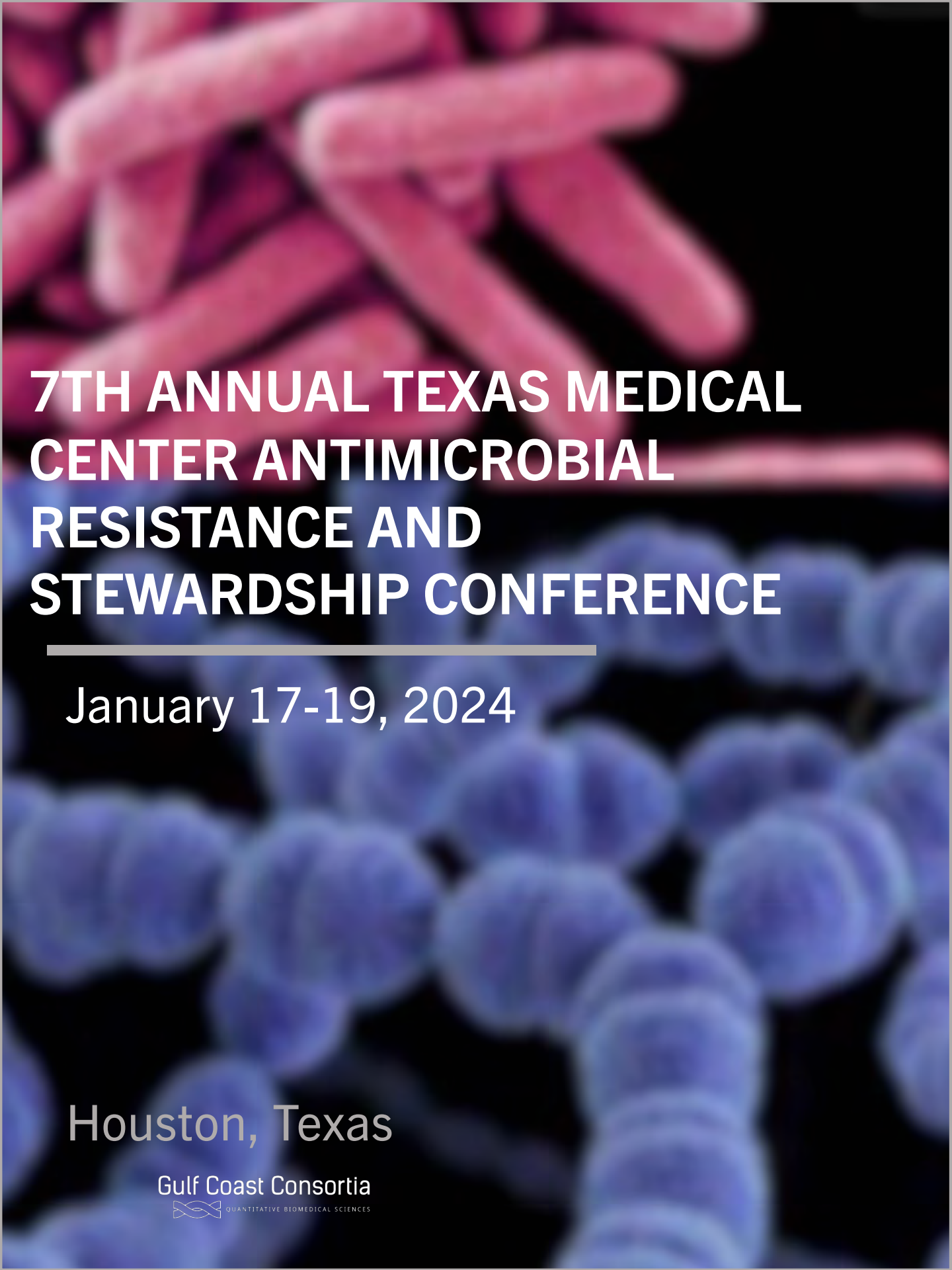

7TH ANNUAL TEXAS MEDICAL CENTER ANTIMICROBIAL RESISTANCE AND STEWARDSHIP CONFERENCE

January 17-19, 2024

Houston, Texas

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

Gulf Coast Consortia
QUANTITATIVE BIOMEDICAL SCIENCES

The Gulf Coast Consortia (GCC), located in Houston, Texas, is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians, and students in the quantitative biomedical sciences who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge. Working together, GCC member institutions provide a cutting-edge collaborative training environment and research infrastructure beyond the capability of any single institution. GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences and currently include Antimicrobial Resistance, Cellular and Molecular Biophysics, Innovative Drug Discovery and Development, Immunology, Mental Health Research, Single Cell Omics, and Translational Pain Research. GCC training programs focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Pharmacological Sciences, Precision Environmental Health Sciences and Antimicrobial Resistance. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, The Institute of Biosciences and Technology of Texas A&M Health Science Center and Houston Methodist Research Institute.

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Gulf Coast Consortia - Research

Tuesday, January 16, 2024
Pre-meeting workshop: Bacterial Genomics

8:30-9:00 *Strain-Level Characterization of Metagenomic Sequencing Data*
Todd Treangen, PhD, Rice University

9:00-9:10 Interactive demo

9:10-9:50 Advance Topics Lecture & Hands-on Training

9:50-10:00 Q&A

10:00-10:30 Networking

10:30-11:15 *Methods for Pathogen Epidemiology Using Whole Genome Sequencing*
Jennifer Spinler, PhD, Baylor College of Medicine

11:15-11:45 Interactive Demo

11:45-12:00 Q&A

Day 1 - Wednesday, January 17, 2024
Mechanisms of Resistance and Drug Discovery

7:00-8:30 Registration

7:30-8:30 *Career Mentoring ID Fellows*
Adarsh Bhimraj, MD, Houston Methodist Hospital
Pablo Okhuysen, MD, MD Anderson Cancer Center
Jill Weatherhead, MD PhD, Baylor College of Medicine

8:30-8:35 *Welcome*
Natasha Kirienko, PhD
Rice University, Houston, TX
Cesar A. Arias, MD, PhD
Houston Methodist Research Institute and Weill Cornell Medical College, Houston, TX
Suzanne Tomlinson, **PhD, MBA**
Gulf Coast Consortia

Session 1
Conveners: **Natasha Kirienko, PhD,** Rice University, Houston, TX
Taryn Eubank, PharmD, University of Houston, Houston, TX

8:35-8:55 *Antibiotic Resistance and Clostridioides difficile: A Driving Force for Treatment Failures and Considerations for New Drug Development*
Chetna Dureja, PhD
Texas A&M, Houston, TX

8:55-9:15 *Emergence of Clonal Dominance in Clinical Isolates of Multidrug-Resistant P. aeruginosa*
Natasha Kirienko, PhD
Rice University, Houston, TX

9:15-9:35 *Cell Membrane Remodeling in Gram-Negative Bacteria*
M. Stephen Trent, PhD
University of Georgia, Athens, GA

9:35-10:05 **Vendor Show and Networking**-Pre-function and Event Hall

Session 2 *T32 Trainee Symposium: Texas Medical Center Training Program on Antimicrobial Resistance (TP-AMR), Emory Training Program on Antimicrobial Resistance, University of Pittsburgh Training Program on Antimicrobial Resistance*

Conveners: **William Shropshire, PhD**, MD Anderson Cancer Center, Houston, TX
Martina Golden, **BA, BS,** Emory University, Atlanta, GA

10:05-10:20 *Impact of Antibiotic Treatment on Lactobacillus Population Dynamics and Intestinal Immune Homeostasis*
Dormarie Rivera-Rodriguez, BS
Emory University, Atlanta, GA

10:20-10:35 *Non-Antibiotic Based Therapeutics to Combat Multi Antibiotic Resistant Bacteria*
Paul Kilgore, PhD
University of Texas Medical Branch, Galveston, TX

10:35-10:50 *Functional Genomics of Difficult-to-Treat Enterococcal Isolates and Their Viral Adversaries*
Madison E. Stellfox, MD, PhD
University of Pittsburgh

10:50-11:05 *Fusobacterium nucleatum Enoyl-ACP Reductase II (FabK): A Narrow-Spectrum Drug Target*
Jacob Rutherford, BS
Texas A&M Health Science Center, Houston, TX

11:05-11:35 **Keynote Lecture**
Probiotics for Staphylococcus aureus: A Translational Approach
Michael Otto, PhD
NIH, Bethesda, MA

11:35-1:45 Lunch/Rapid Fire/Poster Session-Event Hall
11:35-12:15 Lunch
12:15-12:45 Rapid Fire
LiaR-Dependent Gene Expression Contributes to Antimicrobial Responses in Group A Streptococcus
Luis Alberto Vega, PhD, University of Texas Health Science Center at Houston, Poster 6

Alternating Magnetic Fields Enhance the Effects of Antibiotics on Biofilms
Miranda Hairgrove, University of Texas Southwestern Medical Center, Poster 2

Mutations in LiaF of Enterococcus faecalis Associated with Daptomycin Resistance (DAP-R) Differentially Affect Interaction Dynamics with the Histidine Kinase LiaS in Lipid Nanodiscs
Kara Hood, PhD, Houston Methodist Research Institute, Poster 3

Determining the Molecular Mechanism of Antibiotic Resistance by BpeEF-OprC Pump in Burkholderia thailandensis
Mithila Farjana, BSc, University of Oklahoma, Poster 1

Investigating the Potential of Bacteriophage to Limit Uropathogenic E. coli Colonization
Bishnu Joshi, MSTAH, PhD, Baylor College of Medicine, Poster 4

12:45-1:45 Poster Session, Poster #s 1-28, (please note poster 5 will present on day 2)

Session 3
Conveners: **Tim Palzkill, PhD,** Baylor College of Medicine, Houston, TX
Cecilia Tran, PharmD, Houston Methodist Research Institute, Houston, TX

1:45-2:05 *Penicillin Resistance in Group A streptococci*
Randy Olsen, MD, PhD
Houston Methodist and Weill Cornell Medical College, Houston, TX

2:05-2:25 *Novel Therapeutics Against Fungal Infections*
Minh-Hong Nguyen, MD
University of Pittsburgh, Pittsburgh, PA

2:25-2:45 *Antibiotic Resistance in Neisseria Gonorrhoeae*
Yonatan Grad, MD, PhD
Harvard School of Public Health, Boston, MA

2:45-3:15 Networking Break

Session 4 *NIH Antimicrobial Resistance Leadership Group (ARLG)*
Early-stage investigators

Conveners: **Anthony Harris**, **MD,** University of Maryland
Vance Fowler, **MD**, Duke University

3:15-3:30 *Strain Temporal Engraftment and Persistence after Fecal Microbiota Transplantation*
Ahmed Babiker, MSc, MBBS
Emory University School of Medicine

3:30-3:45 *Discovering Disparities in Clinical Characteristics and Outcomes Among Patients Treated in US Hospitals for Carbapenem-resistant Enterobacterales (Bloodstream) Infections*
Felicia Ruffin, PhD
Duke University

3:45-4:00 *Emerging S. aureus Antimicrobial Resistance and Current Prescribing Practices for Patients Presenting to US Emergency Departments with a Purulent Skin and Soft Tissue Infection*
Jesus Torres, MD, MPH
University of California, Los Angeles, David Geffen School of Medicine

4:00-4:15 *Understanding the Molecular Epidemiology of Non-CTX-M ESBL-producing Enterobacterales in the MidAtlantic United States*
Dariusz Hareza, MD
Johns Hopkins University School of Medicine

Session 5 Selected Abstracts

Convener: **Sam Shelburne, MD, PhD**, MD Anderson Cancer Center, Houston, TX
Kara Hood, PhD, Houston Methodist Research Institute, Houston, TX

4:15-4:30 *Evaluation of De Novo Fatty Acid Biosynthesis as a Narrow-Spectrum Approach for Clostridioides difficile Infection*
Chetna Dureja, PhD
Texas A&M University Institute of BioSciences and Technology

4:30-4:45 *Cefepime Heteroresistance is Prevalent Among Clinical Pseudomonas Aeruginosa Bloodstream Isolates and is Associated with Emergence of Resistance in Patients with Hematologic Malignancies*
Stephanie Egge, MD
Oregon Health & Science University

4:45-5:00 *Rates of Resistance and Heteroresistance to Newer ß-lactam/ß-lactamase Inhibitors for Carbapenem-Resistant Enterobacterales*

Christina Lin, MD, PhD
Emory School of Medicine

5:00-6:00 **Reception**-Prefunction

Day 2 - Thursday, January 18, 2024
Translational and Clinical Aspects of Antibiotic Resistance

7:00-8:30 Registration

7:30-8:30 Career Mentoring: *Research Pathways for International Graduates*
Jose Serpa, MD, PhD, Baylor College of Medicine
Anna Konovalova, PhD, University of Texas Health Science Center at Houston

Session 6

Conveners: **Tor Savidge, PhD**, Baylor College of Medicine, Houston, TX

8:30-8:55 *Intrinsic Antibiotic Resistance in Pseudomonas aeruginosa*
Barbara Kazmierczak, PhD
Yale University, New Haven, CT

8:55-9:20 *Mucus-Degrading Microbiome and Graft-Versus-Host Disease*
Robert Jenq, MD
MD Anderson Cancer Center, Houston, TX

9:20-9:45 *Novel Dug Combinations to Address Antimicrobial Resistance*
Warren Rose, PharmD, MPH
University of Wisconsin, Madison, WS

9:45-10:15 **Vendor Show and Networking**-Pre-function and Event Hall

Session 7 *T32 Trainee Symposium: Texas Medical Center Training Program on Antimicrobial Resistance (TP-AMR), Emory Training Program on Antimicrobial Resistance, University of Pittsburgh Training Program on Antimicrobial Resistance*

Conveners: **Paul Kilgore, PhD,** University of Texas Medical Brach, Galveston, TX**.**
Madison E. Stellfox, MD, PhD, University of Pittsburgh, Pittsburgh, PA

10:15-10:30 *Investigating the Role of Metabolism for Antibiotic Combination Therapies in Pseudomonas Aeruginosa*
Martina Golden, BA, BS
Emory University, Atlanta GA

10:30-10:45 *Basis of Commensal Bacillota Resistance to a Novel PolC-type DNA Polymerase III Inhibitor, Ibezapolstat, and the "Narrower" Spectrum of Activity Towards Clostridioides difficile*
Jacob McPherson, PharmD
University of Houston, Houston, TX

10:45-11:00 *Differences in Virulence Between the Two Clades of Multidrug-Resistant K. Pneumoniae ST258*
Nathalie Chen, BS
University of Pittsburgh

11:00-11:15 *Elucidating Molecular Mechanisms Underlying Successful Adaptation to Carbapenem Antimicrobials in High Risk Carbapenem Resistant Escherichia coli Lineages*
William Shropshire, PhD
MD Anderson Cancer Center, Houston, TX

11:15-11:30 *Applications of Caenorhabditis elegans for Identification of Treatments Against Antimicrobial-Resistant Bacteria*
Lois Armendariz, Rice University

11:30-12:00 **Keynote Lecture**
Resistance and New Drugs for Mycobacterium Tuberculosis
Kelly E. Dooley, MD, PhD
Vanderbilt University Medical Center

12:00-2:10 Lunch/Rapid Fire/Poster Session-Event Hall
12:00-12:40 Lunch
12:40-1:10 Rapid Fire
Defining the Mechanisms by Which Phage -Encoded Peptides Inhibit Cell Division in Gram-Negative Bacteria: A Promising Gateway Towards Alternative Therapeutics of Bacterial Infections
Arindam Naha, PhD, University of Texas Health Science Center at Houston, Poster 35

Changes in Antibiotic Susceptibilities Attributed to the Infection Environment
Caroline Black, MSc, Texas Tech University, Poster 32

Epidemiology of infections with Multidrug-Resistant Organisms in Patients with left Ventricular Assist Devices (LVADs)
Dierdre Axell-House, MD, Houston Methodist Research Institute, Poster 31

Identification of A Novel ST307 Sub-clade in Third Generation Cephalosporin Resistant Klebsiella Pneumoniae Causing Invasive Infections in the United States
Selvalakshmi Selvaraj Anand, BS, Rice University, Poster 36

ESBL Bacteremia During the First Year After Solid Organ Transplantation
German Contreras, MD, MSc, University of Texas Medical Branch, Poster 33

Different Mutations in the Rifampin Resistance-Determining Region (RRDR) of RpoB Cause Distinct Phenotypic Changes in Enterococcus faecium
Adeline Supandy, PhD, University of Pittsburgh, Poster 5

1:10-2:10 Poster Session, Poster #s 5, 31-58

Session 8
Conveners: **Cesar A. Arias MD, PhD**, Houston Methodist Research Institute and Weill Cornell Medical College, Houston, TX

2:10-3:10 *Challenging Clinical Cases in Antimicrobial Resistance*
Dierdre Axell-House, MD, Houston Methodist Research Institute and Weill Cornell Medical College, Houston, TX
Michael Rybak, PharmD, PhD, Wayne State University, Detroit, MI
Sam Shelburne, MD PhD, MD Anderson Cancer Center, Houston, TX

Session 9 **ARLG Session 2**
Title: Clinical Research in Antimicrobial Resistance

Conveners: **Vance Fowler**, **MD,** Duke University
Anthony Harris, **MD,** University of Maryland

3:10-3:25 *Mastermind-Ring*
Michael Satlin, MD
Weill Cornell Medical College

3:25-3:40 *OPTIMIZE-GNI*
Thomas Lodise, PharmD, PhD
Albany College of Pharmacy and Health Sciences

3:40-3:55 *Reproducibility of Pseudomonas aeruginosa Phage Susceptibility Testing: A Multicenter Comparison*
Krupa Parmar, PhD
Mayo Clinic

3:55-4:10 *DOOR Application Demonstration*
Toshimitsu Hamasaki, PhD
George Washington University

4:10-4:30 Networking break

Session 10

Conveners: **Rodrigo de Paula Baptista, PhD,** Houston Methodist Research Institute, Houston, TX
Vincent Tam, PharmD, University of Houston, Houston, TX

4:30-4:50: *B-lactamases in Stenotrophomonas maltophilia*
Maria F. Mojica, PhD
Case Western Reserve University, Cleveland, OH

4:50-5:10 *What's Hot in the Treatment of S. aureus bacteremia*
Vance Fowler, MD, MPH
Duke University, Durham, NC

Day 3-Friday, January 19, 2024

7:30-8:20 Career Mentoring: Careers in Microbiology and Diagnostic Stewardship
Audrey Wanger, PhD, University of Texas Health Science Center at Houston
Rodrigo de Paula Baptista, PhD, Houston Methodist Research Institute
Ed Septimus, MD, Harvard Medical School

Session 11

Convenors: **Kevin Garey, PharmD, MS**, University of Houston College of Pharmacy
Ed Septimus, MD, Harvard Medical School

8:30-8:35 Welcome

8:35-9:15 **Keynote Presentation**
Protecting Patients. Combatting Antimicrobial Resistance. An Update from CDC
Arjun Srinivasan, MD
Division of Healthcare Quality Promotion CDC

