹ CFU/mL within 24 h and amplified resistant subpopulations (Growth on PB agar >2 mg/L). The proportion of resistant subpopulations capable of growing on plates containing PB 10 mg/L increased rapidly from <0.01% at 0 h to >99.9% at 24 h. Beyond 96 h of PB exposure, all resistant subpopulations overtook the total population with no discernible difference observed between the subpopulation counts growing on PB containing agar. Virulence analysis in the waxworm model showed a marked decrease in mortality from 80% at 0 h to 20% at 336 h. Lastly, the hazard ratios, as compared to the 0 h baseline, at 24, 48, 72, 96, 144, 192, 240, 288, and 336 h were 1.28, 1.39, 0.821, 0.389, 0.300, 0.508, 0.368, 0.260, and 0.174 respectively, which was statistically significant at 96, 144, 192, 240, 288 and 336 h (p≤0.05).

**Conclusion:** When looking at the individual subpopulations, a rapid selection of resistant AB occurs and propagation of the resistant populations can reach near maximal CFU/mL counts within 24 h. However, there is a significant reduction in virulence as PB resistance is amplified. Therefore, due to the dichotomous nature between virulence and resistance, the results reinforce the need for optimal dose selection in the clinical setting.
Abstract C1

Optimizing Aminoglycoside Selection for KPC-Producing *Klebsiella pneumoniae* with Aminoglycoside Modifying Enzyme AAC(6')-Ib

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¹University of Illinois at Chicago College of Pharmacy, Chicago, IL, USA
²Northwestern University Feinberg School of Medicine, Chicago, IL, USA
³Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru

**Background:** Aminoglycoside (AG) based combinations are a potential treatment option for KPC-producing *K. pneumoniae* (KPC-Kp) infections, which are associated with high mortality rates. The clinical relevance of AAC(6')-Ib, the most common aminoglycoside modifying enzyme (AME), is not clearly understood. Further, the optimal AG for KPC-Kp infections has not been determined. Thus, we aimed to elucidate the most active AG for KPC-Kp harboring aac(6')-Ib.

**Methods:** Two clinical KPC-Kp isolates underwent whole-genome sequencing to characterize resistance mechanisms. MICs were performed and then time-kill experiments were employed to compare the pharmacodynamic activity of amikacin (AMK) (6, 12, 24, 48, 96, and 192 mg/L), gentamicin (GEN) (2, 4, 8, 16, 32, 64 mg/L), and tobramycin (TOB) (4, 16, 64 mg/L) after 0, 1, 2, 4, 6, 8, and 24 hrs incubation at a 10⁸ CFU/mL starting inoculum. AG concentration arrays were anchored around human free maximum concentrations (fCmax). Hill-type models were used to characterize pharmacodynamic activity and determine half-maximal effective concentrations (EC50) of each AG. Bactericidal activity was defined as a ≥3 log₁₀CFU/mL reduction.

**Results:** NU-CRE193 (MICs: AMK=4, GEN=1, and TOB=1mg/L) harbored resistance genes *bla*KPC-3, *bla*SHV-12, *bla*TEM-1, *bla*OXA-9, and *oqxAB*. NU-CRE213 (MICs: AMK=8, GEN=0.25, and TOB=8mg/L) harbored *bla*KPC-3, *bla*SHV-11, *bla*TEM-1, *bla*OXA-9, *oqxAB* in addition to the AME aac(6')-Ib. In time-kill experiments against NU-CRE193 (Figure 1), fCmax concentrations of AMK, GEN, and TOB achieved bactericidal activity within 24, 1, and 2 hrs, respectively. Despite susceptibility of NU-CRE213 to both AMK and GEN (Figure 2), only an fCmax concentration of GEN achieved bactericidal activity (3.64 log₁₀CFU/mL reduction at 4 hrs). To compare aminoglycoside activity between isolates, the EC50 values were calculated for NU-CRE193 and NU-CRE213, as follows: AMK 28.2 and 51.8mg/L, TOB 9.8 and 20.3 mg/L, GEN 2.8 and 3.8mg/L.

**Conclusion:** Amikacin and tobramycin displayed significantly attenuated antibacterial activity in the presence of aac(6')-Ib. These preliminary results suggest that gentamicin may be the preferred aminoglycoside for treatment of KPC-Kp infections. Further studies are warranted.
Figure 1. Representative time-kill results reveal similar killing for each aminoglycoside at $fC_{max}$ concentrations against NU-CRE193

Figure 2. Representative time-kill curves reveal attenuated killing for amikacin and gentamicin at $fC_{max}$ concentrations against NU-CRE213
Abstract C2

**Carbapenem resistant Klebsiella pneumoniae have low potential to form biofilm**

Jaclyn A. Cusumano¹,², Kathryn E. Daffinee,¹ Megan K. Luther¹,²,³, Vrishali Lopes¹, Aisling R. Caffrey¹,²,³, Kerry L. LaPlante¹,²,³,⁴

¹. Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, United States,  2. College of Pharmacy, University of Rhode Island, Kingston, RI, United States,  3. Center of Innovation in Long-Term Support Services, Providence Veterans Affairs Medical Center, Providence, RI, United States  4. Warren Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, RI

**Background:** Klebsiella pneumoniae is a frequently multidrug-resistant organism with a high propensity to form biofilm. K. pneumoniae is the most common carbapenem-resistant Enterobacteriaceae (CRE), and labeled an urgent threat by the CDC. The relationship between K. pneumoniae biofilm formation and specific antimicrobial resistance patterns has not been well defined.

**Methods:** K. pneumoniae isolates (n=139) were evaluated for antimicrobial resistance and biofilm formation (CDC, Providence VA Med. Ctr., Rhode Island Hosp., BEI, and ATCC). Susceptibility was based predominantly on 2017 CLSI breakpoints. Isolates were categorized as multidrug-resistant (MDR: resistant to ≥ 1 antimicrobial in ≥ 3 out of 16 antimicrobial categories) or extensively drug-resistant (XDR: resistant to ≥ 1 antimicrobial in all but ≤ 2 out of 16 antimicrobial categories) based on expert consensus criteria for Enterobacteriaceae (European CDC (ECDC)/CDC, 2012). We collapsed antimicrobial categories described by the ECDC/CDC consensus group into 9 categories: penicillins, cephalosporins, monobactams, carbapenems, protein synthesis inhibitors, fluoroquinolones, folate pathway inhibitors, fosfomycin, and colistin. Biofilm formation was assessed using our previously described modified crystal violet method (OD₅₇₀), and defined by tertile cut-points. Antimicrobial resistance was compared for weak (n=47) versus strong (n=46) biofilm formation by chi-square or Fisher’s exact test. Predictors of strong biofilm formation were identified using logistic regression.

**Results:** MDR isolates were more common among weak (n=46/47, 97.9%) versus strong biofilm formers (n=35/46, 76.1%; p=0.002), whereas XDR was similar between groups (n=12/47, 25.5% vs. n=13/46, 28.3% p=0.77). Resistance to penicillins, cephalosporins, monobactams, carbapenems, protein synthesis, or fluoroquinolones were more common among weak biofilm formers (p<0.05). Carbapenem resistance was inversely associated with strong biofilm formation (odds ratio 0.09; 95% confidence interval 0.02-0.33).

**Conclusions:** Carbapenem resistant K. pneumoniae were 91% less likely to form strong biofilm. Potential trade-off mechanisms between antimicrobial resistance and biofilm formation require further exploration.
Abstract C3

Assessment of the In Vivo Efficacy of Human-simulated Epithelial Lining Fluid (ELF) Exposure of Meropenem/Nacubactam (MEM/NAC) Combination against serine carbapenemase-producing Enterobacteriaceae in Neutropenic Lung Infection Model

Tomefa E. Asempa¹, Ana Motos¹, Kamilia Abdelraouf¹, Caterina Bissantz²*, Claudia Zampaloni²**, and David P. Nicolau¹,³

¹Center for Anti-infective Research and Development, Hartford Hospital, Hartford, CT; ²Roche Pharma Research and Early Development, *Pharmaceutical Science, **Immunology, Inflammation and Infectious Diseases, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, 4070 Basel, Switzerland; ³Division of Infectious Diseases, Hartford Hospital, Hartford, CT