9:15-9:45 *Antimicrobial Resistance from the Global Perspective*
Debra Goff, PharmD
Ohio State University

9:45-10:15 **Vendor Show and Networking**-Pre-function and Event Hall

Session 12

Conveners: **Charlene Offiong, PharmD**, Houston Health Department
Clare Gentry, MD, University of Texas Health Science Center

10:15-10:45 *Optimizing Phage-Antibiotic Combination Therapy*
Michael J. Rybak, PharmD, MPH, PhD
School of Medicine, Wayne State University

Session 13

Conveners: **Kady Phe, PharmD**, Baylor St Luke's Medical Center
Anne Gonzales-Luna, PharmD, University of Houston College of Pharmacy

10:45-11:15 *MDRO Colonization in ICU Patients: Results from the DYNAMITE Cohort Study*
Max Adelman, MD
Houston Methodist Research Foundation

11:15-1:25 Lunch/Rapid Fire/Poster Session-Event Hall
11:15-11:55 Lunch
11:55-12:25 Rapid Fire Presentations

Situations Predisposing Primary Care Patients to Use Antibiotics Without a Prescription in the United States
Lindsey Laytner, PhD, Baylor College of Medicine, Poster 65

Sociodemographic Factors Associated with Knowledge of Antibiotic Risks Among an Outpatient Population
Eva Amenta, MD, Baylor College of Medicine/MEDVAMC, Poster 62

Characterization of Non-Carbapenemase Producing Carbapenem-Resistant Klebsiella pneumoniae in a Health System in Houston, Texas
Petar Jordanov, BS, Houston Methodist Research Institute, Poster 63

Influence of the COVID-19 Pandemic on Antimicrobial Resistance Patterns in Pediatric Group A Streptococcus Infections in Houston, TX
Aya Aboulhosn, MD, University of Texas Health Science Center Houston, and Children's Memorial Hermann Hospital, Poster 61

Geospatial and Genomic Epidemiology of Clinical Burkholderia pseudomallei Isolates in Cambodia
Rachelle Koch, MSc, University of Texas Southwestern Medical Center, Poster 64

Basis of Fidaxomicin Resistance in Clostridioides difficile: A Systematic Review and Meta-Analysis
ThanhPhuong Le, PharmD, University of Houston, Poster 66

12:25-1:25 Posters Session, Poster #s 61-88

Session 14

Conveners: **Ashley Drews, MD**, Houston Methodist Research Institute
Jamie Thomas, PharmD, Memorial Hermann

1:25-2:00 **Keynote Presentation**
Myths in Infectious Disease
Elizabeth Dodds-Ashley, PharmD
Duke University

2:00-2:30 *Evolving Epidemiology and Treatment of Invasive S. aureus Infections in Children*
Sheldon Kaplan, MD
Texas Children's Hospital and Baylor College of Medicine

2:30-3:00 *Neonatal Stewardship*
Michael Chang, MD
University of Texas Health Science Center Houston

Session 15 The Role of New Vaccines and Stewardship

Moderator **Ed Septimus, MD**, Harvard Medical School

3:00-3:55 *RSV Vaccines: The Road to Licensure*
Hana M. El Sahly, MD
Baylor College of Medicine

RSV Vaccines: Moving on to Recommendations
Robert Atmar, MD
Baylor College of Medicine

3:55 Closing Comments

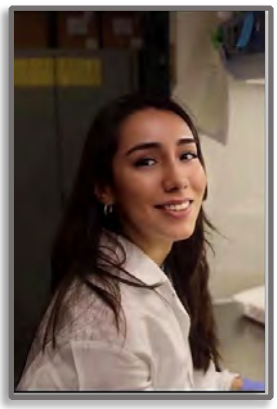
Presenters
(in alphabetical order)

Max Adelman, MD, MSc

Assistant Professor of Medicine, Academic Institute
Assistant Clinical Member, Research Institute
Houston Methodist
Weill Cornell Medical College

Genomic Epidemiology and Clinical Impact of MDRO Colonization in ICU Patients: Results from the DYNAMITE Cohort Study

Dr. Adelman is a clinically trained in both Infectious Diseases and Critical Care Medicine and his research interests sit at the intersection of these fields. His current clinical and translational research focuses on the clinical and immune impact of gut colonization with multi-drug resistant bacteria and yeasts, including the emerging multi-drug resistant fungus Candida auris. He has received funding from Houston Methodist Research Institute to examine colonization in patients at high risk for adverse outcomes, including critically ill patients and patients after solid organ transplantation. He has extensive prior experience in COVID-19 outcomes and clinical trials research, as well as in other topics relevant to both Infectious Diseases and Critical Care including C. difficile infection and sepsis.

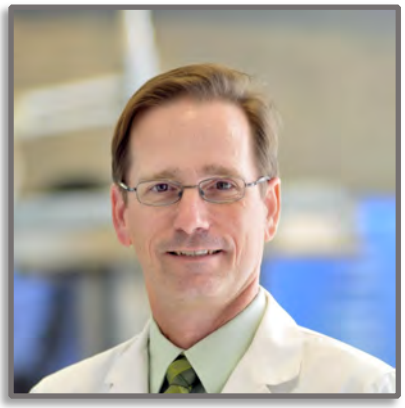


Lois Armendariz

Graduate Student, Biochemistry and Cell Biology
MBID Fellowship Training Program
Rice University

Applications of Caenorhabditis elegans for Identification of Treatments Against Antimicrobial-Resistant Bacteria

Lois Armendariz is currently a 3rd-year Biochemistry and Cell Biology PhD candidate at Rice University studying the role of mitochondria in innate immunity. She is in her second year of the NIAID T32 Molecular Basis of Infectious Disease Program. Her project aims to identify novel treatments against Pseudomonas aeruginosa by conducting host-pathogen interactions studies using Caenorhabditis elegans.



Robert L. Atmar, MD
Professor
Medicine
Baylor College of Medicine
RSV Vaccines: Moving on to Recommendations

Robert L. Atmar, M.D., is the John S. Dunn Research Foundation Clinical Professor in Infectious Diseases in the Departments of Medicine and Molecular Virology & Microbiology at Baylor College of Medicine. He is a member of BCM's Vaccine Treatment & Evaluation Unit and the Digestive Diseases Center, and he also serves as the chief of the Infectious Diseases Service at Ben Taub Hospital.

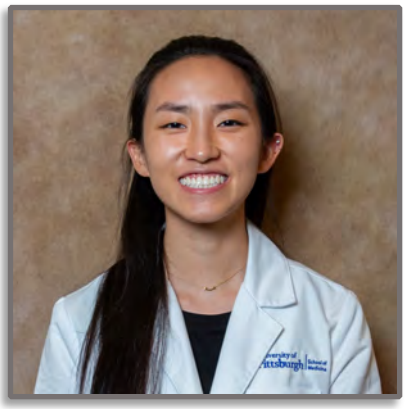
Dierdre Axell-House, MD
Assistant Professor
Infectious Diseases
Houston Methodist Research Institute
Challenging Clinical Cases in Antimicrobial Resistance

Dr. Dierdre Axell-House is an Assistant Professor of Infectious Diseases in the Department of Medicine at Houston Methodist and is a physician scientist in the fields of antibiotic resistance and infections in immunocompromised patients. Her research interests concern daptomycin resistance in Enterococcus faecium, mucormycosis, and cardiac device infections.

Dr. Axell-House is the recipient of the Clinical Scholars Award given by Houston Methodist (newly granted 2023).

Michael L. Chang, MD
Associate Professor of Pediatrics
Co-Director Antimicrobial Stewardship
Children's Memorial Hermann Hospital
Smaller is Better? Challenges of Anti-Infective Stewardship in the Neonatal Intensive Care Unit

Michael Chang, MD has been with UTHealth Houston McGovern Medical School for 8 years, and is physician co-director of pediatric antimicrobial stewardship at Children's Memorial Hermann Hospital. After completing his fellowship training at UT Southwestern Medical School in Dallas under the mentorship of Drs. George McCracken, John Nelson, and Octavio Ramilo, Dr. Chang took a position as the sole pediatric infectious diseases provider for Eastern Oklahoma based at the Children's Hospital at Saint Francis in Tulsa, Oklahoma. Honing his patient safety and quality improvement skills while in Tulsa, he helped the pediatric intensive care unit become the first unit within the Saint Francis hospital system to have zero central line associated bloodstream infection for an entire year. During the SARS-CoV-2 pandemic Dr. Chang, helped to develop and update pediatric treatment guidance for the Memorial Hermann system, as well as providing information and updates to the pediatric faculty and residents. Dr. Chang was awarded the Excellence in Teaching award for Pediatric Subspecialties in 2016, 2017, and 2019, and was awarded "Attending of the Year" for 2020 by the McGovern Medical School Pediatric Residency Program. Further highlighting his focus on education, Dr. Chang frequently represents UTHealth Houston and Children's Memorial Hermann Hospital to local, national, and international media outlets, including Yahoo! News, Time magazine, CNN, and NPR.



Nathalie Chen, BS
Graduate Student
University of Pittsburgh

Differences in Virulence Between the Two Clades of Multidrug-Resistant K. Pneumoniae ST258

Nathalie is an MD PhD student at the University of Pittsburgh School of Medicine. She graduated from Carnegie Mellon University in 2018 and worked at the NIH in the IRTA program before starting medical school. She is now a second year graduate student in Daria Van Tyne's lab studying classical Klebsiella pneumoniae.

Elizabeth S. Dodds Ashley, PharmD, MH
Professor, Medicine, and Operations Director for the Duke Antimicrobial Stewardship Outreach Network
Duke University
Myths in Infectious Disease

Elizabeth S. Dodds Ashley, PharmD, MHS, is a Professor of Medicine and Operations Director for the Duke Antimicrobial Stewardship Outreach Network (DASON) based at Duke University. She has been an active antimicrobial stewardship pharmacist for more than 20 years. Her work and research in stewardship span a variety of patient care settings including large academic medical centers, community hospitals and long term care facilities. She has served as a member of the Antimicrobial Resistance Working Group at the Centers for Disease Control, and an expert panel member of the Transatlantic Taskforce for Antimicrobial Resistance among other appointments. She is a current liaison member and first pharmacist on the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) representing SIDP. She is actively involved in several professional societies engaged in stewardship including SHEA and SIDP for which recently served as President.

Keynote presenter

Kelly E. Dooley, MD, PhD
Professor, Medicine
Director, Infectious Diseases
Vanderbilt University Medical Center

Resistance and New Drugs for Mycobacterium Tuberculosis

Dr. Dooley is Professor of Medicine and the Director of the Division of Infectious Diseases at Vanderbilt University Medical Center. Her research focuses on tuberculosis therapeutics with an emphasis on clinical trials of TB drugs and HIV/TB co-treatment, as well as clinical pharmacology of TB and HIV drugs. She is lead investigator for trials of therapeutics for drug-sensitive and drug-resistant TB, TB-HIV, and pediatric TB meningitis. She is a contributor to TB trials in the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium of the CDC and is a consultant to World Health Organization on TB therapeutics and pharmacology.

Keynote presenter

Chetna Dureja, PhD
Postdoctoral Research Associate
Texas A & M, IBT, Houston

Evaluation of De Novo Fatty Acid Biosynthesis as a Narrow-Spectrum Approach for Clostridioides difficile Infection

Dr. Dureja is a passionate molecular microbiologist, dedicated to improving people's lives through translational research in infectious diseases. Her research focuses on unraveling the molecular pathways that govern the emergence and dissemination of AMR in pathogenic microorganisms. Her commitment stems from the belief that a comprehensive understanding of these mechanisms is crucial for developing effective interventions to preserve antibiotic efficacy. She is currently working as a postdoctoral research associate at Texas A & M, IBT, Houston. Her key research objectives include understanding molecular mechanisms of antimicrobial resistance and their impact on patient care and to investigate the therapeutic potential of new anti-C. difficile agents. Throughout her postdoctoral research, she has co-authored many articles. Recently her work was accepted in Nature Communications, where they unraveled the mechanism of metronidazole resistance in C. difficile. This work has revised the paradigm by which epidemic C. difficile spread around the world, showing that epidemic strains co-evolved resistance to fluoroquinolone and metronidazole.

Holding a Ph.D. from Jawaharlal Nehru University, New Delhi, India, her doctoral research significantly contributed to understanding how commensal E. coli, isolated from individuals with no prior antibiotic exposure, served as a reservoir for antimicrobial resistance genes. This research shed light on the complex dynamics of antibiotic resistance and its implications for public health. As a university topper, she continues to push the boundaries of scientific knowledge.
In collaboration with industry sponsors, she played a pivotal role in the groundbreaking discovery of anti-infective molecules for drug-resistant M. tuberculosis. These molecules have progressed to advanced preclinical studies, with the goal of becoming treatments for TB disease.

Beyond her research, she is deeply involved in fostering a culture of scientific thinking. She has contributed to various training and mentoring programs, aiming to inspire curiosity in children at the school level and the general public. Currently serving as IBT's Postdoctoral Co-President and as a postdoc representative for Texas A&M IBT on the AMR Scholars Steering Committee (SSC), she is dedicated to advancing scientific knowledge and shaping the next generation of researchers.

Selected Abstract

Stephanie Egge, MD
Assistant Professor
Infectious Diseases
Oregon Health & Sciences University

Cefepime Heteroresistance is Prevalent Among Clinical Pseudomonas aeruginosa Bloodstream Isolates and is Associated with Emergence of Resistance in Patients with Hematologic Malignancies

Stephanie Egge is an Assistant Professor of Infectious Diseases at Oregon Health & Sciences University investigating heteroresistance and novel cephalosporin resistance among Gram-negative bacteria. She completed her internal medicine residency training 2017-2020 at Louisiana University Health Sciences Center and an infectious diseases clinical fellowship at University of Texas/MD Anderson Cancer(2020-2022). As a T32 research fellowship in the Gulf Coast Consortia's Training Program for Antimicrobial Resistance (TPAMR, 2022-2023), she worked under the mentorship of Dr. William R. Miller, MD (Weil-Cornell/Houston Methodist) where she gained expertise in pseudomonal cefiderocol heteroresistance, associated resistance markers/mechanisms, and impacts on unanticipated treatment failure associated with evolution to overt drug resistance. She has continued interest in unraveling mechanisms of pseudomonal antimicrobial resistance, identifying high risk clinical isolates/scenarios for treatment failure, and optimizing stewardship/treatment algorithms for common and novel anti-pseudomonal antibiotic use to optimize infection outcomes in the immunocompromised patient populations.

Selected Abstract

Hana El Sahly, MD
Professor
Molecular Virology & Microbiology
Baylor College of Medicine
RSV Vaccines: The Road to Licensure

Hana El Sahly, M.D is a Professor in the Department of Molecular Virology & Microbiology at Baylor College of Medicine.

Her research experience focuses on clinical vaccine development in healthy populations, and also in elderly persons, adolescents, and certain at-risk populations. These include vaccines against SARS-CoV2 (COVID-19), influenza, biodefense agents, and malaria. She is the principal investigator of BCM's Vaccine and Treatment Evaluation unit, and currently the chair of the Food and Drug Administration Vaccine and Related Biological Advisory Committee (VRBPAC).

Vance Fowler, MD, MPH
Professor
Medicine and Molecular Genetics & Microbiology, Duke University Medical Center
What's Hot in the Treatment of S. aureus bacteremia

Vance Fowler, MD, MHS, Departments of Medicine and Molecular Genetics & Microbiology, Duke University Medical Center. Dr. Fowler is the Florence McAlister Distinguished Professor of Medicine. He has over 2 decades of continuous support as PI from the NIH for clinical and translational research in Staphylococcus aureus and other antibiotic-resistant bacterial infections. Dr. Fowler created the S. aureus Bacteremia Group, co-founded the International Collaboration on Endocarditis, and has been the Contact PI of the Antibacterial Resistance Leadership Group since its inception in 2014. He has over 350 peer-reviewed publications with >33,000 citations.

Debra Goff, PharmD, FIDSA, FCCP
Professor, Pharmacy Practice
Ohio State University
Infectious Diseases Specialist, Global Antibiotic Stewardship
Antimicrobial Resistance from the Global Perspective

Dr. Goff is an Infectious Diseases Clinical Pharmacist, Professor of Pharmacy Practice and Antibiotic Stewardship Ambassador for The Ohio State University (OSU) Global One Health Institute in Columbus Ohio, USA. She is an awarding winning global "change maker" in infectious diseases. Dr. Goff is one of twenty-five global health experts selected by the World Health Organization (WHO) to implement antibiotic stewardship programs in low middle-income countries. Dr. Goff is the Program Director for the Train the Trainer Antibiotic Stewardship Mentoring Program founded in 2012 with South African pharmacists and physicians. Her program continues to expand to include neonatal ASP and other countries including Lebanon and six Latin American countries in collaboration with country experts and neonatal experts at Nationwide Children's Hospital in Columbus OH. She received the OSU 2019 Distinguished International Outreach and Engagement Award for her global work and the 2017 American College of Clinical Pharmacy Global Health Award. Dr. Goff is the Principal Investigator on the first US study with private practice dentists to assess their antibiotic use and provide guidance on the use of antibiotics in dentistry. Dr. Goff speaks to dental study clubs, dental schools, the FDI World Dental Federation and US Dental CE Academy providing antibiotic stewardship education to over 3,800 dental providers in over 80 countries. Her TEDx talk titled antibiotics "just in case" there's infection has over 28,500 views on YouTube. She uses Twitter (@idpharmd) to connect with her 10,000 followers. She has 150 publications and 50 grants.

Martina Golden, BS
PhD Candidate
Chemistry
Emory University
Investigating the Role of Metabolism for Antibiotic Combination Therapies in Pseudomonas Aeruginosa

Martina earned her B.S. in Chemistry from the University of St. Thomas where she started her research in antibacterials. She worked with Dr. J. T. Ippoliti to synthesize novel analogs of Linezolid aimed to minimize toxicity associated with long-term tuberculosis treatment. In 2020, she moved to Emory to start her PhD in Chemistry and joined the lab of Dr. Bill Wuest to expand her synthetic chemistry skills and knowledge of antibacterials. Her work focuses on synthesizing antibacterial natural products and analogs thereof to understand how their structure is related to their activity. In addition, she studies their mechanism of action alone and in combination with FDA-approved antibiotics. The ultimate goal is to discover a novel mechanism of action or combination therapy to combat the eminent antibiotic resistance crisis.

Yonatan Grad, PhD
Professor
Immunology and Infectious Diseases
Harvard University

Antibiotic Resistance in Neisseria gonorrhoeae

Yonatan Grad is the Melvin J. and Geraldine L. Glimcher Associate Professor in the Department of Immunology and Infectious Diseases at the Harvard TH Chan School of Public Health, and a member of the Division of Infectious Diseases at Brigham and Women's Hospital. The Grad laboratory uses interdisciplinary methods—including molecular microbiology, pathogen genomics, and mathematical modeling—to study how pathogens evolve and spread through populations, with the motivation of improving clinical and public health strategies to decrease the burden of disease. A major theme of the lab's work is antimicrobial resistance, with a particular focus on Neisseria gonorrhoeae, the causative agent of the sexually transmitted disease gonorrhea.

Toshimitsu Hamasaki, PhD
Professor
Biostatistics and Bioinformatics
George Washington University
DOOR Application Demonstration

Toshimitsu Hamasaki is a Professor of the George Washington University Biostatistics Center and the Department of Biostatistics and Bioinformatics. His research interests include the design, monitoring, analyses, and reporting of clinical trials. He is the author of more than 200 peer-reviewed publications. Dr. Hamasaki is the Editor-in-Chief of Statistics in Biopharmaceutical Research, an Official Publication of the American Statistical Association (ASA). He was a member of the Steering Committee for the Adaptive designs CONSORT Extension (ACE) Project, an extension to the CONsolidated Standards of Reporting Trials (CONSORT) Statement for adaptive clinical trials. Dr. Hamasaki is an elected member of International Statistical Institute, a fellow of the ASA and the Society for Clinical Trials.

Dariusz (Darek) Hareza, MD, MHS
Infectious Disease Fellow
Johns Hopkins University
Understanding the Molecular Epidemiology of Non-CTX-M ESBL-producing Enterobacterales in the MidAtlantic United States

Dariusz (Darek) Hareza, MD, MHS is a 3rd year infectious diseases fellow at Johns Hopkins University. Under the mentorship of Pranita Tamma and Sara Cosgrove, Darek studies the molecular epidemiology and clinical outcomes of patients infected with non-CTX-M extended-spectrum beta-lactamase producing Enterobacterales. He is also an Antibiotic Resistance Leadership Group (ARLG) fellow where he receives additional mentorship, research support, and the opportunity to participate as a non-voting member of the Gram-Negative Committee. He received his MD at the Albert Einstein College of Medicine, his MHS at Johns Hopkins University, and attended internal medicine residency at the University of Chicago.

Julian Hurdle, PhD
Professor
Microbiology
Institute of Bioscience and Technology, Texas A&M Health Science Center

Antibiotic Resistance and Clostridioides Difficile; A Driving Force for Treatment Failures and Considerations for New Drug Development

Julian G. Hurdle, Ph.D., is a leading scientist in translational research on resistance to antibiotics and drug discovery targeted at Clostridiodes difficile. He is a Professor of Microbiology in the Institute of Biosciences and Technology in the Department of Translational Medical Sciences at Texas A&M Health Science Center. He received his B.S. from the University of West Indies, Cave Hill Campus in Barbados, graduating with first class honors in Biology and Chemistry. He obtained his Ph.D. in Microbiology from the University of Leeds, United Kingdom and undertook postdoctoral training and research at University of Tennessee Health Science Center and St Jude Children's Research Hospital. Dr. Hurdle regularly serves on NIH study sections and is an editorial board member of top-tier journals in infectious diseases. His translational research characterizes the genetic mechanisms of antibiotic resistance and their impact on treatment outcomes, while discovering innovative therapeutic concepts to counter antibiotic-resistant bacteria. Dr. Hurdle has been continuously extramurally funded, namely by the National Institute of Health. His research is published in leading peer-review journals and is credited with the recent breakthrough explaining the evolution and mechanism of resistance to metronidazole in C. difficile, how it contributed to the pandemic spread of this pathogen, and its association with poorer clinical outcomes in patients.

Robert R. Jenq, MD
Deputy Department Chair, Genomic Medicine
Associate Professor, Genomic Medicine
Associate Professor, Stem Cell Transplantation
MD Anderson Cancer Center

Mucus-Degrading Microbiome and Graft-Versus-Host Disease

Dr. Jenq is a physician-scientist who specializes in the care of adults undergoing hematopoietic cell transplantation and also lead a research group. He is an Associate Professor and Deputy Chair in the Department of Genomic Medicine at MD Anderson, and also co-founded and directs the Microbiome Core Facility. His research pertains to the microbiome as a biomarker and modulator of cancer treatment outcomes.

Sheldon L. Kaplan, MD
Professor
Division of Infectious Diseases
Department of Pediatrics
Baylor College of Medicine
Attending Physician, Infectious Disease Service
Texas Children's Hospital
Evolving Epidemiology and Treatment of Invasive S. aureus Infections in Children

Dr. Kaplan is Professor in the Division of Infectious Diseases in the Department of Pediatrics at the Baylor College of Medicine and an attending physician on the Infectious Disease Service at Texas Children's Hospital in Houston, TX.

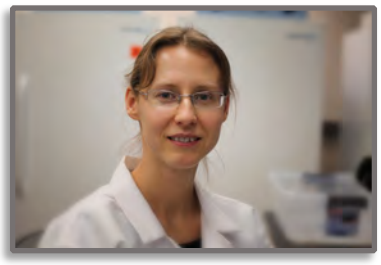
Dr. Kaplan has published over 260 peer-reviewed articles, over 140 invited articles, chapters, or reviews and is a co-editor of the Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 5th, 6th, 7th and 8th Editions. He is Editor-in-Chief--Pediatrics as well as the Co-Editor of the Pediatric Infectious Diseases section of UpToDate®. His current research interests include infections in children caused by Staphylococcus aureus and Streptococcus pneumoniae. Dr. Kaplan is a Past President of the Pediatric Infectious Diseases Society and a past member of the Anti-Infectives Advisory Committee of the FDA and served for 7 years on the Subboard of Pediatric Infectious Diseases of The American Board of Pediatrics including 2 years as chair. In 2011 he received the Arnold J. Rudolph Baylor Pediatric Award For Lifetime Excellence In Teaching. In 2019 he received the European Society for Paediatric Infectious Diseases Distinguished Award for Education and the Distinguished Physician Award of the Pediatric Infectious Diseases Society He also has an Endowed Chair in the Department of Pediatrics at the Baylor College of Medicine named in his honor.

Barbara Kazmierczak, MD, PhD
Gustavus and Louise Pfeiffer Research Foundation MD-PhD Program Director, Professor, Medicine and Microbial Pathogenesis, and Vice Chair for Basic Research (Medicine) at Yale University
Intrinsic Antibiotic Resistance in Pseudomonas aeruginosa

Barbara Kazmierczak, MD, PhD is the Gustavus and Louise Pfeiffer Research Foundation MD-PhD Program Director, Professor of Medicine and Microbial Pathogenesis, and Vice Chair for Basic Research (Medicine) at Yale University. Kazmierczak joined the faculty at Yale University in 2001 as a physician-scientist studying host-pathogen interactions with a focus on P. aeruginosa and its innate immune recognition by the host. Dr. Kazmierczak's research has been funded for over 20 years by the NIH, as well as investigator awards from the Donaghue Foundation and the Burroughs Wellcome Fund. She has served as a Section Editor for PLoS Pathogens and as a member of multiple study sections for NIH/CSR. In recognition of her accomplishments, Kazmierczak has been elected to the American Society for Clinical Investigation, the Interurban Clinical Club, the Connecticut Academy of Arts and Sciences, and is a Fellow of the Infectious Diseases Society of America and of the American Academy for Microbiology.

Paul B. Kilgore, PhD
Postdoctoral Trainee
University of Texas Medical Branch
Non-Antibiotic Based Therapeutics to Combat Multi Antibiotic Resistant Bacteria

Paul Kilgore is a postdoctoral research fellow in the laboratory of Ashok Chopra at the University of Texas Medical Branch. He received his B.S. in Microbiology from the University of Georgia where he studied Salmonella Typhimurium virulence factors. Paul received his PhD in Microbiology & Immunology from the University of Texas Medical Branch where he developed vaccines to protect against pneumonic plague caused by Yersinia pestis. Currently, Paul is studying non-antibiotic-based therapeutics to combat multidrug resistant bacterial infections with an emphasis on host-acting therapies. He is funded by the Gulf Coast Consortia Training Program in Antimicrobial Resistance (TPAMR) T32 training grant.



Natasha Kirienko, PhD
Associate Professor
BioSciences
Rice University

Emergence of Clonal Dominance in Clinical Isolates of Multidrug-Resistant P. aeruginosa

Dr. Kirienko is an Associate Professor at BioSciences Department at Rice University, where she started her independent lab in 2015. She is the President-Elect of Texas Branch ASM and the Chair of the Antimicrobial Resistance Cluster of the Gulf Coast Consortia. Dr. Kirienko started working on host-pathogen interactions during her postdoc at Massachusetts General Hospital / Harvard Medical School under Fred Ausubel and Gary Ruvkun, where she used the model nematode Caenorhabditis elegans to understand virulence mechanisms of Pseudomonas aeruginosa and to identify novel drug treatments. She has continued these projects in her own lab, augmenting them with additional projects on the characterization of acute virulence factors produced by P. aeruginosa (siderophores, rhamnolipids, pyocins), and their impact on mammalian cell survival. During her time at Rice, she has trained 9 graduate and over 50 undergraduate students in her lab.

Christina Lin, MD, PhD
Research Chief Resident
Emory University

Rates of Resistance and Heteroresistance to Newer ß-lactam/ß-lactamase Inhibitors for Carbapenem-Resistant Enterobacterales

Christina Lin, MD, PhD graduated from the Yale School of Medicine and the Yale School of Graduate Studies with a PhD in Microbiology in May 2020. Her PhD research focused on how a critical virulence factor, the Type III Secretion System (T3SS), is expressed in the opportunistic bacterial pathogen Pseudomonas aeruginosa. She completed her internal medicine residency at Emory School of Medicine. During residency, she participated in the Global Health Distinction and Global Health Residency Scholars Program with medical rotations in Tuba City, AZ on the Navajo reservation and Black Lion Hospital in Addis Ababa, Ethiopia. Currently in her research chief resident year, she is studying the antibiotic resistance patterns of carbapenem-resistant Enterobacterales, as well as the epidemiology and clinical outcomes of infected patients. She has matched to Stanford for the joint Infectious Diseases/EIS fellowship to start in July 2024. Her career goals are to research bacterial pathogenesis and antibiotic resistance from the perspectives of global and public health.

Selected Abstract

Thomas Lodise, PharmD, PhD
Professor
Pharmacy and Health Sciences
Albany College
OPTIMIZE-GNI

Thomas Lodise, Pharm.D., Ph.D., is a Professor at Albany College of Pharmacy and Health Sciences, Albany, New York. He is also an infectious diseases clinical pharmacy specialist at the Stratton VA Medical Center, Albany, New York. His research encompasses three interrelated domains: pharmacokinetics (PK)/pharmacodynamics (PD), epidemiology, and outcomes. He has published over 230 peer-reviewed articles in numerous medical and pharmacy journals. He is a scientific editor for Pharmacotherapy and Journal of Antimicrobial Chemotherapy. He is an editorial board member for Antimicrobial Agents and Chemotherapy, Open Forum Infectious Diseases, Antibiotics, and Diagnostic Microbiology and Infectious Diseases. He is the current PK lead for the Antibacterial Resistance Leadership Group (ARLG) (https://arlg.org), an initiative funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

Jacob K. McPherson, PharmD
Ph.D. of Pharmacology Graduate Student
Post-Doctoral Fellow, TMC Training Program in AMR
University of Houston College of Pharmacy
Basis of Commensal Bacillota Resistance to a Novel PolC-type DNA Polymerase III Inhibitor, Ibezapolstat, and the "Narrower" Spectrum of Activity Towards Clostridioides difficile

Dr. Jacob McPherson first became interested in antimicrobial resistance studying the Texas epidemiology of non-susceptible Clostridioides difficile, a leading Gram-positive pathobiont. He received a Bachelor of Science in Cellular and Molecular Biology from the University of Texas at Austin before going on to pursue a PharmD/PhD dual degree program at the University of Houston College of Pharmacy where he continues to study C. difficile infection (CDI). He is a current Gulf Coast Consortia T32 postdoctoral fellow of antimicrobial resistance. His current work focuses on elucidating the structural and kinetic features of commensal Bacillota non-susceptibility to a novel antibiotic, ibezapolstat (IBZ), a Gram-positive selective spectrum (GPSS) PolC-type DNA polymerase III (PolC) inhibitor for the treatment of C. difficile infection (CDI).

He is trained in classical clinical microbiology for the study of antimicrobial resistance, including but not limited to minimum inhibitory concentrations (MIC) and nucleic acid amplification test (NAAT) detection of mechanisms of non-susceptibility. Recently however, he has gained an appreciation for the application of advanced techniques and technologies, like electron cryogenic microscopy (cryo-EM) and molecular dynamics (MD), to better understand the biophysics of drug-target interactions in the Receptor Theory framework of thinking. He hopes is that pairing advanced in silico techniques with classical in vitro assays will better characterize the drug-target interactions in the study of antimicrobial resistant pathogens, such as the microbiome-sparing GPSS nature of the IBZ-PolC interaction for the treatment of CDI.

Maria F. Mojica, PhD
Senior Instructor
Molecular Biology and Microbiology
Case Western Reserve University
B-lactamases in Stenotrophomonas maltophilia

Dr. Maria F. Mojica is a Microbiologist and Master of Science in Biological Sciences from Universidad de Los Andes (Bogota, Colombia). She obtained her Ph.D. in Biochemistry from Case Western Reserve University under the mentorship of Dr. Robert Bonomo. Dr. Mojica is currently a Senior Instructor for the Department of Molecular Biology and Microbiology at Case Western Reserve University. Her research focuses on antimicrobial resistance, specifically mechanistic and structure-function relationship studies on metallo-β-lactamases (MBLs), development of MBL inhibitors, and β-lactam resistance in Stenotrophomonas maltophilia and Burkholderia cepacia complex.

Minh-Hong Nguyen, MD
Professor, Medicine (tenured), University of Pittsburgh, Director Transplant Infectious Diseases Program and Antimicrobial Management Program, University of Pittsburgh Medical Center
Novel Therapeutics Against Fungal Infections

Dr Nguyen is a tenured Professor of Medicine at the University of Pittsburgh, and Co-Director of the Center for Healthcare Mycology and Fungal Genomics at the University of Pittsburgh. She is also Director of Transplant Infectious Diseases and Antimicrobial Management Program at the University of Pittsburgh Medical Center. Her longstanding research interests are in epidemiology of fungal infections, antifungal drug resistance, fungal diagnostics, and molecular pathogenesis of Candida infections. Her laboratory has been continuously funded by the National Institutes of Health and other sources to investigate molecular genetics of fungi, and the pathogenesis of invasive infections by these pathogens. In these roles, she has established molecular detection of echinocandin resistance by screening for FKS mutations among Candida species. She has also established a molecular method to screen for azole resistant Aspergillus fumigatus from clinical samples. Most recently, as PI of NIH-funded projects, her research group has shown, using MinION Nanopore whole genome sequencing, that bloodstream infections (BSIs) caused by Candida species are due to a population of genetic and phenotypic diverse clonal isolates that might differ in antifungal resistance determinants and virulence. These data refute the longstanding paradigm of single organism BSI and suggest a new population-based paradigm of candidemia.

Randall Olsen, MD, PhD
Professor of Clinical Pathology and Genomic Medicine,
Academic Institute
Full Clinical Member, Research Institute
Houston Methodist
Weill Cornell Medical College

Penicillin Resistance in Group A streptococci

Randall Olsen received his Ph.D. (Pathology and Microbiology, 2001) and M.D. (2003) from the University of Nebraska. After completing a clinical pathology residency at Baylor College of Medicine (2006) and a hematopathology fellowship at The Methodist Hospital (2007), he joined the faculty of The Methodist Hospital and Houston Methodist Research Institute.

As a clinical pathologist, Randall Olsen is the Medical Director of the Molecular Diagnostics Laboratory and Co-Medical Director of the Microbiology Laboratory at Houston Methodist. He is also a Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College.

Randall Olsen's research has focused on the study of molecular pathogenesis and host-pathogen molecular interactions of Group A Streptococcus and related pathogens. Recently, this line of investigation has led to the discovery of gene mutations that cause reduced susceptibility to beta-lactam antibiotics.

Michael Otto, PhD
Senior Investigator
Laboratory of Bacteriology
NIAID, NIH

Probiotics for Staphylococcus aureus: A Translational Approach

Dr. Otto is one of the leading worldwide scientists in the field of Gram-positive bacterial pathogenesis. He focuses on the role of staphylococci and other Gram-positive bacteria in the interaction with the human host, addressing both beneficial and harmful aspects during colonization and infection by integrative use of molecular microbiology, immunology, and biochemistry approaches. He has made significant contributions for example to our understanding of virulence mechanisms of community-associated MRSA, the role of small peptide toxins in Staphylococcus aureus pathogenesis and host interaction, and the molecular underpinnings of staphylococcal biofilm formation. His laboratory currently focuses on mechanisms of gut, nose, and skin colonization by S. epidermidis and S. aureus and studies whether S. aureus decolonization can be achieved by probiotic microbiome-editing. Dr. Otto completed his diploma in biochemistry in 1994 and his PhD in microbiology in 1998 at the University of Tuebingen in Germany. He then took a position as principal investigator at the National Institute of Allergy and Infectious Diseases in Hamilton, Montana and moved his laboratory to the NIH main campus in Bethesda, Maryland, after receiving tenure in 2008. Dr. Otto has published more than 280 manuscripts, mostly in the field of staphylococcal pathogenesis, and given multiple presentations at US and international conferences. He serves on several editorial boards and is section editor for Gram-positive pathogens at PLoS Pathogens.

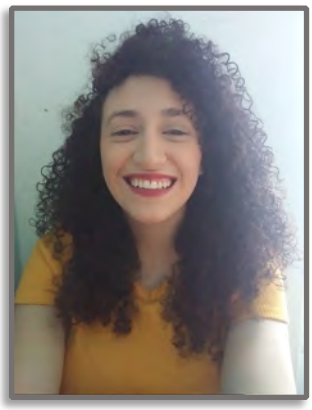
Keynote presenter

Krupa Parmar, MS
Research Technologist/ Fellow
Infectious Diseases Research Laboratory
Mayo Clinic
Reproducibility of Pseudomonas aeruginosa Phage Susceptibility Testing: A Multicenter Compariso

Krupa Parmar is a Phage Researcher at Mayo Clinic's Infectious Diseases Research Laboratory in Rochester, MN. She is a qualified microbiologist and has experience in bacteriophage research for 9+ years.

Her research experience involves work on phage therapy targeting enteric pathogens and phages controlling anaerobic sulfate-reducing bacteria in petroleum oil wells in India. During her doctoral studies in Germany, Krupa delved into understanding the intricate dynamics among antibiotics, phages, and bacteria, unraveling their impact on bacterial community structures.

Currently positioned at Mayo Clinic, Krupa's research focuses on several fronts. She leads efforts in testing phages tailored to combat staphylococcal biofilms in prosthetic joint infections, tackling multi-drug resistant bacteria. Additionally, she works with phage susceptibility testing for the ARLG clinical trial for cystic fibrosis. Her study extends to investigating the stability of phages in phage-nanopolymer assemblies for wound healing applications and standardizing phage susceptibility testing methods. Beyond these endeavors, Krupa Parmar actively explores the immune response triggered by phage therapy, aiming to pave the way for innovative approaches in bacteriophage research.