Background: NAC is a novel dual action β-lactamase inhibitor with in vitro activity against class A, class C, and some class D β-lactamases and antibacterial activity against Enterobacteraeaceae. NAC is being developed as a combination therapy with MEM for the treatment of serious Gram-negative bacterial infections. This study evaluated the efficacy of the human-simulated ELF exposure of MEM/NAC, compared with those of MEM or NAC alone against class A carbapenemase-producing Enterobacteriaceae isolates in the neutropenic murine lung infection model.

Methods: Twelve clinical MEM resistant Enterobacteriaceae isolates harboring class A carbapenemases (KPC-2, KPC-3 and IMI) were utilized in the study. MEM and MEM:NAC (1:1) combination MICs were determined in triplicate via broth microdilution. ICR mice were rendered transiently neutropenic, and lungs were inoculated with 50 µL bacterial suspensions of 10⁷ CFU/ml. Regimens in mice that simulated the human ELF exposures following doses of MEM 2g q8h and NAC 2g q8h (1.5h infusions) as monotherapies and in combination were established. Treatment mice received MEM human-simulated regimen (HSR), NAC HSR or MEM/NAC HSR and control mice were vehicle-dosed. Treatment was started 2h after inoculation and continued for 24h. Efficacy was assessed as the change in log₁₀CFU/lung at 24h compared with 0h controls.

Results: MEM and MEM/NAC MICs were 8 - >64 mg/L and 0.5 - 4 mg/L, respectively. The average log₁₀CFU/lung at 0h across all isolates was 6.31 ± 0.26. Relative to 0h control, the mean bacterial growth at 24h in the untreated control mice, MEM HSR, and NAC HSR treatment groups were 2.91 ± 0.27, 2.68 ± 0.42, and 1.73 ± 0.75 log₁₀CFU/lung, respectively. MEM/NAC HSR resulted in an average CFU reduction of -1.50 ± 0.59 log₁₀CFU/lung.

Conclusions: MEM/NAC human-simulated ELF exposure produced enhanced efficacy against MEM resistant Enterobacteriaceae isolates. These data support a potential role for MEM/NAC for treatment of lung infections due to class A carbapenemase-producing Enterobacteriaceae and warrant further studies.
Abstract C4

Activity of minocycline, polymyxin B, sulbactam and meropenem against multi-drug resistant and non-multi drug resistant Acinetobacter baumannii in a 72-hour in vitro pharmacodynamic model

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Background: Acinetobacter baumannii is a serious public health threat according to the Centers for Disease Control and Prevention (CDC), and treatment options are becoming increasingly scarce, particularly against multi-drug resistant (MDR) strains. Consequently, re-evaluation of old drugs is imperative to optimize outcomes.

Methods: We simulated a 72-hour in vitro pharmacokinetic (PK)/ pharmacodynamic (PD) bacteremia model with starting inocula of 10^6 CFU/mL using MDR and non-MDR A. baumannii human blood isolates. MDR was defined as non-susceptible to ≥1 agent in ≥3 antimicrobial classes using previously described criteria. The MDR strain was susceptible to minocycline, polymyxin B and sulbactam, but resistant to meropenem with minimum inhibitory concentrations (MICs) of 2-4mcg/mL for minocycline, 2mcg/mL for polymyxin B, 4mcg/mL for sulbactam, and 128mcg/mL for meropenem. The non-MDR strain was susceptible to all agents with an MIC of 0.5mcg/mL for minocycline, polymyxin B and meropenem, and an MIC of 2mcg/mL for sulbactam. Antimicrobial regimens simulated free concentrations for the following human doses: minocycline (200mg load, then 100mg every 12h, t1/2 11h); polymyxin B 0.5-1.25mg/kg every 12h, t1/2 8h; meropenem 1g and 2g every 8h, t1/2 1h; sulbactam 1g every 6h, t1/2 1h; and combination regimens with minocycline, and meropenem+ sulbactam. Activity was determined by plating bacterial counts at 0, 4, 8, 24, 32, 48 and 72 hours. Antimicrobial susceptibility was evaluated at 24, 48 and 72 hours using E-tests and CLSI-recommended breakpoints.