Dormarie E. Rivera Rodríguez
Ph.D. Candidate
Emory University
Impact of Antibiotic Treatment on Lactobacillus Population Dynamics and Intestinal T Cell Regulatory Function

Dormarie is a fourth-year Ph.D. candidate in the Immunology and Molecular Pathogenesis (IMP) program and an ARTDTP fellow at Emory University. She obtained her B.S. degree in Biomedical Sciences from the University of Puerto Rico in Ponce (UPRP) in the summer of 2020. She is currently mentored by Drs. David S. Weiss and Luisa Cervantes-Barragan to study how oral antibiotic use affects the host microbiome-immune system interactions. Her dissertation aims to demonstrate how commonly prescribed antibiotics, such as ciprofloxacin, select for microbiota species, like Lactobacillus, that subsequently alters the intestinal immune regulatory functions.

Warren Rose, PharmD, MPH
Associate Professor
Pharmacy and Medicine
University of Wisconsin-Madison
Novel Dug Combinations to Address Antimicrobial Resistance

Warren Rose is an Associate Professor of Pharmacy and Medicine (tenure) at the University of Wisconsin-Madison. His translational research employs three distinct themes of pharmacology with multiple layers of projects to study multi-drug resistant pathogens. These research areas surround understanding the translational effects of antimicrobials including i) antibiotic efficacy such as combination therapy and resistance suppression, ii) impacts on bacterial pathogenicity (toxins and virulence factors, and iii) antibiotic effects on host-pathogen interactions including innate immune responses and pathogen immune evasion/dysregulation. His research has been continuously funded by diverse sources including NIH (R01/R21), professional societies/organizations, and the pharmaceutical industry. Dr. Rose has received awards from pharmacy and infectious diseases societies spanning Young Investigator of the Year to Distinguished Investigator Award in his career. He has been an appointed member to the Editorial Board of Antimicrobial Agents and Chemotherapy since 2016. He is an Honorary Fellow of both the Infectious Diseases Society of America and the American College of Clinical Pharmacy. Dr. Rose holds clinical appointments within the Department of Pharmacy at UW Health where he works with the Antimicrobial Stewardship Team.

Felicia Ruffin, PhD, MSN, BSN, BA
Clinical Research Program Leader
Duke University Medical Center

Discovering Disparities in Clinical Characteristics and Outcomes Among Patients Treated in US Hospitals for Carbapenem—Resistant Enterobacterales (Bloodstream) Infections

Felicia Ruffin is a Clinical Research Program Leader at Duke University Medical Center in Durham, North Carolina. For over a decade and a half, she has provided leadership for a large lab focused on translational research designed to understand antimicrobial resistance and the determinants of the outcomes of bacterial infections. Dr. Ruffin's research has defined contemporary microbiology, epidemiology, and outcomes of Gram-positive and Gram-negative bacterial bloodstream infections. Most recently she was awarded an EVERYONE Diversity Seed grant from the Antimicrobial Resistance Leadership Group (ARLG) to evaluate disparities among patients with multidrug resistant (MDR) bacterial infections. Her research interests include the development of interventions that address change at the individual level and social and policy changes that are likely to impact health equity.

Jacob Rutherford, BSc

Graduate Student

Texas A&M University Institute of Biosciences and Technology

Fusobacterium nucleatum Enoyl-ACP Reductase II (FabK): A Narrow-Spectrum Drug Target

Jacob Rutherford is a 5th year PhD candidate in the lab of Dr. Julian Hurdle at Texas A&M University's Institute of Biosciences and Technology. He received his Bachelor of Science in Microbiology from North Carolina State University in 2017. He worked at the Plum Island Animal Disease Center as an ORISE fellow for a year, before joining the PhD program at the IBT in 2019. His graduate work investigates the enoyl-ACP reductase, FabK, as a narrow-spectrum drug target; validating FabK as a target in Fusobacterium nucleatum and utilizes high-throughput screening to identify novel inhibitors of FabK.

Michael J. Rybak, PharmD, MPH, PhD
Professor of Pharmacy
Director, Anti-Infective Research Laboratory
Department of Pharmacy Practice
Eugene Applebaum College of Pharmacy & Health Sciences/School of Medicine, Wayne State University
Optimizing Phage-Antibiotic Combination Therapy and Challenging Clinical Cases in Antimicrobial Resistance

Michael J. Rybak, Pharm.D., M.P.H., PH.D., FCCP, FIDSA, FIDP is Professor of Pharmacy, Department of Pharmacy Practice, Director, Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy & Health Sciences, Wayne State University. He is also adjunct Professor of Medicine, Division of Infectious Diseases, School of Medicine at Wayne State University and Adjunct Clinical Professor at the University of Michigan College of Pharmacy. He is affiliated with the Detroit Medical Center and is a member of their antimicrobial stewardship committee.

Dr. Rybak's research focus is antimicrobial pharmacokinetics and pharmacodynamics (PK/PD) and the assessment of infectious diseases health outcomes including their relationship to bacterial resistance.

Dr. Rybak is funded by the National Institute for Allergy and Infectious Diseases (NIAID) and via several investigator-initiated grants from the State of Michigan public health department and from Pharmaceutical Industry. He has published more than 450 manuscripts and authored more than 20 book chapters on antimicrobial PK/PD, resistance and antimicrobial stewardship. He is the co-editor-in-chief of the journal Infectious Diseases and Therapy, Associate Editor for Clinical Infectious Diseases, Scientific editor for Infectious Diseases for the journal Pharmacotherapy and editorial board member for the journal Antibiotics and for Contagion. Dr. Rybak is the recipient of a number of scholarship awards including the ACCP and ASHP awards for sustained contributions to the literature, the ACCP Therapeutics Frontiers Lecture award and the ACCP Infectious Diseases Practice Network Distinguished Investigator award. He was recently inducted into the Academy of Scholars at Wayne State University for recognition of outstanding excellence in scholarship.

Michael Satlin, MD
Infectious Diseases Physician
Associate Professor
Medicine and Pathology and Laboratory Medicine
Weill Cornell Medicine
Mastermind-Ring

Dr. Michael Satlin an infectious diseases physician and Associate Professor of Medicine and of Pathology and Laboratory Medicine at Weill Cornell Medicine. He is the Clinical Director of the Transplantation-Oncology Infectious Diseases Program at Weill Cornell. He completed medical school at the University of Virginia School of Medicine and internal medicine residency and infectious diseases fellowship training at NewYork-Presbyterian Hospital/Weill Cornell. His research focuses on the epidemiology, prevention, and treatment of multidrug-resistant Gram-negative infections, with a focus on immunocompromised hosts. He has authored or co-authored over 110 peer-reviewed manuscripts. He is a Senior Editor of Journal of Antimicrobial Chemotherapy-Antimicrobial Resistance and serves on the Editorial Boards of Journal of Clinical Microbiology, Clinical Infectious Diseases and Open Forum Infectious Diseases, and Transplant Infectious Diseases. He is a Member of the Clinical and Laboratory Standards Institute's (CLSI) Subcommittee on Antimicrobial Susceptibility Testing and Co-Chair of its Breakpoint Working Group. He also serves on IDSA's guidance panel for the treatment of antibiotic-resistant Gram-negative infections.

Samuel Shelburne, MD, PhD
Professor
Infectious Diseases and Genomic Medicine
MD Anderson Cancer Center
Challenging Clinical Cases in Antimicrobial Resistance

Dr. Shelburne is a Professor in the Departments of Infectious Diseases and Genomic Medicine at MD Anderson Cancer Center (MDACC) in Houston, TX. He is the Deputy Chair for Research Development and leader of Genomic Infectious Diseases at MDACC. He received his BA in Art History from Princeton University, attended the University of Texas Medical Branch in Galveston for medical school, and then completed his residency and infectious diseases fellowship at Baylor College of Medicine in Houston, TX. His laboratory focuses on using genomics to investigate a broad array of clinically important infectious diseases areas such as invasive disease due to group A streptococci and antibiotic resistance.

William Shropshire, MPH, PhD
Postdoctoral Fellow
MD Anderson Cancer Center

Elucidating Molecular Mechanisms Underlying Successful Adaptation to Carbapenem Antimicrobials in High Risk Carbapenem Resistant Escherichia coli Lineages

William Shropshire, PhD is a second year T32 Gulf Coast Consortia Training Program in Antimicrobial Resistance (TPAMR) Postdoctoral fellow working under the primary supervision of Dr. Samuel Shelburne within the Department of Infectious Diseases at the University of Texas MD Anderson Cancer Center. Dr. Shropshire has had over a decade of research experience that primarily focuses on infectious diseases genomics and epidemiology. He has especially been interested in applying next generation sequencing analyses to these rapidly evolving fields. His contributions span a diverse range of topics, from molecular mechanisms of antimicrobial resistance to genomic epidemiology of infectious disease outbreaks.

His current T32 project focuses on elucidating genomic and transcriptomic factors contributing to the progressive development of carbapenem resistance within Escherichia coli causing invasive infections. His research has highlighted the clinical impact of extended-spectrum beta-lactamase (ESBL) positive Enterobacterales infections in cancer patients and how amplification of ESBL encoding genes can lead to a spectrum of □-lactam resistance phenotypes. Through this project, Dr. Shropshire is collecting preliminary data that will support an upcoming Mentored Research Scientist Development (K01) Award submission where his goal is to characterize the full spectrum of carbapenem survival mechanisms that contribute to complicated, chronic infections.

Arjun Srinivasan, MD
Deputy Director for Program Improvement
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Protecting Patients. Combating Antimicrobial Resistance. An Update from CDC

Dr. Srinivasan is the Deputy Director for Program Improvement in the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention and a Captain in the United States Public Health Service. He is board certified in Infectious Diseases. Before coming to CDC he was as Assistant Professor of Medicine in the Infectious Diseases Division at the Johns Hopkins School of Medicine where he was the founding director of the Johns Hopkins Antibiotic Management Program and the associate hospital epidemiologist. His primary responsibilities include oversight and coordination of efforts to eliminate healthcare associated infections and reduce antibiotic resistance. His research and investigative areas of concentration have included outbreak investigations, infection control, multi-drug resistant gram negative pathogens and now focus on hospital antibiotic stewardship. Dr. Srinivasan has published more than 100 articles in peer-reviewed journals on his research in healthcare epidemiology, infection control and antimicrobial use and resistance.

Keynote presenter

Madison Stellfox, MD, PhD
Infectious Diseases Fellow
University of Pittsburgh Medical Center
Functional Genomics of Difficult to Treat Enterococcal Isolates and Their Viral Adversaries

Madison is currently an infectious disease fellow and postdoctoral scholar the University of Pittsburgh Medical Center (UPMC). She obtained her PhD in Biochemistry and Molecular Genetics from the University of Virginia, studying human centromere epigenetics with Dr. Daniel Foltz. Afterwards, she obtained her MD from New York Medical College in Valhalla, NY where she developed a clinical and research interest in infectious diseases. She has since completed her internal medicine residency at UPMC and has continued on at UPMC for her fellowship training in infectious diseases, serving as Chief ID Fellow for the 2021-2022 academic year. She is currently a T32 post-doctoral scholar at the University of Pittsburgh working in the laboratory of Dr. Daria Van Tyne. Madison's research focuses on the adaptations of vancomycin-resistant enterococci during recurrent and persistent infections as well as the clinical use of enterococci-targeting bacteriophages. In addition to her research activities, Madison also recently joined the Early-Career Editorial Board at mBio.

Jesus R. Torres, MD, MOH, MSc
Assistant Professor of Emergency Medicine
Department of Emergency Medicine
David Geffen School of Medicine
University of California, Los Angeles

Emerging S. aureus Antimicrobial Resistance and Current Prescribing Practices for Patients Presenting to US Emergency Departments with a Purulent Skin and Soft Tissue Infection

Dr. Torres is an assistant professor of emergency medicine at UCLA. He started his career as a research assistant for the EMERGEncy ID NET group, a network of emergency departments that conducts infectious disease research, and is now co-investigator. He trained at UCSF in emergency medicine and completed the National Clinician Scholars Program (NCSP) at UCLA for his research fellowship. Dr. Torres also earned an MPH in quantitative methods from Harvard and an MSc in health policy from UCLA. He is interested in skin and soft tissue infections, antimicrobial resistance, and the strategic utilization of emergency departments as surveillance networks for emerging infectious disease and equity in clinical research.

M. Stephen Trent, PhD
Distinguished Professor
Infectious Diseases
Univeristy of Georgia
Cell Membrane Remodeling in Gram-negative Bacteria

M. Stephen Trent earned a bachelor's degree in chemistry at the University of Virginia and a Ph.D. at the James H. Quillen College of Medicine at East Tennessee State University. He was a Kirschstein NIH Postdoctoral Fellow in the laboratory of Dr. Christian R. H. Raetz at Duke University before establishing his own laboratory in 2002. Dr. Trent is currently a Foundation Distinguished Professor at the University of Georgia (UGA) in the School of Veterinary Medicine and a member of the Center for Vaccines and Immunology. Prior to UGA, he was a Professor in the Department of Molecular Biosciences at the University of Texas in Austin. He has served or is serving as an Editorial Board Member, Guest Editor, or Associate Editor for Molecular Microbiology, Journal of Biological Chemistry, mBio, Innate Immunity, Proceedings of the National Academy of Sciences, and PLoS Pathogens. Dr. Trent has served as a panel member for multiple grant-funding agencies, including as a permanent study section member for NIH, and on the scientific advisory boards of several biopharmaceutical companies. He has multiple teaching awards for his instruction of undergraduate, graduate, and medical students. For his research accomplishments, he has received a Distinguished Alumni Award, the Zoetis Award for Research Excellence, the Alois Nowotny Award for Research Excellence, The Lamar Dodd Creative Research Award, and was appointed Fellow to the American Academy of Microbiology (2014) and to the American Association for the Advancement of Science (2023). Dr. Trent has over 125 publications that include patents, book chapters, and research manuscripts. His research program has been funded by the Cystic Fibrosis Foundation, the Department of Defense, the Henry Jackson Ford Foundation, and the National Institutes of Health with approximately 25 million in extramural funding.

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Influence of the COVID-19 Pandemic on Antimicrobial Resistance Patterns in Pediatric Group A *Streptococcus* Infections in Houston, TX

Aya Aboulhosn[1], Maria G. Segura[1], Misu A. Sanson[1], Luis A. Vega[1], Sakina Chinwala[1], Lauren Sommer[2], J. Chase McNeil[2], and Anthony R. Flores[1]

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Group A *Streptococcus* (GAS) is a human-specific pathogen that causes a wide spectrum of disease including severe invasive disease associated with high morbidity and mortality. Despite nearly 100 years of use, penicillin (and its derivatives) remains the backbone of GAS therapy with no documented resistance. However, resistance to commonly used second-line therapies such as macrolides and clindamycin has been steadily increasing over the past several years to the point that macrolide-resistant GAS is now considered an emerging threat. We previously reported increased frequency of second-line antimicrobial resistance in GAS strains derived from invasive infections compared to non-invasive infections in the Houston pediatric population. Given recent surges of pediatric GAS infections associated with the later stages of the COVID-19 pandemic, we sought to compare pre-pandemic (2013-2019) and pandemic (2020-present) rates of GAS antimicrobial resistance. GAS isolates were collected from the clinical microbiology laboratory at Texas Children's Hospital under a protocol approved by Baylor College of Medicine. The pre-pandemic period included the years 2013 through 2019 and the pandemic years 2020 through June 30, 2023. Demographic information and disease types [invasive (INV), skin and soft tissue infection (SSTI), and pharyngeal (PHG)] were abstracted from the medical record. All GAS strains were *emm* typed and resistance to tetracycline, erythromycin, and clindamycin were determined using disk diffusion. Nonsusceptibility was defined by a zone of inhibition interpretation of either intermediate or resistant. We analyzed a total of 2,506 GAS isolates over the two study periods (n=1640, pre-pandemic; n=866 pandemic). The overall nonsusceptibility to at least one antimicrobial increased from 19% in the pre-pandemic period to 40% in the pandemic (P<0.0001) – driven primarily by increased frequency of nonsusceptibility within types *emm1*, *emm12*, and *emm28*. Interestingly, *emm12* and *emm28* GAS strains were the only *emm* types to increase significantly in frequency during the pandemic (38% each) compared to the pre-pandemic (20% and 15%, respectively) period (P<0.05). Nonsusceptibility to clindamycin was most prominent increasing nearly 4-fold (6.8% versus 25.3%) during the pandemic period. Less common or rare *emm* types (<10 isolates combined over the 2 study periods) were noted to have significantly increased

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frequency of nonsusceptibility to any of the tested antimicrobials (80%) during the pandemic period compared to the pre-pandemic (45%) (*P*=0.0034). Finally, in contrast to previous studies, the frequency of any antimicrobial resistance was similar between GAS derived from different disease types during the pandemic period (INV, 37.4%; SSTI, 42%; and PHG 41.1%). In conclusion, increased frequency of GAS resistance to second-line antimicrobials was observed during the pandemic compared to pre-pandemic years. Clinicians should be aware of the possible reduced effectiveness of clindamycin in pediatric GAS infections. Additional studies are needed to identify any genetic changes associated with increased frequency of resistance and potential new GAS clone emergence.

Poster 8

The Use of Secondary Metabolites from *Zingiber officinale* as an Adjuvant Treatment to Multidrug-Resistant Bacteria

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Background: Antibiotics were introduced to the world in the 20th century, and the threat of bacterial infections became a problem of the past. However, as the utilization of these drugs increased, so did the number of resistant bacteria due to the selective pressure placed on them. Today, antibiotic resistance is an issue that is at the forefront of the World Health Organization's (WHO) agenda due to the threat that it poses to public health. Recent innovations have targeted utilizing secondary plant metabolites to treat antibiotic-resistant bacteria[1]. More specifically, *Zingiber officinale* secondary metabolites have demonstrated antimicrobial properties that are effective against multi-drug resistant bacteria when administered adjuvant to antibiotics[1].

Goals: This analysis aims to review recent literature and experimental data evaluating the efficacy of secondary plant metabolites from *Zingiber officinale* as a treatment against multidrug-resistant bacteria.

Methods: A keyword search was performed of medical literature using the terms "Zingiber officinale" and "antibiotic resistance".

Results: One study aimed to determine the effect of medicinal plants on the inhibition of the AcrAB-ToLC efflux pump found in drug-resistant *Salmonella typhimurium*[2]. The presence of this efflux pump is one of the mechanisms by which antibiotic-resistant bacteria persist in the presence of antibiotics. Evidence from the study showed that the secondary metabolite, lariciresinol, from *Zingiber officinale* has a synergistic effect with ciprofloxacin and tetracycline in the treatment of drug-resistant *Salmonella typhimurium*[2]. Lariciresinol was shown to decrease the minimum inhibitory concentration (MIC) by 2-to-4 folds in combination with ciprofloxacin and tetracycline[2]. EtBr efflux inhibition assays, which are used to determine AcrAB-ToLC efflux pump activity, showed an increased EtBr accumulation which means that the the efflux pumps had decreased activity. The results from the study concluded that lariciresinol, from *Zingiber officinale*, could potentially lead to the inhibition of the AcrAB-ToLC efflux pump found in drug-resistant *Salmonella typhimurium*[2].