Results: For MDR A. baumannii, polymyxin B, sulbactam, meropenem 2g + minocycline, and minocycline+ polymyxin B demonstrated an initial reduction in CFU/mL. However, only polymyxin B alone and in combination with minocycline demonstrated consistent bacteriostatic activity over 72h and 48h, respectively. Minocycline+ polymyxin B (compared to polymyxin B monotherapy) demonstrated indifference in activity for the first 48 hours, but isolate regrew by 72h simultaneously with a rise in MIC. For non-MDR A. baumannii, all treatments yielded an initial reduction in CFU/mL, but regrew by 72h associated with a rise in MIC. Polymyxin B+ minocycline (compared to polymyxin B monotherapy) demonstrated improved activity during first 24 hours, and enhanced activity (≥2log increased kill compared to most active drug) by 48 and 72 hours. Regardless of agent (monotherapy or combination therapy), both isolates showed increased MIC at 24h, 48h and 72h that ranged from 1 to 7-fold for both isolates for all models.

Conclusions: Despite initial reduction in CFU/mL, all regimens (monotherapy and combination therapy) resulted in isolate regrowth, except minocycline+ polymyxin B for non-MDR A. baumannii. This may be due to rapid development of resistance which was observed for both isolates regardless of initial susceptibility. Optimal doses, frequencies and combinations require further exploration.
Abstract C5

Searching for the Optimal Treatment Regimen for Metallo-ß-Lactamase Producing Enterobacteriaceae: Aztreonam and Ceftazidime/Avibactam vs. Aztreonam and Meropenem/Vaborbactam

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Background: Pathogens harboring metallo-ß-lactamase (MBL) enzymes pose a serious threat to public health. Aztreonam (ATM) is not hydrolyzed by MBLs but is inactivated by other ß-lactamases, which are often co-harbored in MBL-producers. Ceftazidime/avibactam (CAZ/AVI) and meropenem/vaborbactam (MER/VBR) are novel ß-lactam/ß-lactamase inhibitors (BL/BLI) with potent activity against serine ß-lactamase producing Enterobacteriaceae. Combining ATM with BL/BLI agents may provide activity against Enterobacteriaceae producing serine and MBLs.

Methods: Two clinical E. coli (EC-1, EC-2) isolates were used. MICs were determined in triplicate and modal values are reported. Time kill analyses were performed in triplicate at standard inoculum (10^6). Each agent was tested alone and in combination at either fCmax or ¼, ½, 1, 2, or 4x MIC based on MIC. Bactericidal activity was ≥3 log10 reduction in CFU/mL from the starting inoculum. Synergy was ≥2 log10 reduction in CFU/mL compared to the most active agent alone. Antagonism was ≥2 log10 increase in CFU/mL compared to the most active agent alone.

Results: Genotypic/phenotypic susceptibilities are in Table 1. Against EC-1, ATM alone at fCmax had no activity. When combined with CAZ/AVI or MER/VBR, respectively, synergy was observed with average log10 decrease in CFU/mL at 24 hours of 3.92 and 5.04 (Figure 1a). Synergy seemed to be driven solely by the addition of the BLI as ATM/CAZ and ATM/MER did not demonstrate synergy (Figure 1a). Against EC-2, ATM alone at 1/4x MIC showed no activity (Figure 1b). Combining ATM with either CAZ/AVI or MER/VBR did not improve the activity or demonstrate synergy (Figure 1b). Interestingly, removing CAZ significantly improved the activity of ATM/AVI.

Conclusion: There were no significant differences in activity or synergy observed between the combinations of ATM with either CAZ/AVI or MER/VBR against serine- and MBL-producing E. coli. Synergy appears to be driven by the ATM-BLI combinations, with ATM-AVI demonstrating more consistent synergy than ATM-VBR. Further studies including more isolates and combinations are warranted.