Conclusions: Evidence from the study supports further research into the use of secondary metabolites from *Zingiber officinale* to fight the growing number of antibiotic-resistant bacteria. Future research could be done on the effect that lariciresinol has on different antibiotic-resistant bacteria. Additionally, different secondary metabolites from different plants should be used as they were used in the study to determine the efficacy of other potential plants as adjuvant therapy to antibiotics.

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Comparative Analysis of Vancomycin-Resistant Enterococci: Gut Colonization Vs. Clinical Isolation in ICU Patients

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Enterococci bacteria are commonly found in the human gut microbiome and the environment.[1] While these bacteria have the potential to cause infections, the emergence of antibiotic-resistant strains, notably Vancomycin-Resistant Enterococci (VRE), poses a serious public health concern.[1] Our study focuses to investigate the prevalence of VRE in both gut colonization and clinical isolates obtained from patients admitted to the intensive care unit (ICU).

Patients included in the DYNAMITE study patients either had a positive stool culture for VRE or a clinical isolate containing enterococcus species. This cohort consisted of patients admitted to ICUs at both Houston Methodist Hospital and Memorial Hermann Hospital, including the Cardiovascular ICU (CICU), Medical ICU (MICU), Neurological ICU (NICU), and Surgical & Liver ICU (SLICU). Stool samples were cultured on selective media to detect VRE colonization, and the results were subsequently confirmed using MALDI-TOF. The clinical presentation of enterococcus species was determined by extracting positive laboratory cultures from various sources collected throughout the patient's hospital stay.

Among the cohort of 59 patients analyzed, 27 (45.8%) exhibited positive clinical isolates for *Enterococci*. Within this group, 10 patients (5.9%) tested positive for VRE, while 44 patients (74.6%) showed the presence of VRE in stool cultures. Notably, within the ICUs, the distribution was as follows: 23 patients (39.0%) in the Cardiovascular ICU (CICU), 17 (28.8%) in the Medical ICU (MICU), 8 (13.5%) in the Neurological ICU (NICU), and 11 (18.6%) in the Surgical & Liver ICU (SLICU). Across all ICUs, *E. faecium* was identified as the predominant VRE strain in stool cultures, present in over 70% of patients within each ICU.

On the other hand, when examining bacterial cultures featuring *Enterococcus* species, different patterns emerged: *E. faecalis* and other *Enterococcus* species predominated in CICU patients, both E. faecalis and *E. faecium* were prevalent in MICU patients, E. faecalis was prominent in NICU patients, and E. faecium was predominant among SLICU patients.

In conclusion, our study sheds light on the prevalence of VRE in both gut colonization and clinical isolates obtained from ICU patients. The emergence of VRE, especially *E. faecium*, as a dominant strain in stool cultures among ICU patients, highlights the significance of monitoring and managing antibiotic-resistant strains in healthcare settings. While VRE was detected in a smaller subset of patients, the findings emphasize the need for vigilant surveillance and infection control measures to attenuate the spread of these resistant bacteria, particularly in critical care environments. Understanding the dynamics of *Enterococcus* species and their varying prevalence among different ICU settings underscores the importance of tailored interventions aimed at minimizing the impact of antibiotic resistance in hospital-acquired infections.

Acknowledgements: P01 DYNAMITE Project (1P01AI152999-01) Sponsored by the National Institutes of Health/National Institute for Allergy and Infectious Diseases

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Poster 7

Organizational Readiness Assessment for a National Antimicrobial Stewardship Intervention

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Introduction: Scaling up a successful antimicrobial stewardship effort on a national level relies on engagement of individual hospitals. The organizational readiness for change assessment survey (ORCA) is a tool to assess a site's readiness for implementation and identify barriers to change. Domains measured by the ORCA include evidence assessment (perceived strength of evidence for the proposed change), leader culture, staff culture, leadership behavior, membership (team member roles), opinion leaders, and general resources (available to facilitate implementation). As we rolled out the "Kicking CAUTI" antibiotic and diagnostic stewardship intervention on a national scale, we administered the ORCA survey to participating sites at baseline.

Hypothesis/Aims: We examined baseline ORCA scores and differences between the ORCA subscales to provide actionable information for implementation of antibiotic stewardship programs.

Methods: We collected baseline ORCA surveys from healthcare personnel from 40 VA medical centers participating in the "Kicking CAUTI" campaign to reduce testing for and treatment of asymptomatic bacteriuria treatment among hospitalized patients. Surveys were distributed by email to prescribing providers, nurses, pharmacists, infection preventionists, and quality managers. Only sites that submitted greater than six ORCA surveys were included. Mean Likert scores were calculated for each ORCA subscale on a scale of 1-5 (5 highest).

Results: Among the participating sites, 17/40 (43%) completed at least six surveys, with a total of 153 surveys included for analysis. The largest group of respondents was physicians with 40% of the surveys, followed by pharmacists at 19% and nurses at 14%. The highest ranked mean among all sites on the ORCA was in the evidence subscale with a mean of 4.3, (SD 0.6), (**Table 1**). The lowest ranked mean among all sites was in resources with a mean of 3.3 (SD 0.8) (**Table 1**). Breaking down the resources domain into individual questions identified that staffing support was driving the low score with a mean of 2.9 (SD 1.1).

Table 1
ORCA scores for subscales
N=17 sites

Subscale	Overall, mean (SD)
Evidence assessment	4.3 (0.6)
Leader culture	3.7 (0.8)
Staff culture	3.8 (0.7)
Leadership behavior	3.6 (0.9)
Measurement	3.5 (0.9)
Opinion leaders	3.8 (0.8)
General resources	3.3 (0.8)

Conclusions: The high score for the evidence subscale suggests that all sites perceive that the evidence base for refraining from testing or treating asymptomatic bacteriuria is strong. The lowest scoring domain across all sites in this antibiotic stewardship project was the resources available for achieving change, specifically a lack of staff to support stewardship efforts. Limited resources remain a potential barrier to implementing a national antimicrobial stewardship intervention.

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Sociodemographic Factors Associated with Knowledge of Antibiotic Risks Among an Outpatient Population

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Background: The rise in antibiotic resistance continues to pose a challenge to both individual and public health. Understanding which sociodemographic groups are aware of the potential risks associated with antibiotic use is essential for developing targeted educational interventions. We studied the relationship between individuals' sociodemographic factors (e.g., insurance status, healthcare system, and health literacy) and their knowledge of antibiotic risks.

Methods: We surveyed patients in public clinics and private emergency department waiting rooms in Houston from January 2020 through June 2021. Respondents' knowledge about risks associated with antibiotic use was assessed with an open-ended question, "Do you know about any risks associated with antibiotic use?" Their answers were then categorized into themes. If the patient mentioned either side effects of antibiotics or antimicrobial resistance, this respondent was classified as having knowledge of antibiotic risks. We performed Chi-square tests on the sociodemographic factors and knowledge of antibiotic risks.

Results: We surveyed 564 individuals (median age of 51), with 72% identifying as female, 46.6% as Hispanic, and 33% as Black or African American. When asked about knowledge of antibiotic risks, 355 (63%) respondents mentioned at least one risk associated with antibiotics. Risks mentioned included side effects of antibiotics (270/355, 76%), and antibiotic resistance (105/355, 29%). Younger age (18-64 years) was associated with a lack of knowledge of antibiotic risks (p=0.036). None of the measured modifiable risk factors (insurance status, healthcare setting, education level, and health care literacy) were associated with knowledge of antibiotic risk.

Conclusion: This study reveals a gap in patients' knowledge about antibiotic risks among our survey respondents, with only 63% reporting knowledge of any adverse effects. Younger individuals in our survey cohort were least informed about side effects of antibiotics or knowledge of antibiotic resistancecompared to other age groups. Our results suggest that patients from all socioeconomic groups may benefit from additional education about the risks associated with antibiotics.

Acknowledgments
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Poster 31

Epidemiology of Infections with Multidrug-Resistant Organisms in Patients with Left Ventricular Assist Devices (LVADs)

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Left ventricular assist devices (LVADs) constitute one of the limited options available to patients with refractory heart failure. Infection is the most common adverse event after LVAD placement, and difficult to eradicate when attributable to the LVAD itself. LVAD-attributable infections (LVADI) thus lead to significant antibiotic exposure and higher risk for antibiotic resistance. However, the epidemiology of multidrug-resistant organisms (MDROs) causing LVADI has not been described.

We conducted a retrospective cohort study of patients (pts) ≥18 years old with LVADs implanted from 2016 to 2022 at our institution. Infections were defined as LVADI if i) there was a positive culture from LVAD components, with or without concomitant blood cultures, or ii) there were positive blood cultures with radiologic evidence of LVADI. MDROs were defined according to the Centers for Disease Control (CDC) criteria. Primary outcome was mortality, and multivariate logistic models were built and adjusted for patient demographics and Charlson's Comorbidity Index.

A total of 252 pts were implanted with new LVADs, with 104 (41.2%) pts developing LVADI. Of the 52 episodes of bloodstream infection (BSI) in 41 pts, 36.5% were caused by MDRO, with Methicillin-Resistant *Staphylococcus aureus* (MRSA) and MDR *Pseudomonas aeruginosa* most frequent. There were an additional 64 pts with 99 infections with positive LVAD component cultures, with a total of 115 pathogens isolated. Of these, 20% were MDRO, with MRSA and MDR Enterobacterales most frequent. Multivariate logistic models showed that pts with LVADI did not have higher odds of mortality (OR =1.61; 95% CI [0.92 – 2.81]; p=0.1), however pts with MDRO LVADI had a greater than 3 times odds of mortality (OR = 3.34; 95%CI [1.68 – 6.64]; p<0.001) compared to pts without MDRO LVADI.

Our review provides initial insight as to the burden of antibiotic resistance among bacteria causing LVADI. The frequency of LVADI in our cohort is higher than what has previously been reported, possibly due to higher vigilance. The MDROs MRSA, MDR *Pseudomonas aeruginosa*, and MDR Enterobacterales are prominent in this population. Further study is needed to elucidate the risk factors for acquiring MDRO LVADIs and contributing factors to mortality in LVAD pts.

Acknowledgements: This work is supported by NIH Loan Repayment Program award L30AI154520 and Houston Methodist Clinical Scholars Award to DBA and NIH/NIAID grants K24AI121296, R01AI134637, R01AI148342-01, and P01AI152999 to CAA.

Poster 12

Combating Antimicrobial Resistance: A Global Health Imperative and Advocacy Approach

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Background: Antimicrobial resistance (AMR) throughout the world is an ever-growing concern. As medical and surgical interventions continue to progress, the need for a sustainable path to address public health concerns related to AMR has become pivotal in order to ensure the improvement of future population health in developing countries. As the cost of developing novel antibiotics continues to rise (Ventola, 2015), the need for advocacy for underserved populations throughout the globe who face AMR becomes even greater.

Goals: Conduct a comprehensive review of relevant literature and data to analyze the current status of AMR within underserved populations. Next, further examine how different forms and methods of advocacy may be effective for these populations within various healthcare systems across the world.

Methods: A keyword and boolean operator search was conducted on peer-reviewed articles consisting of the following phrase “Antimicrobial resistance and global health and advocacy.” Each pertinent article and corresponding data was examined prior to inclusion.

Results: Evidence was found to illustrate the growing need for continued research into the development of novel antimicrobial drugs in underserved and marginalized populations. In addition to providing incentives for research through tax credits and grants (Dutescu and Hillier, 2021), advocacy for underserved populations globally may be effective when focused on providing these and additional monetary incentives for research into drugs most needed in many marginalized communities, such as antibiotics, antiparasitics, antivirals, tuberculosis medications, and vaccines (CDC, 2020). Advocacy efforts should be adjusted to maximize effectiveness when used in varying contexts, such as increasing awareness of AMR (Baekkeskov et. al., 2020), advocating for national or state legislative policy, and advocacy in local community efforts .

Conclusion: The results support further investigation of how AMR impacts various global health populations and underserved groups to ensure that future advocacy efforts can be appropriately directed and effectively utilized

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Poster 32

Changes in Antibiotic Susceptibilities Attributed to the Infection Environment

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While certain aspects of the host-pathogen interface are common to all sites of infection, other factors can be highly specific to the localized environment. For example, chronic infections are often polymicrobial with the specific microbial consortia present varying greatly between patients. Additionally, nutrient and atmospheric composition shifts between different sites of infection. Herein, we demonstrate that antibiotic susceptibility profiles of pathogens can dramatically shift with changes in the microbial consortium, oxygen levels, or carbon source availability. Specifically, we demonstrate that *Enterococcus faecalis* grown in a polymicrobial community containing other common wound pathogens (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) demonstrated increased susceptibility to gentamicin due to heme cross-feeding allowing more gentamicin to enter the cell via altered proton motive force. However, performing the same AST in anaerobic conditions reversed this phenotype. When *E. faecalis* was grown in community with *A. baumannii*, it exhibited decreased susceptibility to cephalexin as *A. baumannii* likely produces a beta-lactamase allowing for the neutralization of the antibiotic. Further research demonstrated that environmental conditions, like available carbon sources, can also influence antibiotic susceptibilities. *P. aeruginosa* exhibits increased susceptibility to kanamycin when grown in minimal media containing glycerol, as compared to minimal media with malonate, but decreased susceptibility to ciprofloxacin. Overall, these results demonstrate that environmental conditions, such as community members and available nutrient sources, play a role in determining an individual bacterium's antibiotic susceptibility. By accounting for the infection environment when determining antibiotic susceptibilities, we can more effectively treat persistent infections, leading to improved patient outcomes.

Acknowledgements: I would like to thank Dr. Catherine Wakeman for her guidance, as well as the rest of the Wakeman lab for their support. I would also like to thank our funding sources: NIH/NIAID (R01AI173686), NIH/NIGMS (R15GM128072) as well as a TTU Mid-career grant.

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Organizational Readiness Assessment for a National Antimicrobial Stewardship Intervention

Authors: Braund, S[1]; Amenta, E[1,2]; Grigoryan, L[3]; Trautner, B.W[1,2]

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Introduction: Scaling up a successful antimicrobial stewardship effort on a national level relies on engagement of individual hospitals. The organizational readiness for change assessment survey (ORCA) is a tool to assess a site's readiness for implementation and identify barriers to change. Domains measured by the ORCA include evidence assessment (perceived strength of evidence for the proposed change), leader culture, staff culture, leadership behavior, membership (team member roles), opinion leaders, and general resources (available to facilitate implementation). As we rolled out the "Kicking CAUTI" antibiotic and diagnostic stewardship intervention on a national scale, we administered the ORCA survey to participating sites at baseline.

Hypothesis/Aims: We examined baseline ORCA scores and differences between the ORCA subscales to provide actionable information for implementation of antibiotic stewardship programs.

Methods: We collected baseline ORCA surveys from healthcare personnel from 40 VA medical centers participating in the "Kicking CAUTI" campaign to reduce testing for and treatment of asymptomatic bacteriuria treatment among hospitalized patients. Surveys were distributed by email to prescribing providers, nurses, pharmacists, infection preventionists, and quality managers. Only sites that submitted greater than six ORCA surveys were included. Mean Likert scores were calculated for each ORCA subscale on a scale of 1-5 (5 highest).

Results: Among the participating sites, 17/40 (43%) completed at least six surveys, with a total of 153 surveys included for analysis. The largest group of respondents was physicians with 40% of the surveys, followed by pharmacists at 19% and nurses at 14%. The highest ranked mean among all sites on the ORCA was in the evidence subscale with a mean of 4.3, (SD 0.6), (**Table 1**). The lowest ranked mean among all sites was in resources with a mean of 3.3 (SD 0.8) (**Table 1**). Breaking down the resources domain into individual questions identified that staffing support was driving the low score with a mean of 2.9 (SD 1.1).

Table 1
ORCA scores for subscales
N=17 sites

Subscale	Overall, mean (SD)
Evidence assessment	4.3 (0.6)
Leader culture	3.7 (0.8)
Staff culture	3.8 (0.7)
Leadership behavior	3.6 (0.9)
Measurement	3.5 (0.9)
Opinion leaders	3.8 (0.8)
General resources	3.3 (0.8)

Conclusions: The high score for the evidence subscale suggests that all sites perceive that the evidence base for refraining from testing or treating asymptomatic bacteriuria is strong. The lowest scoring domain across all sites in this antibiotic stewardship project was the resources available for achieving change, specifically a lack of staff to support stewardship efforts.

Limited resources remain a potential barrier to implementing a national antimicrobial stewardship intervention.

Financial Support: AHRQ R18- HS028776-02

Poster 14

The Evolving State of Collateral Sensitivity Treatment Regimens as a Potential Solution yo Multidrug Resistant Bacteria

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Background: Antibiotic resistance has been an increasingly emergent problem since it began to develop concurrent with the implementation of penicillin in the 1940s, and potential solutions have long been a source of contention. A treatment option that has recently garnered renewed interest is the use of collateral sensitivity (CS) to maximize the efficacy of existing therapies that would otherwise be ineffective. Specifically, CS uses an initial drug course to induce a state of increased sensitivity to a second drug, capitalizing on the cost of resistance mechanisms to create an evolutionary pressure that drives the organism towards a desired state of susceptibility[1].

Goals: The goal of this analysis is to review recent literature and experimental data evaluating the efficacy of CS as a treatment against multidrug resistant bacteria.

Methods: A keyword search was performed of medical literature using the terms “collateral sensitivity” and “antibiotic resistance”.

Results: There is recent evidence that specific drug combinations can complement one another in the context of CS[1], with a recent study demonstrating for example that dequalinium chloride (DC) induces nfxB-mediated resistance to ciprofloxacin that is accompanied by an increased susceptibility to aminoglycosides and β-lactams in *Pseudomonas aeruginosa*[2]. Specifically this study used the aminoglycoside tobramycin, and the authors showed a transient induction of CS to tobramycin using DC in organisms that had been resistant led to up to a 6 fold reduction in minimum inhibitory concentration (MIC) while not inducing significant lasting resistance to ciprofloxacin[2]. The effect was shown to be aminoglycoside specific, with the MIC for the aminoglycoside amikacin being reduced by as much as 10.6-fold through DC induced CS[2].

Conclusions: The results support further investigation of CS as a potential aid against certain drug resistant organisms but also highlight a need for further research to establish new drug combinations and optimize the protocols to maximize efficacy and minimize worsening resistance. Studies such as those discussed here are promising, but at present they fall short of providing actionable solutions to the problem at hand.

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Poster 33

ESBL Bacteremia During the First Year After Solid Organ Transplantation

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Background: There is limited contemporary data on the outcomes of ESBL bacteremia in solid organ transplant recipients.

Objectives: This study aims to compare the risk of 30-day mortality and recurrence of ESBL Enterobacteriaceae bacteremia in patients with solid organ transplant (SOT) within the first year of transplantation and after the first episode of bacteremia using data from a large multinational network TriNetx.

Methods: Patients aged ≥ 18 years with a history of solid organ transplant (lung, heart, kidney, and liver) and the first episode of bacteremia secondary to an ESBL and non-ESBL Enterobacteriaceae were included in the study. We used propensity score matching to balance the cohorts. The 30-day hazard ratios were calculated.

Results: We identified 31,191 patients with SOT and the first episode of Enterobacteriaceae bacteremia. Patients with ESBL bacteremia compared to non-ESBL showed a higher hazard ratio (HR) for sepsis (HR 1.638, 95% CI 1.446–1.855, p <0.001) and bacteremia recurrence (HR 1.824, 95% CI 1.570–2.119, p <0.001) within in the 30 days of the first episode. Yet, the mortality rate was lower in those individuals with ESBL bacteremia (HR 0.471, 95% CI 0.358–0.620, p=0.005).

Conclusion: This retrospective study with a large number of patients with Enterobacteriaceae bacteremia in patients with SOT showed that despite having a high risk of a recurrent episode of bacteremia and sepsis among those with an ESBL bacteremia the mortality rate was not significantly higher compared to those with a non-ESBL bacteremia.

Acknowledgments: The present work is supported by the National Institute of Health (NIH) Training Physician-scientists in Emerging Infectious Diseases Research at the University of Texas Medical Branch at Galveston and the Translational Science Award (UL1 TR001439) from the National Center for Advancing Translational Sciences at the National Institutes of Health (NIH).

Poster 15

Candida Species Develop Antifungal Resistance in Urinary Catheter Infections Despite Lack of Antifungal Treatment

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Catheter-associated urinary tract infections (CAUTIs) are the most common healthcare associated infections. CAUTIs begin when microbes colonize and form biofilms within the bladder and the walls of the catheter. These biofilms typically consist of multiple species and are capable of growth so prolific as to occlude the catheter, necessitating frequent catheter exchanges and impacting patient quality of life. CAUTIs can present as symptomatic or asymptomatic. Currently there are no methods to predict if a patient with an asymptomatic CAUTI will later develop serious symptoms including bladder, kidney, and even bloodstream infections. *Candida*, a fungal genus that includes many opportunistic pathogens, is the second most common cause of CAUTIs. Currently there are only three major classes of antifungal drugs approved to treat *Candida* infections. While *Candida* has been widely studied in the context of bloodstream, oral, and vulvovaginal infections, few studies have assessed its role in CAUTIs. Our lab is studying *Candida* CAUTIs using a set of CAUTI isolates collected from individuals receiving outpatient care from the urology clinic at Washington University, St. Louis (Nye *et al.* 2023 *Nature Communications*). Our preliminary studies assessed the antimicrobial susceptibility patterns of these strains via Minimum Inhibitory Concentration assays. Notably, none of the individuals from whom the *Candida* species were isolated received antifungal treatment within the past year. We report that despite the lack of direct selective pressure from antifungal treatment, virtually all the isolates were resistant to either (or both) fluconazole or caspofungin, two critical frontline antifungals representing two different classes of relevant antifungal drugs. Furthermore, when antimicrobial susceptibility was measured in artificial urine medium, some isolates showed enhanced resistance. In conclusion, as has been found in clinical isolates from other infection sites, *Candida* antifungal resistance in the urinary tract is an urgent problem.

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Poster 16

Characterization and Clinical Effects of Colonization by Multidrug-Resistant Pathogens in Immunocompromised and Critically Ill Patients

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Antimicrobial resistance poses a rapidly emerging global health threat with the Centers for Disease Control and Prevention (CDC) classifying vancomycin-resistant enterococci (VRE) and extended spectrum β-lactamase producing/carbapenem resistant Enterobacterales (ESBL-E/CRE) as major health threats. Risk of acquiring such an infection increases significantly with prolonged hospitalization, previous antibiotic exposure, as well as immunosuppression. In a prospective observational study, 200 patients admitted to an intensive care unit (ICU) in a major metropolitan hospital were recruited to examine rates of colonization by antimicrobial resistant pathogens within their gastrointestinal tracts. Stool samples were cultured on media selective for VRE, ESBL-E, and CRE (species identification confirmed by MALDI-TOF) as well as *Clostridiodes difficile*. Clinical characteristics surrounding hospitalization were analyzed to elucidate factors driving colonization and patient outcomes. Fifty percent of enrolled patients (n=100) exhibited colonization in ≥1 stool sample by ≥1 organism of interest. Of the colonized patients, 46% were colonized by VRE (predominantly *Enterococcus faecium* (87%)), 61% by mutidrug resistant (MDR) gram-negative bacteria (ESBL-E and/or CRE) (*Klebsiella spp.* (43%) followed by *Escherichia coli* (30.5%)), and 37% by *C. difficile*, with 29% of colonized patients exhibiting co-colonization by multiple organisms (see Table 1). In comparing those who were colonized by an organism of interest to those who showed no colonization during their ICU stay, there were no significant differences in demographics, origin location prior to hospital admission, or antibiotic use in the 90 days leading up to hospitalization. However, colonized patients were admitted with a base Charlson Comorbidity Index score significantly higher than their non-colonized counterparts (5.1 vs. 4.3, p=0.03) and were more likely to be solid organ transplant recipients (35% vs 21%, p=0.03), with 88% of colonized organ transplant recipients undergoing transplantation operations during the same hospitalization as their enrollment. Furthermore, colonized patients tended to stay in the ICU significantly longer than non-colonized patients (median of 17 vs. 8 days, p=0.003), although further analysis should be done to account for confounding correlating causes. Twenty-eight percent of colonized individuals had a parallel MDR infection with a positive clinical culture during their admission, significantly higher than in non-colonized (9%). Overall mortality rates were similar between cohorts (21% of colonized vs. 22% of non-colonized); however, colonized patients were less likely to be discharged directly home following admission (28% vs. 43%) as many patients colonized at any point during their hospitalization required continue care or rehabilitation. While these findings suggest that patients who become colonized may enter the hospital with more underlying health comorbidities and

remain sicker for longer periods post-admission, more extensive analysis is crucial to better understand the complex dynamics of pathogenic acquisition in order to actively mediate risks and prevent future infection.

Table 1. Colonization of Patients by Organism

Colonization Status	**Number of Patients (N=200)**
No colonization	**100**
VRE Only	**25**
MDR Gram-Negative Only (ESBL-E and/or CRE)	**27**
***C. difficile* Only**	**19**
Colonization by Multiple Organisms	**29**
MDR Gram-Negative and VRE	*11*
MDR Gram-Negative and C. difficile	*8*
VRE and C. difficile	*7*
MDR Gram-Negative, VRE, and C. difficile	*3*

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Poster 17

A Prospective Randomized Clinical Trial to Assess Antibiotic Pocket Irrigation on Tissue Expander Breast Reconstruction

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Background: Around 50% of women with breast cancer undergo mastectomy followed by reconstruction using tissue expanders (TEs) prior to placement of a permanent breast implant. While there are biopsychosocial benefits to reconstructive surgery, there is a risk of complications of up to 30%. The most common complication is a bacterial infection, which is accompanied by increased medical costs, longer hospital stays, and delays in cancer treatment. In an effort to reduce these infections, many surgeons have implemented the use of a triple antibiotic pocket irrigant (TAPI), consisting of a g cefazolin, 80 mg gentamicin, and 50,000 units of bacitracin in 500 mL saline. Despite its widespread use, studies assessing the efficacy of pocket irrigation are lacking. This study investigated the efficacy of TAPI in a randomized clinical trial and via microbiome approaches.

Methods: Inclusion criteria for the clinical trial were: patients with unilateral breast cancer that opted for bilateral mastectomies (therapeutic on the side with breast cancer; prophylactic on the side without) and TE-based reconstruction. A total of 16 patients met the inclusion criteria and were enrolled in the study. The patients were split evenly between saline (control) and the TAPI (test) treated pocket irrigation. Clinical trial consisted of a 2 minute pocket irrigation post mastectomy and TE and acellular dermal matrix (ADM) reconstruction during the initial surgery. The patients then underwent a second surgery where the tissue expander was removed to perform breast implant or autologous flap reconstruction. Biopsies were collected from each breast for every patient and during both surgeries, with skin and underlying breast parenchyma obtained during the first surgery and skin, breast parenchyma, ADM, TE, and capsule collected for the second surgery. Samples were cultured for microbial growth and processed for microbiome analyses.

Results: All patients underwent surgery without any complications, contributed all samples required, none were lost to follow up, and there were no statistical differences between intervention groups when assessing age, smoking, BMI, or other comorbidities. No patient in either group developed an infection. Bacteria were isolated from 5 patients, with 7 isolates obtained from 3 patients in the TAPI treated group and 4 isolates obtained from 2 patients in the saline treated group. Coagulate negative staphylococci were the most isolated bacterial species. TAPI treatment or cancer did not affect the bacterial composition of any of the samples. No significant differences in bacterial abundance were observed in skin or breast biopsies across TAPI treatment, cancer, or from surgery one to surgery two. However, there was a significant increase in bacterial abundance in ADM and capsule from samples without cancer that were treated with TAPI compared to those treated with saline. There were no significant differences in alpha diversity metrics among ADM, capsule, breast, skin, or tissue samples

regardless of treatment or cancer status. However, a significant difference in the microbial diversity was observed for breasts without cancer treated with TAPI compared to saline based on the Beta Diversity of ADM and capsule samples.

Conclusions: TAPI did not reduce bacterial abundance or impact microbial diversity compared to saline irrigation of pockets in breasts with cancer. TAPI did increase bacterial abundance and affected microbial composition on capsule and ADM samples from breasts without cancer. Our results indicate that more research is needed to understand whether TAPI is effective at preventing infections post reconstruction.

Poster 18

Evaluation of De Novo Fatty Acid Biosynthesis as a Narrow-Spectrum Approach for Clostridioides difficile infection

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Clostridioides difficile infection (CDI), a leading cause of hospital-acquired diarrhea, results from dysbiosis caused by broad-spectrum antibiotics. The IDSA/SHEA recommends fidaxomicin (FDX) and vancomycin (VAN) as first choice antibiotics. However, recurrence following treatment is common and resistance has emerged to these agents. Furthermore, recent disappointing clinical trial outcomes for CDI antibiotic candidates emphasize the need for novel strategies for CDI and to maintain the drug discovery pipeline. Our analysis of drug targets in *C. difficile* identified enoyl ACP reductase II (*Cd*FabK) as being conserved and distinct from other enoyl-ACP reductase (ENRs) isoforms present in most gut flora species. ENRs catalyze the final step of *de novo* fatty acid cycle (FAS-II). Herein, we investigated inhibition of *Cd*FabK as a potential therapeutic strategy that spares the microbiome. To test this concept, we employed the *Cd*FabK inhibitor phenylimidazole-**296** in a series of *in vitro* and in *vivo* experiments. **296** inhibited *Cd*FabK with IC_{50} of 3.31 μM. Against *C. difficile* isolates of diverse genetic backgrounds, **296** had MIC_{90} of 2 μg/ml, which was comparable to vancomycin (1 μg/ml). Pharmacokinetically, **296** (100 mg/kg) appeared non-absorbed from the intestinal tract of C57BL/6J mice. When mice were given 25 mg/kg/bid of **296** for 3 days, their microbiomes resembled the untreated and vehicle control mice; importantly, **296**-treated mice retained colonization resistance to *C. difficile*. Interestingly, in mice **296** did not significantly disrupt Clostridia, although these species encode FabK. This was likely due to most Clostridia species also encoding a FabT transcriptional regulator that enables them to use host fatty acids to bypass inhibition, which we confirmed *in vitro* with representative species. On the other hand, *C. difficile* encode a FapR regulator that precludes bypass with host lipids. Both vancomycin and fidaxomicin significantly altered the microbiomes of mice, with the former promoting Proteobacteria and depleting Bacteroidota and Firmicutes, whereas the latter enriched Bacteroidota; both agents also reduced Clostridia. Efficacy was evident in a colitis CDI murine model, with **296** displaying dosed-dependent efficacy with greater survival of mice than those treated with vancomycin. These studies demonstrate *Cd*FabK as a target for microbiome-sparing antibiotics and establish the phenylimidazole inhibitors as a good starting point for new anti-CDI drugs.

Poster 19

Evaluation of Alternative Iron-Depleted Media and Chelator Pairs for Cefiderocol Susceptibility Testing

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Cefiderocol (FDC) is a novel siderophore cephalosporin used to treat infections caused by multidrug resistant Gram-negative pathogens. Currently, FDC susceptibility testing is performed by the broth microdilution (BMD) method using iron-depleted cation-adjusted Mueller Hinton broth (ID-CAMHB). Unfortunately, ID-CAMHB is not commercially available, and it is labor-intensive to make. Therefore, this study explores alternative media for BMD testing of FDC. A set of clinical isolates (*A. baumannii*, n = 10; *P. aeruginosa*, n = 9 and an ATCC control) that are clonally diverse (by Fourier-transform infrared spectroscopy) were evaluated in Tryptic soy broth (TSB) in conjunction with various chelators. TSB was selected because of its synthetic composition which is expected to have less inter-batch variation of iron content. Iron chelators tested were deferiprone (DFP; 5-30 µg/mL), 2-2' dipyridyl (25-50 µg/mL), and deferoxamine (0.5-60 µg/mL). Minimal inhibitory concentrations (MICs) of FDC for the isolates were compared to the ID-CAMHB reference using linear regression of log2 MIC values. In selected isolates, a time-kill assay was used to verify killing profiles for FDC (0-32 µg/mL) over 24h. Of the media tested, TSB with 15 µg/mL DFP had the highest MIC correlation in *P. aeruginosa* (r^2=0.95). Killing profiles of 2 isolates (FDC MIC = 4 µg/mL) were comparable over 0-32 µg/mL of FDC. The corresponding results for *A. baumannii* were less satisfactory (r^2=0.12). Our results are promising for identifying alternative growth medium and iron chelator pairs for FDC MIC testing. Further evaluations with other media, manufacturers, and a larger cohort of clinical isolates are warranted.

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Poster 20

Cefepime Heteroresistance is Prevalent Among Clinical *Pseudomonas aeruginosa* Bloodstream Isolates and is Associated with Emergence of Resistance in Patients with Hematologic Malignancies

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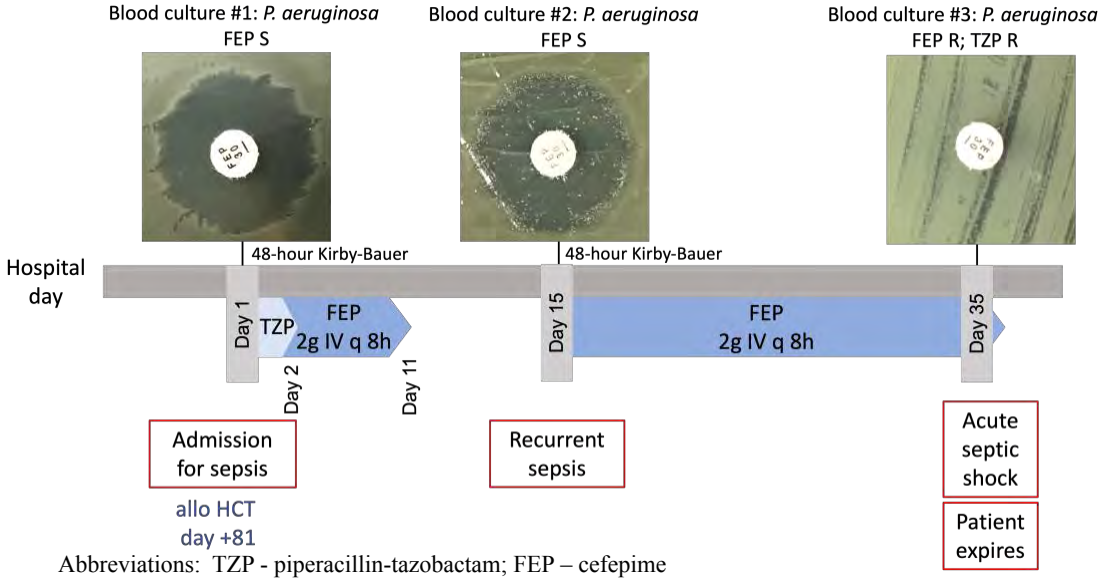
Introduction: *P. aeruginosa* (PA) is a leading antimicrobial resistance threat that causes severe, life-threatening infections in patients with hematologic malignancy (HM) and neutropenic fever (NF). Prompt initiation of appropriate antibiotic therapy is critical, as mortality rates of HM patients with NF correlate directly with delays in effective antibiotic therapy. Cefepime (FEP) is a first-line empiric regimen for patients with NF, largely due to its anti-pseudomonal activity. Heteroresistance (hR) is a phenomenon whereby minority subpopulations of an isolate possess an antibiotic-resistant phenotype below detectable limits of standard clinical microbiology techniques. Data assessing FEP hR clinical patterns is sparse; however, a single center study from China estimated a roughly 60% prevalence of FEP hR among *P. aeruginosa* bloodstream isolates, with an underlying HM found to be a risk factor associated with hR. This phenotype was associated with high rates of treatment failure compared to non-hR infections. The aim of this study was to evaluate the prevalence of FEP hR among HM patients at a single institution in the United States.
Methods: A biorepository compromising 24 *P. aeruginosa* clinical bloodstream isolates obtained from the HM population in Portland, Oregon between 2016-2023 was evaluated for FEP hR. All isolates underwent Kirby-Bauer (KB) disk diffusion testing read at 24-hours and 48-hours. Heteroresistance was defined as presence of breakthrough colony growth within the primary zone of inhibition.
Results: Fifteen isolates (62%) displayed evidence of breakthrough colonies within the KB zone of inhibition. Of fifteen heteroresistant isolates; two came from patients who had recurrent *P. aeruginosa* bacteremia during FEP treatment, and those subsequent isolates were banked within our repository available for assessment of phenotypic changes compared to index culture. In both cases, FEP resistance emerged during AST-directed FEP therapy (**Figure 1**) and both patients succumbed to sepsis during the recurrent bacteremic episode.
Conclusion: FEP heteroresistance is prevalent among clinical bloodstream isolates of *P. aeruginosa* in the HM population. FEP hR was associated with rapidly fatal sepsis due to breakthrough bacteremia with a FEP-resistant isolate during FEP treatment, emphasizing the clinical implications of FEP hR in these patients. Future studies are needed to assess the underlying mechanism and overall clinical impact of the FEP hR phenotype.

Figure 1. Clinical course of a patient with failure of FEP therapy associated with FEP hR.