<table>
<thead>
<tr>
<th></th>
<th><strong>EC-1</strong> (NDM, CMY2/FOX, CTX-M-1, TEM)</th>
<th><strong>EC-2</strong> (NDM-5, OXA-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>&gt;256</td>
<td>0.25</td>
</tr>
<tr>
<td>ATM/AVI</td>
<td>16</td>
<td>0.25</td>
</tr>
<tr>
<td>ATM/VBR</td>
<td>128</td>
<td>0.25</td>
</tr>
<tr>
<td>CAZ</td>
<td>&gt;256</td>
<td>&gt;256</td>
</tr>
<tr>
<td>CAZ/AVI</td>
<td>&gt;256</td>
<td>&gt;256</td>
</tr>
<tr>
<td>MER</td>
<td>64</td>
<td>256</td>
</tr>
<tr>
<td>MER/VBR</td>
<td>128</td>
<td>&gt;256</td>
</tr>
</tbody>
</table>
Figure 1a. EC-1

Figure 1b. EC-2
Abstract D1

24-Hour Pharmacokinetic Relationships for Intravenous Vancomycin and Novel Urinary Biomarkers of Acute Kidney Injury

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Background: Vancomycin induces exposure-related acute kidney injury; yet only troughs are generally monitored in patients. In rat models, intraperitoneal dosing results in highly variable drug exposures. Thus, intravenous (IV) vancomycin was used to assess pharmacokinetic-toxicodynamic (PK-TD) relationships with nephrotoxicity.

Methods: Male Sprague-Dawley rats received IV vancomycin via an internal jugular vein catheter. Total daily doses ranging from 150 mg/kg/day to 400 mg/kg/day were administered as a single or twice daily injection over 24 hours (h). Controls received IV saline. Plasma sampling was conducted via a 2nd dedicated catheter, with up to 8 samples in 24h. Twenty-four-hour urine was collected during this time and assayed for kidney injury molecule 1 (KIM-1), osteopontin (OPN) and clusterin using the MILLIPLEX MAP Rat Kidney Panel. Vancomycin in plasma was quantified via LC-MS/MS. PK analyses were conducted using Pmetrics for R. PK exposures during the first 24h (i.e. AUC0-24, CMAX0-24, CMIN0-24) were calculated from Bayesian posteriors. PK-TD relationships were assessed with Spearman’s rank coefficient (rs) and the best fit mathematic model (e.g. exposure response curve fitting in GraphPad v.7).

Results: Forty-five vancomycin treated and 5 control rats contributed PK-TD data. A 2-compartment model fit the data well (Bayesian: observed vs. predicted R²=0.963). An exposure-response relationship was found between AUC0-24 vs KIM-1 and osteopontin (R²=0.61 and R²=0.66) and CMAX24 vs KIM-1 and osteopontin (R²=0.50 and R²=0.55) by 4-parameter Hill fit. A weaker relationship was found for CMIN0-24h vs KIM-1 and osteopontin (R²=0.47 and R²=0.32) by 4-parameter Hill fit. Spearman’s rs showed significant correlations between AUC0-24 vs. KIM-1, AUC0-24 vs. osteopontin and CMAX0-24 vs. osteopontin (p<0.001, rs=0.53, rs=0.75, rs=0.65).

Conclusions: Vancomycin induced kidney injury is most driven by AUC or CMAX. Clinical monitoring should focus on CMAX and AUC and move away from trough only sampling.
Abstract D2

Through the Looking-Glass of Resistance: Polymyxin Exposure and the Differentiation of MCR-1 populations

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Background: The incursion of mobile colistin resistance (mcr-1) has worrying clinical repercussions. The relevance of subpopulation (SUBPOP) differentiation on polymyxin B (PB) pharmacodynamics requires further study.