Abbreviations: TZP - piperacillin-tazobactam; FEP – cefepime

Poster 21

Discovery of Novel Broad-Spectrum Antibiotics and Inhibitors for β-lactamases Using Combinatorial Chemistry Approaches

Jiayi Fan
Mentor: Dr. Timothy Palzkill

Abstract:
Antibiotic treatment is one of the main approaches to combat bacterial infections. However, the rise of antibiotic resistance due to the emergence, spread, and persistence of multidrug-resistant bacteria has become one of the major challenges in modern medicine and a threat to public health. Currently, β-lactams are the most widely used class of antibiotics. Resistance to β-lactams is primarily caused by the bacterial production of β-lactamase enzymes, which hydrolyze and inactivate the drugs. Prevalent β-lactamases such as KPC-2, OXA-48, and NDM-1 are able to hydrolyze a broad set of substrates including carbapenems, which are the last resort β-lactam antibiotics. Discovery of β-lactamase inhibitors is one avenue to address the antibiotic resistance problem. Alternatively, finding a new drug target to screen for novel antibiotics is another strategy to combat drug resistance. The targets of β-lactams are penicillin-binding proteins (PBPs). PBPs are involved in the terminal steps of peptidoglycan cross-linking, which provides for bacterial cell wall structure and integrity. Gram-negative bacteria have an outer membrane outside the peptidoglycan layer that can decrease antibiotic penetration, making Gram-negatives less susceptible to many β-lactams compared to Gram-positive bacteria. In the outer membrane of Gram-negative bacteria, a β-barrel assembly machine (BAM) catalyzes the integration of β-barrel proteins into the outer membrane. The BAM subunit A (BamA) is conserved in all Gram-negative species and is essential for cell viability. Since BamA is exposed at the surface of outer membrane, we can bypass the question of whether inhibitors can penetrate the bacterial outer membrane in order to function. Therefore, BamA is an excellent target for the development of new antibiotics.

In this study, we will use combinatorial approaches including established DNA-encoded small molecule libraries and a focused combinatorial peptide library to discover, produce, and validate new inhibitors against beta-lactamases and novel antibiotics that act on BamA.

Poster 1

Determining the Molecular Mechanism of Antibiotic Resistance by BpeEF-OprC Pump in *Burkholderia thailandensis*

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Burkholderia pseudomallei is a significant gram-negative pathogen that causes melioidosis, an infectious disease in humans and animals. *Burkholderia thailandensis* (BT) is the closest species to *B. pseudomallei* (BP). Trimethoprim-sulfamethoxazole (TMP-SFX) is the oral antimicrobial used to treat melioidosis patients. Previous studies showed that environmental and clinical isolates of *Burkholderia* species exhibited widespread trimethoprim resistance and that deletion of the BpeEF-OprC pump resulted in significant MIC reductions for trimethoprim. Further studies showed that this pump has very narrow substrate specificity whereas the homologous transporter AcrB (AcrB of AcrAB-TolC efflux systems in *E. coli*) can efflux a wide range of structurally unrelated substrates. The molecular mechanism of substrate specificity of BpeF transporter is not yet clear. It is known that substrates and inhibitors bind to the hydrophobic trap in the distal pocket of AcrB, which contains several phenylalanine residues (F136, F178, F610, F615, F617). These residues are important for substrate/inhibitor binding. However, sequence comparison shows that BpeF lacks these residues. To unravel the mechanism of substrate recognition by the BpeF transporter, we successfully cloned the BpeF transporter and mutated the important residues. If mutation on a residue changes the antibiotic susceptibility pattern and efflux function (decrease), that residue will be considered an important binding residue of BpeF.

Poster 22

Characterizing the Cefazolin Inoculum Effect (CzIE) in Methicillin Susceptible *Staphylococcus aureus* Strains (MSSA) Recovered from Patients with Bacteremia at a Houston Hospital System

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Background: *Staphylococcus aureus* is a significant human pathogen responsible for a variety of infections including skin and soft tissue infections, pneumonia, bacteremia, endocarditis, and osteomyelitis. The contemporary epidemiology of invasive *S. aureus* infections is shifting with a resurgence of MSSA across the world. The mainstay of therapy for MSSA bloodstream infections are β-lactam antibiotics including the semisynthetic penicillinase-resistant penicillins (oxacillin, nafcillin, etc.) and cefazolin. Cefazolin has emerged as the treatment of choice due to its ease of administration and reduced adverse events compared to anti-staphylococcal penicillins; however, some studies have suggested worse outcomes for deep-seated MSSA infections treated with cefazolin in the presence of the CzIE. This effect is dependent on staphylococcal β-lactamases and defined as an increase in the cefazolin minimum inhibitory concentration (MIC) to ≥ 16 µg/ml in the presence of a high bacterial inoculum (10^7 CFU/ml). The gold standard for detection of the CzIE is broth microdilution at high inoculum, a time and labor-intensive method that is not practical for the clinical microbiology lab. Thus, we have developed a colorimetric nitrocefin-based rapid test to detect MSSA strains that exhibit the CzIE.

Goal: Determine the prevalence of the CzIE in MSSA isolates collected from bloodstream infections in patients at a Houston hospital system, and the performance of the CzIE rapid colorimetric test.

Methods: Seventy-seven MSSA isolates collected from index cultures of adult patients with monomicrobial bacteremia from July to October 2023 were included. The CzIE was determined using broth microdilution at standard (10^5 CFU/ml) and high (10^7 CFU/ml) inocula using three biological replicates and a cutoff cefazolin MIC of ≥16 µg/mL at high inoculum. The nitrocefin rapid test was performed using three technical replicates using methods previously described.

Results: Based on the gold standard methodology, the prevalence of the CzIE was 52% (40/77). The nitrocefin rapid test correctly identified 29 of 40 strains harboring the CzIE, with a sensitivity of 73%. Similarly, it accurately identified 30 of 37 strains without the CzIE, with a specificity of 81%. There were 11 false negative and 7 false positive results with a false negative and false positive rate of 14% and 9%, respectively, and with an overall accuracy of 77%.

Conclusions: Overall, these results suggest that there is a high prevalence of MSSA isolates harboring the CzIE by standard method. Further efforts are needed to standardize the performance of the colorimetric test. Future directions will aim to determine the impact of the CzIE on clinical outcomes.

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Poster 43

A Phase 2, Randomized, Double-Blind Study of Ibezapolstat Compared with Vancomycin for the Treatment of *Clostridioides difficile* Infection

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Background. Ibezapolstat (IBZ) is Gram-positive selective spectrum antibiotic that inhibits the bacterial DNA polymerase IIIC currently in clinical trial development for the treatment of *C. difficile* infection (CDI) in adults. In the open-label, non-comparative, phase 2a study, 10 of 10 IBZ-treated CDI patients experienced clinical cure. The purpose of the phase 2b study was to assess the safety and efficacy of IBZ versus vancomycin (VAN) for treatment of CDI.

Methods. Phase 2b was a randomized, double-blind, active-comparator study. Participants with signs and symptoms of CDI and a positive enzyme immunoassay toxin test result were recruited from 12 centers in the USA and randomly assigned (1:1) to receive oral IBZ 450 mg every 12 h or oral VAN 125 mg every 6 h for 10 days. The primary endpoints were clinical cure at the end of therapy visit and safety. The trial is registered with ClinicalTrials.gov, number NCT04247542.

Results. Thirty-two patients were recruited; the primary efficacy analysis included 16 IBZ-treated patients and 14 VAN-treated patients. 15 of 16 (93.8%) patients given IBZ had a clinical cure versus 14 of 14 (100%) patients given VAN (treatment difference: -6.3%; 95% CI: -30.7-19.4%). IBZ was well tolerated; three IBZ-treated patients experienced mild and self-limited adverse events possibly related to drug and one VAN-treated patient experienced a moderate adverse event possibly drug-related. No changes in therapy were required for any adverse event.

Conclusions. In the phase 2b study, IBZ had a clinically comparable cure rate and safety profile to oral vancomycin. Of 26 CDI patients enrolled during IBZ phase 2 trials, 25 of 26 experienced clinical cure after 10 days of treatment, for an overall success rate of 96%. These results warrant further development in phase 3 trials.

Poster 23

The Crash of Antibiotic Stewardship in the Wake of the Global Covid-19 Pandemic

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Background: Increasing antibiotic use has led to the rise of antimicrobial resistance due to unnecessary overprescription in the medical field. The first article to propose the idea of Antibiotic Stewardship was published in 1996 by John E. McGowan Jr and Dale N. in the USA. The main focus was to emphasize the idea that antibiotics are a nonrenewable resource that should only be incorporated when absolutely necessary in order to slow the rate of resistance. Antimicrobial stewardship has been described as a set of interventions, a philosophy, and an ethic maintained by healthcare providers. By 1997 the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) included guidelines for prevention of antibiotic resistance in hospitals[1].

Goals: The goal of this analysis is to review recent literature regarding the Covid-19 pandemic and the rise of antibiotic resistance.

Methods: A keyword search was performed of medical literature using the terms “Covid-19” and “antibiotic resistance”.

Results: During the Covid-19 pandemic various researchers began scrambling to find treatment options for the disease. Many of the trials focused on drugs like Ivermectin, Doxycycline, Azithromycin, Chloroquine, and Hydroxychloroquine. The results of these trials were mostly insignificant and increased antiviral, antibiotic, and antiparasitic consumption with no benefit[2]. The Infectious Diseases Society of America stated that only 8% of Covid-19 patients acquired fungal or bacterial infections that required use of antibiotics. However, around 72% of Covid-19 patients were given broad-spectrum antibiotics even with no indications of bacterial infection[2]. The increase of PPE use such as gloves, face masks, and gowns also poses a problem. Many of these products are made from non-biodegradable polymers like polycarbonate, polyethylene, and polyurethane. These plastics never fully degrade and will eventually become microplastics. The physicochemical properties of microplastics make it a stable substrate for microbes and creates a pathway for antimicrobial gene resistance exchange[2]. The microbes involved with these microplastics can travel across the globe to give rise to new generations of resistant microbes.

Conclusions: The data supports further investigation of the long term effects of overuse of antibiotics during the Covid-19 pandemic and where the future of healthcare stands in regard to antimicrobial resistance. This also highlights the need for more regulations and protocols involving the use of antibiotics, antivirals, and even antiparasitic drugs to prevent further irreversible microbial resistances.

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Poster 24

Understanding the Role of Methicillin Resistant *Staphylococcus aureus* Urease on Catheter-Associated Urinary Tract Infections

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Background: Catheter-associated urinary tract infections (CAUTI) are one of the most common hospital-associated infections in the United States. CAUTI can be caused by a wide range of uropathogens, including *Staphylococcus aureus. S. aureus* CAUTI are particularly problematic, as these infections often disseminate to bacteremia and are commonly resistant to antibiotics, making them difficult to treat. Furthermore, *S. aureus* produces the enzyme urease, which promotes crystal formation on the catheter that subsequently results in catheter encrustations, further antibiotic recalcitrance, and chronic infection. Notably, most epidemiologic reports for *S. aureus* CAUTI come from veterans affairs hospitals, where the in-patient population is overwhelmingly male. Thus, my goal is to use a cohort of *S. aureus* catheter-associated isolates obtained from individuals with long term urinary catheterization to determine the prevalence of methicillin resistant *S. aureus* (MRSA) in non-hospitalized patients and the contribution of urease activity to recalcitrant biofilm formation.

Methods: To test this, we performed whole-genome sequencing on *S. aureus* clinical isolates from individuals with long term urinary catheters. We also assessed urease activity produced by these isolates and generated urease mutants to determine the enzyme's contribute to biofilm formation.

Results: Within our cohort of non-hospitalized individuals with long term catheterization 19% of *S. aureus* strains were isolates from women and 12% of isolates were MRSA. With urease activity assays, we found that catheter-associated isolates display varied levels of urease activity. Furthermore, we have found that sequential *S. aureus* isolates from the same patient display temporal increases in urease activity. Notably, while urease did not contribute to biofilm formed in rich media, it promoted biofilm in artificial urine media.

Conclusions: Together, our data suggest that *S. aureus* urease is an important virulence factor in CAUTI. Urease activity is variable between clinical isolates of CAUTI, emphasizing the importance of studying clinical isolates instead of only well-characterized strains of *S. aureus*, which typically displayed lower urease activity compared to clinical isolates in our assay. Furthermore, urease may promote persistence within the urinary tract by enhancing biofilm formation in urine.

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Poster 2

Alternating Magnetic Fields Enhance the Effects of Antibiotics on Biofilms

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Prosthetic join infections (PJIs) are a dreaded complication of total joint arthroplasties—one of the most common orthopedic surgeries in the United States. Treatment of PJI is complicated by the formation of biofilm on the implant surface. The gold standard of PJI treatment is a 2-step revision surgery along with an extended antibiotic regimen. Due to the prolonged treatment, PJIs are associated with decreased quality of life for patients. They also add significant healthcare costs, approximately $1.85 billion annually in the United States. It was previously shown that alternating magnetic fields (AMF) can decrease biofilm on metallic surfaces through a thermally driven effect and can enhance the activity of antibiotics. It remains unclear whether this synergistic effect occurs across antibiotic and pathogen space. Biofilms were cultured on stainless steel rings with representative strains of *S. aureus, S. epidermidis,* and *P. aeruginosa.* Treatment groups included control, AMF-only, antibiotic-only, and combination of antibiotic and AMF. Groups undergoing AMF treatment were placed in a solenoid coil calibrated to reach peak temperatures of 50°C, 65°C, 70°C, and 80°C. AMF was delivered as a single pulse or multiple pulses for various pathogen-antibiotic combinations. Rings were processed and harvested at 1- and 24-hours post-treatment. Across different strains of *S. aureus*, there was a temperature-dependent reduction in biofilm seen with multiple antibiotics. Treatment with a single 120-second pulse of AMF reaching a peak temperature of 80°C combined with linezolid demonstrated an average 5.38-log reduction in biofilm burden compared to control. This compared to linezolid alone which resulted in an average 0.75-log decrease. Similar decreases were seen with minocycline (6.07-log with AMF vs 2.70-log without AMF) and trimethoprim-sulfamethoxazole (TMP-SMX) (6.01-log with AMF vs 2.45-log without AMF). Strains of *S. epidermidis* responded similarly with linezolid (4.87-log with AMF vs 1.4-log without), minocycline (4.91-log with AMF vs 1.69-log without), and TMP-SMX (5.11-log with AMF vs 1.65-log without). In addition, a single 120-second pulse was superior to three 40-second pulses in strains of *S. aureus* and *S. epidermidis.* Strains of *P. aeruginosa*, when treated with ciprofloxacin and three 40-second pulses of AMF reaching 80°C, displayed a 4.15-log decrease compared to control, while ciprofloxacin alone resulted in a 3.17-log decrease. Similarly, ceftazidime-avibactam resulted in an average 3.84-log decrease with AMF compared to 2.70-log decrease without. In conclusion, our findings suggest that AMF works synergistically with antibiotics in reducing biofilm burden across a range of pathogen-antibiotic combinations, and that this may pave the way for an alternative treatment for PJI.

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Poster 2

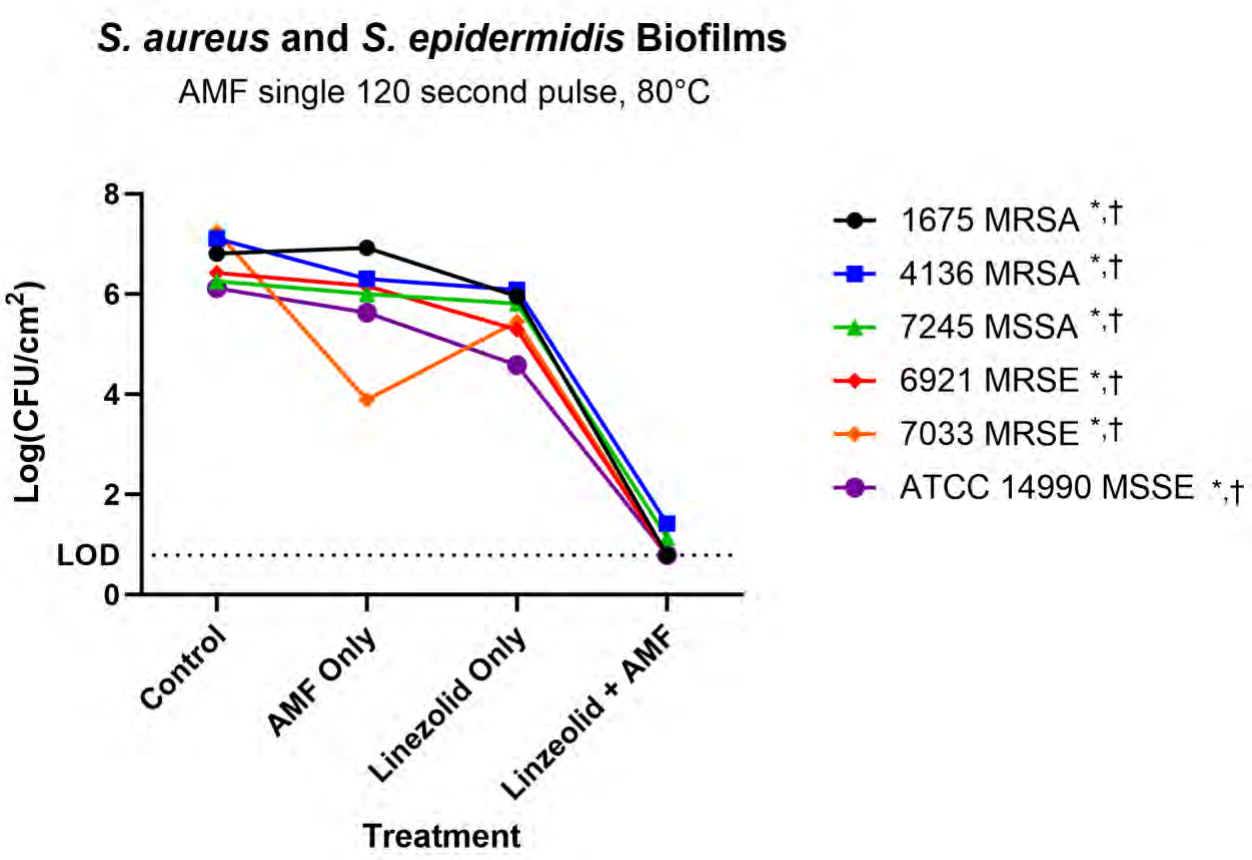

Figure 1. Biofilm burdens of S. aureus and S. epidermidis strains across various treatment groups. All strains except 6921 MRSE were treated with 2 ug/ml linezolid, while 6921 MRSE was treated with 1 ug/ml.