Methods: Time kill (TK) studies were conducted using two, isogenic Escherichia coli strains: i) wild type (WT) (MICs PB<0.25 mg/L, kanamycin = 1 mg/L) and ii) mcr-1-harboring (mcr1a) (MICs PB = 8 mg/L, kanamycin = 128 mg/L). A 10^8 cfu/mL starting inoculum was composed of four varying proportions of mcr1a:WT at 1%:99%, 10%:90%, 50%:50%, and 90%:10%. Exposure to PB 0, 0.25, 0.5, 1, 2, 4, 8, 16, and 32 mg/L over 24 h was studied. Total counts and mcr1a-only counts were determined by plating samples on agar with 0 and 4 mg/L of kanamycin. A simulations from a previously published, mechanism-based model was used to describe the TK data. For each of the 4 proportions, cohorts of 2500 simulated patients were used to predict the likelihood of mcr-1 proliferation by SUBPOP selection after treatment by front-loaded PB.

Results: PB≤8 mg/L resulted in rapid initial killing followed by total regrowth by 24 h in all arms. PB 16 and 32 mg/L against mcr1a 1%:WT 99% produced counts below the quantification limit, but regrew by 24 h. Counts of mcr1a-SUBPOPs showed that at all PB exposures studied, mcr1a out competed the WT. The slope of observed versus simulated plots ranged between 0.78-1.4 and 0.63-1.2 for total counts and mcr1a-only counts, respectively. Exposures of front-loaded PB to mcr1a 1%:WT 99% showed that, compared to stasis, 54.6, 21.9, 13.3, and 1.9% of the 2500 subjects would achieve log_{10} reductions in area under the cfu curve of >0, >1, >2, and >3, respectively, over 12 h. Attainment dropped by 24 h, consistent rapid selection and proliferation of mcr1a over WT.

Conclusion: The ability for mcr-1-harboring strains to rapidly out-compete WT strains is cause for serious concern in the clinic, highlighting the need for novel, effective treatment versus mcr-1-positive bacteria.
Abstract D3

Dosing Vancomycin in the Super Obese: Less is More

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¹Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI, U.S.A.; ²Department of Pharmacy, Morton Plant Hospital, Clearwater, FL, U.S.A.

Background. Vancomycin remains the mainstay of therapy against methicillin-resistant Staphylococcus aureus. National guidelines recommend empirical dosing based on total body weight with trough-level therapeutic drug monitoring (TDM), an approach that may not be optimal in obese and super obese patients. Furthermore, nomograms for empirical vancomycin dosing based on estimated kidney function predate standardization of creatinine assays.

Methods. We conducted a population pharmacokinetic study using data obtained from routine peak and trough TDM of vancomycin in obese (body mass index ≥ 30 kg/m²) adults. Pregnant women and patients with severe renal impairment (estimated creatinine clearance < 30 mL/min) or unstable renal function (50% or 0.5 mg/dL absolute increase in serum creatinine within the first 48 hours) were excluded. Population pharmacokinetic models were constructed using the non-parametric adaptive grid algorithm in the Pmetrics™ package for the R environment. All models were parameterized as 1-compartment systems with first-order elimination to facilitate translation to practice. Discrimination between covariate-structured models was based on the log likelihood ratio and Akaike’s Information Criterion. Simulations using the final covariate-structured model were performed to identify vancomycin doses which optimize the probability of efficacy (area under the curve [AUC] ≥ 400 mg*hr/L) and minimize the probability of acute kidney injury (AUC < 700 mg*hr/L).

Results. A total of 346 patients, encompassing a wide range of body weight (69.6 to 293.6 kg) and body mass index (30.1 to 85.7 kg/m²) values were included. In the final covariate-structured model, vancomycin clearance was modeled using a linear combination of age, serum creatinine, sex, and allometrically scaled body weight. Simulation demonstrated that maintenance doses above 4,500 mg/day were not required to achieve AUC values ≥ 400 mg*hr/L in obese and super obese patients at clinically relevant values of vancomycin clearance.

Conclusions. Empirical vancomycin dosing informed by common clinical variables, including standardized creatinine, with subsequent individualization using peak and trough TDM can optimize therapy in obese and super obese adults.
Abstract D4

Cloud-Based Monte Carlo Simulation Platform to Provide Robust Anti-infective Dose Assessment

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1Institute for Clinical Pharmacodynamics, Inc. Schenectady, NY, USA

**Background:** The ability to rapidly assess the adequacy of dosing regimens for older antibiotics based on pharmacokinetic (PK)-pharmacodynamic (PD) target attainment (TA) is hindered by a lack of portable and easy-to-use applications. Herein, the development and utility of an open-source, cloud-based Monte Carlo simulation (MCS) platform are detailed, using extended interval aminoglycoside dosing as a demonstration.

**Methods:** To perform PK-PD TA, the platform utilizes the following prerequisites: (1) a population PK model; (2) patient covariates relevant for parameter estimation, including demography and laboratory information; (3) a PK-PD target; and (4) proposed dosing regimens for evaluation. Based on the underlying covariate relationships, stratification of dosing regimens by patient group is possible, with allocation of a desired number of MCS iterations to each for construction of PK parameter distributions resembling those seen in patient care. The resultant PK exposures, such as maximum concentration (Cmax) or area under the concentration-time curve (AUC), are then assessed relative to the PK-PD target of interest for each simulated patient, with PK-PD TA calculated as the fraction of patients attaining the specified target. The app architecture is implemented in R/Shiny with mrgsolve used to fully replicate population PK models. An example using extended interval gentamicin dosing as implemented via the Hartford nomogram and a PK-PD target of a Cmax:MIC ≥ 10 is provided.

**Results:** Models reported from the literature for gentamicin were replicated in mrgsolve and incorporated into the Shiny app. Simulation performance was qualified using literature data distinct from the model reports. The application allowed for simulation of PK-PD TA for user-defined dosing regimens (dose and interval) for patients within customizable renal function bins at fixed MIC values. Built-in functionality allows the user to export PK-PD TA output tables and figures. When implementing dosing regimens used to derive the Hartford nomogram, predicted PK-PD TA is 0.477-0.724 at an MIC of 2 mg/L. This 3,000 patient simulation (1,000 patients per renal bin) took approximately 30 seconds to run. Testing with up to 10 renal function bins (10,000 simulated patients) produced comprehensive output in less than two minutes. Example code and development steps will be provided.

**Conclusions:** The MCS platform provides an efficient and user-friendly method for clinical dose assessment, and may serve as a template for both existing drugs and those under development.
Abstract D5

Increased Clinical Failure Rates Associated with Reduced Metronidazole Susceptibility in Clostridioides difficile

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Background: Current national guidelines suggest limiting metronidazole (MTZ) use due to increased treatment failures in patients with Clostridioides difficile infections (CDI). However, the reason for these increased failure rates are unclear. We hypothesized an increase in the minimum inhibitory concentration (MIC) of MTZ to C. difficile may contribute to these poor response rates. The objective of this study was to examine clinical response rates in patients with CDI who received MTZ monotherapy vs. other therapies stratified by MTZ susceptibility.

Methods: Stool samples that tested positive for C. difficile (2017-8) were collected from 2 large academic hospital systems in Texas. C. difficile was isolated from stool and visually screened for growth on heme-containing agar plates with MTZ at 2 mg/L (defined as reduced susceptibility). Blinded investigators reviewed electronic medical records to identify the treatment received and determine clinical success or failure for each patient. Treatment failure rates were assessed in patients that received MTZ monotherapy vs. other therapies stratified by MTZ susceptibility. Results were analyzed using multivariate logistic regression analysis.

Results: A total of 172 C. difficile isolates were included of which 55.8% displayed reduced susceptibility to MTZ. Clinical success rates with MTZ varied based on disease severity (mild-moderate: 80.4%; severe/severe-complicated: 64%). Treatment success rates were higher in patients infected with MTZ susceptible isolates (88.4%) compared to those infected with isolates showing reduced MTZ susceptibility (60.5%; p=0.004.) In multivariate logistic regression after controlling for disease severity, patients infected with strains displaying reduced MTZ susceptibility and treated with MTZ were more likely to experience treatment failure compared to patients with susceptible isolates (OR=6.8; 95% CI:1.96-23.8; p=0.003). In patients given non-MTZ based therapies, reduced susceptibility to MTZ was not predictive of failure to other treatments.

Conclusion: This is the first report to demonstrate that increased clinical failure rates for MTZ monotherapy are associated with reduced susceptibility to MTZ.