** indicates significant difference ($p < 0.05$) between combination and control groups, † indicates significant difference ($p < 0.05$) between combination treatment and antibiotic alone.*

Poster 25

Elucidation of the Molecular Signal for the Regulator of Capsule Synthesis Stress Response

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The Regulator of Capsule Synthesis (Rcs) envelope stress response is highly conserved in Enterobacteriaceae. Rcs is activated by multiple host immune factors and antibiotics, which target the bacterial cell envelope. These include 1) cationic antimicrobial peptides, that disrupt the outer membrane by targeting polyanionic lipopolysaccharide (LPS), and 2) lysozyme and ß-lactam antibiotics that target the peptidoglycan (PG) cell wall. Rcs regulates expression of many genes to prevent or mitigate cell envelope damage, and as such, Rcs is essential for survival in the host, virulence, and antibiotic resistance. Despite its importance, how Rcs detects envelope damage remains unknown. Rcs is a signal transduction pathway consisting of six components, including the sensor protein RcsF. RcsF forms a complex with several outer membrane proteins (OMP), which allows RcsF to co-localize with LPS at the cell surface. Assembly of RcsF/OMP complex is required for RcsF signaling, but the underlying reasons have not been resolved. The overall goal of my project is to identify a molecular signal and the mechanism of RcsF activation. Our hypothesis is that RcsF monitors perturbations in LPS packing through direct interaction with LPS. Mutations that alter LPS charge and structure induce Rcs in a Mg2+-dependent manner. I showed that increased expression of eptA, which modifies LPS and strengthens lateral interactions in a cation-independent manner, also causes a reduction in Rcs signaling in an LPS biosynthesis mutant, providing strong evidence for LPS lateral interactions as a potential Rcs signal. Moreover, the addition of divalent cations during PG synthesis inhibition by antibiotics such as A22 and mecillinam also leads to a significant reduction in Rcs activity. My result support two initial conclusions. First, RcsF seems to monitor LPS packing at the outer membrane and not the LPS structure itself. Second, stabilizing LPS packing alleviates Rcs signaling, not only when LPS is targeted but also when peptidoglycan biosynthesis is inhibited. Together, these findings suggest that disruptions to LPS packing, not cell wall, may be a direct and universal signal for Rc induction.

Acknowledgments.

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Poster 3

Mutations in LiaF of *Enterococcus faecalis* Associated with Daptomycin Resistance (DAP-R) Differentially Affect Interaction Dynamics with the Histidine Kinase LiaS in Lipid Nanodiscs

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Background: Daptomycin (DAP) is an antimicrobial peptide used to treat vancomycin-resistant enterococcal (VRE) infections. Mutations within the three-component signaling system LiaFSR drive the development of DAP-R. Deletion of the isoleucine residue 177 in LiaF (LiaFΔI177) is sufficient to increase DAP tolerance in a susceptible strain. Previous *in vivo* data suggests that LiaF interacts with the histidine kinase LiaS and potentially regulates its activity. The molecular dynamics governing system activation versus repression and the effect of mutations that confer DAP-R are unclear. Here we aim to understand the interaction dynamics between the LiaFS proteins in solution and within a native lipid environment.

Methods: *E. faecalis* LiaF, LiaFΔI177, and LiaS were purified from *E. coli* using an N-terminal 6X-His tag on each protein. Native lysine residues on the target protein were labeled with Nanotemper Technologies (NTT) 2nd Generation Red-NHS dye. Spectral shift was measured by NTT Monolith X. Nanodiscs were assembled with MSP1D1 (Sigma Aldrich), 16:0-18:1 phosphatidylglycerol (Avanti Polar Lipids), and purified Lia proteins before detergent removal with SM-2 BioBeads (BioRad). Discs were separated by size exclusion chromatography. Dynamic light scattering and nano-differential scanning fluorimetry were measured by NTT Prometheus Panta. Data analysis and graphs were created in NTT MO2 Control and Prometheus Analysis softwares, respectively.

Results: *E.faecalis* LiaF, LiaFΔI177, and LiaS were all found to self-interact in solution, with K_D of 3.25 mM (95% CI 1.82-5.8 mM), 2.13 mM (95% CI 1.93-2.35 mM), and 1.32 mM (95% CI 0.89-2.15 mM), respectively. LiaF and LiaFΔI177 interact in solution with a K_D of 3.77 mM (95% CI 3.41-4.17 mM). The difference in affinity between LiaF and the mutant suggests that the propensity of self-interaction could account for differential regulation of LiaS. LiaS has a much lower affinity for LiaFΔI177 than itself, with a measured K_D of 5.86 mM (95% CI 4.49-7.66 mM). LiaF has a much higher affinity for LiaS than itself (K_D of 206 nM, 95% CI 78-544 nM); however, the variability of replicates indicate that stoichiometry and critical concentration of LiaS may highly influence its association with LiaF. Dynamic light scattering of nanodisc assembly mixtures indicated that both WT and the mutant LiaF were likely forming a complex with LiaS in solution before nanodisc assembly. Qualitatively, the stability of LiaF, LiaF-LiaS, LiaFΔI177-LiaS, and LiaS-occupied nanodiscs vary as a function of temperature, suggesting a difference in complex dynamics with LiaS between LiaF and the mutant LiaFΔI177 in a native lipid environment.

Conclusions: These data together suggest that LiaF and LiaS interact directly both in solution and within lipid nanodiscs. The dynamics or stability of the interaction is altered in the presence of the mutant protein LiaFΔI177, which could underly the mechanism by which it increases DAP tolerance in *E. faecalis.*

Poster 3

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Poster 26

How Phage-Antibiotic Combinations Suppress Resistance and Improve Clearance of AMR E. Coli

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The rapid rise of antimicrobial resistance is an urgent and ongoing medical emergency. In 2014, the World Health Organization (WHO) claimed that a post-antibiotic era, in which chemical antibiotics are largely ineffective, is a possibility for the 21st century. In 2019, a CDC report claimed that such a post-antibiotic era had already arrived. By 2050, AMR pathogens are expected to kill upwards of 10 million people per year. AMR *E. coli* is of particular concern, as it was associated with over 600,000 deaths in 2019, the most out of all reported pathogens.

The AMR crisis has highlighted the need for alternative options to chemical antibiotics. One promising option is bacteriophage (phage) therapy, which has shown effective killing of AMR pathogens in vitro and promising results in compassionate use cases. Phage is often used in combination with antibiotics, and interactions between the two can have synergistic effects on pathogen killing. Another potential benefit of phage-antibiotic combination is the suppression of phage resistance. Much like with chemical antibiotics, bacteria can develop resistance to phages, a potential roadblock in the application of phage therapy. However, some phage-antibiotic combinations have been shown to prevent the development of phage resistance.

To further explore this relationship, we tested multiple phage-antibiotic interactions at a wide range of concentrations against a single strain of Extraintestinal Pathogenic *E. Coli.* We found that phage resistance consistently developed at high concentrations of different phages tested. However, introduction of Ceftazidime, a third generation cephalosporin antibiotic, at sublethal concentrations suppressed resistance development. Our next step is to expand this testing to additional antibiotics to identify what may determine an antibiotic's ability to suppress phage resistance. Additionally, we will sequence bacteria that develop resistance in order to identify frequent mechanisms of resistance and how antibiotics influence these mechanisms.

This research will help determine how antibiotics can be used in combination with phage to not only improve pathogen killing, but also to suppress or eliminate the development of phage resistance. This will help inform the selection of antibiotic phage pairings and improve the feasibility of phage therapy on a larger scale.

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Poster 27

A Single-Center Quality Improvement Project to Reduce Antibiotic Utilization in Gastroschisis Patients

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Gastroschisis (GS) is a congenital abdominal wall defect affecting ~4 in 10,000 babies. Care for GS patients varies widely. Studies suggest that standardization of care in other patient populations improves patient outcomes. This quality improvement (QI) project aimed to standardize the multidisciplinary care of GS patients from birth to discharge to improve patient outcomes at Children's Memorial Hermann Hospital (CMHH).

A retrospective chart review of all GS patients treated at CMHH from December 2008 to May 2020 was conducted to establish a baseline group. Multiple outcomes on comprehensive GS patient care were tracked, including antibiotic exposure. We created a guideline which critically reviewed newborn sepsis risk at birth using the Neonatal Sepsis Calculator®developed by Kaiser Permanente. Outcomes measured were % or newborns started on antibiotics at birth, the duration of antibiotic use when initiated at birth and type of antibiotic used. Balancing measure was % of newborns with suspected or confirmed bacterial infection within the first 48 hours of life that had delayed antibiotic initiation.

Cycle 1 involved implementation of the developed guidelines in November 2020. Cycle 2 involved placing printed guidelines at the newly admitted patient bedside and team reeducation. We compared outcomes of patients born 0-6 months and 6-24months post guideline implementation, respectively. ANOVA/Wilcoxon and Fisher's exact tests were used to compare continuous and categorical variables, respectively, and an F test was used to compare differences in variability between outcomes.

Patients were similar in baseline characteristics including sex, gestational age, and complexity of GS. In the baseline group (n=161) 93.2% newborns received antibiotics at birth, of these 45.3% received antibiotics for greater than 48 hours. In Cycle 1 (n=9), 55.6% received antibiotics at birth, of these, 40% received antibiotics for greater than 48 hours. In Cycle 2 (n=26), 42.3% received antibiotics at birth, of these, 9.1% received antibiotics for greater than 4 hours. Antibiotic exposure was reduced in Cycles 1 and 2 compared to baseline (baseline: 97.5% vs cycle 1: 77.8% vs cycle 2: 61.5%; $P<0.001$). Of the newborns receiving antibiotics at birth, there was a significant reduction in the percentage receiving antibiotics for greater than 48 hours between baseline, cycle 1 and cycle 2 groups respectively ($p=0.045$). The mean duration of antibiotics use for baseline, cycle 1, and cycle 2 was 3.44 days (SD=3.053), 2.8 days (SD=1.643), and 2.182 days (SD=3.628), respectively. However, this was not statistically significant.

This QI project has resulted in a significant decrease in antibiotic usage with no increase in diagnosed infections. Future work will focus on sustainability of the implemented guidelines and creation of guidelines for antibiotic utilization for suspected late onset sepsis.

Poster 28

Development and Validation of LC-MS/MS for Quantifying Omadacycline From Stool for Gut Microbiome Studies

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Abstract

Clostridioides difficile is an Antimicrobial Resistance Urgent Threat listed by CDC. Omadacycline is a novel tetracycline-class antibiotic and is *in vitro* potent active against *C. difficile*. A clinical trial is underway to examine the effect of omadacycline on human gut microbiome and its pharmacokinetics/pharmacodynamics (PK/PD). Quantifying fecal omadacycline is important but remains technically challenging because of epimerization of omadacycline and complexity of fecal samples. Additionally, epimerization of tetracycline-class antibiotic affects antimicrobial activity and toxicity, however, epimerization of omadacycline in gut remains unclear. This study developed and validated a new liquid chromatography-tandem mass spectrometry (LC-MS/MS) method to quantify omadacycline and its epimerization in stool to facilitate microbiome studies. Omadacycline was extracted in a methanol-water-ethylenediaminetetraacetic acid (ETDA) solvent containing deuterated omadacycline as internal standard, followed by dilution. In an optimal gradient elution mode, omadacycline and its C4 epimer were separated within 5 min on reversed-phase C18 column. The method showed a broad working range of 0.1-200 ng/ml with a limitation of detection (LOD) of 0.03 ng/ml, little fecal matrix effect, good intra-day and inter-day accuracy (90-101%), precision (2-15%), and recovery rate (99-105%). The method was sufficiently sensitive to quantify omadacycline in human fecal samples (n=82) collected during a 10-day therapy course and at follow-up (day 13 and day 30) that ranged from 1 to 4,785 μg/g. Further analysis revealed that ~9.0% of omadacycline was epimerized in fecal matrix control while 37.4% was epimerized in human fecal samples. This study developed and validated a novel, simple, sensitive, and accurate method utilizing LC-MS/MS to quantify omadacycline and demonstrated remarkable epimerization of omadacycline in the human gut. This has important implications for future studies of omadacycline and other tetracycline-class antibiotics as part of gut microbiome studies.

Keywords: Omadacycline; chromatography; LC-MS/MS; epimer; epimerization; human gut microbiome

Poster 69

Mechanisms of Gelofusine Protection against Polymyxin B-Associated Renal Injury

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Polymyxins are a last-resort treatment option for multidrug-resistant Gram-negative bacterial infections, but they are associated with nephrotoxicity. Gelofusine was previously shown to reduce polymyxin-associated kidney injury in an animal model. However, the mechanism(s) of renal protection has not been fully elucidated. Here, we report the use of a cell culture model to provide insights into the mechanisms of renal protection. Murine epithelial proximal tubular cells were exposed to polymyxin B. Cell viability, polymyxin B uptake, mitochondrial superoxide production, nuclear morphology, and apoptosis activation were evaluated with or without concomitant gelofusine. A megalin-knockout cell line was used as an uptake inhibition control. Methionine was included in selected experiments as an antioxidant control. A polymyxin B concentration-dependent reduction in cell viability was observed. Increased viability was observed in megalin-knockout cells and methionine significantly increased cell viability, reduced mitochondrial superoxide production, and improved nuclear morphology. Gelofusine, but not methionine, significantly reduced polymyxin B uptake and ratio of Bax/Bcl-2 protein (a biomarker of intrinsic apoptosis). Gelofusine and methionine were more effective at reducing renal cell injury in combination than either agent alone. The mechanisms of renal protection by gelofusine involve decreasing cellular drug uptake, reducing subsequent oxidative stress and apoptosis activation. These findings would be valuable for translational research into clinical strategies to attenuate drug-associated acute kidney injury.

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Poster 41

Evaluation of the Clinical Impact of Rapid Diagnostic Testing with BioFire® FilmArray® Blood Culture Identification 2 Panel on Antimicrobial Stewardship Interventions

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The management of bloodstream infections (BSIs) may be improved with rapid diagnostic identification. Culture and susceptibility reporting with conventional methods may take up to 72 hours, risking delayed therapy. The updated Biofire® FilmArray® blood culture identification (BCID) 2 panel is able to detect extended-spectrum beta-lactamase (ESBL) and carbapenemase encoding genes amongst other resistance markers, allowing for enhanced antimicrobial stewardship intervention. Additionally, the new panel detects additional organisms such as *Enterococcus faecium*, *Enterococcus faecalis,* and *Stenotrophomonas maltophilia.* Discrepancies have been reported between the updated panel and conventional methods, raising the need to evaluate the performance of the panel and determine opportunities for appropriate early antimicrobial stewardship interventions. This was a single-center, retrospective chart review of patients at Baylor St. Luke's Medical Center (BSLMC) before and after the implementation of the updated BCID panel (BCID1 vs BCID2, respectively). Patients were eligible to be included if they were ≥18 years old and had a positive blood culture with an accompanying BCID panel result. Patients were excluded if they received concomitant treatment for an unrelated infection or a monomicrobial BSI with *Staphylococcus* species. The primary endpoint was time to initiation of optimal antimicrobial therapy from index blood culture, defined as pathogen and resistance gene directed therapy per hospital treatment algorithm. Secondary endpoints included 30-day all-cause mortality, 60-day hospital readmission due to BSI, time to active antimicrobial therapy, genotype-phenotype discordance, hospital length of stay (LOS), intensive care unit (ICU) LOS, and pharmacist intervention rate. Active antimicrobial therapy was defined as empiric therapy shown to be active against index isolate(s) with an antimicrobial susceptibility report. Out of 517 patients screened for eligibility, 178 patients were included into the study. There were 103 patients in the BCID1 group and 75 patients in the BCID2 group. Time to optimal antimicrobial therapy was shorter in the BCID2 group compared to the BCID1 group (21.9 hours vs. 27.8 hours; $p = 0.27$, respectively). Time to active therapy was shorter in the BCID2 group compared to the BCID1 group (3.3 hours vs. 7.7 hours; $p = 0.02$, respectively). Hospital LOS was also shorter in the BCID2 group compared to the BCID1 group (6 days vs. 18 days; $p < 0.01$, respectively). All other secondary endpoints were similar between the two groups. Based on preliminary data, the time to optimal therapy was numerically shorter in the BCID2 group. Further data collection is ongoing to determine additional benefits.

Acknowledgements: None

Poster 42

Investigation of Fecal pH As a Gut Dysbiosis Marker in Healthy Volunteers Given Omadacycline or Vancomycin

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Antibiotic exposure impacts the gut microbiome and microbial-derived gut metabolites, including bile acids and short-chain fatty acids (SCFAs). Antibiotic-induced metabolomic changes can lead to alterations in fecal pH; however, whether fecal pH can serve as a surrogate marker for gut dysbiosis is not known. Our previous study demonstrated in vitro activity of omadacycline against *Clostridioides diffcile* and oral (PO) omadacycline has distinct metagenomic and metabolomic profiles compared to PO vancomycin. The purpose of this study was to assess the impact of intravenous (IV) omadacycline on fecal pH. From October 2020 to June 2023, healthy individuals aged 18 to 40 were randomized in a 1:1:1 ratio to receive standardized treatment dosing of omadacycline (IV or PO) or vancomycin (PO) for 10 days. Fecal samples were collected at baseline, daily during therapy, and at two follow-up visits. Fecal pH was measured using the Compact pH Meter (Horiba Advanced Techno, Japan), which was calibrated using pH 4.01, 7 and 10 solutions for each batch of samples. Approximately 50-100 mg of feal samples was treated with NaCl or deionized H_2O and 200 µL of supernatant was pipetted onto pH meters after samples were centrifuged. Descriptive statistics were used to summarize and compare daily pH changes between antibiotic groups. A total of 274 fecal samples from 24 healthy volunteers (27 ± 5 years of age; 58% male; 24.7 ± 4.3 kg/m^2 body mass index) were analyzed in this study. At baseline, the mean fecal pH in the IV omadacycline group was 6.73 ± 0.46 compared with PO omadacycline (6.02 ± 0.40) and PO vancomycin (6.27 ± 0.18). The highest pH was observed on day 5 in both IV and PO omadacycline groups (7.29 ± 0.72 and 6.82 ± 0.79, respectively) and on day 10 in the PO vancomycin group (6.97 ± 0.39). Overall, fecal pH fluctuated and increased during antibiotic course in all three groups. These findings suggests that antibiotic exposure leads to a slightly alkaline fecal pH in healthy volunteers. Further studies investigating the correlation between fecal pH, SCFA concentrations, and gut microbiome changes are warranted to assess the utility of fecal pH as a surrogate marker for gut dysbiosis.

Poster 63

Characterization of Non-Carbapenemase Producing Carbapenem-Resistant *Klebsiella pneumoniae* in a Health System in Houston, Texas

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Background: Infections with carbapenem-resistant *Klebsiella pneumoniae* are associated with increased mortality compared to carbapenem-susceptible organisms. Rapid diagnostics such as the GeneXpert® CARBA-R or Biofire® BCID2 provide molecular detection of common carbapenemase genes (i.e. KPC, NDM, IMP, VIM, OXA-like) and allow for targeted antimicrobial therapy based on the identified gene and early isolation to prevent further transmission. However, non-carbapenemase producing carbapenem-resistant (NCP-CR) organisms are an emerging threat, and molecular epidemiology and clinical outcomes of these organisms are limited.

Methods: In this study, we characterized clinical and genotypic profiles of collected NCP-CR *Klebsiella pneumoniae* (KP) bloodstream isolates of adult hospitalized patients between October 2022 and June 2023 within seven hospitals of the Houston Methodist System. Patients were included in the analysis if blood culture isolate was resistant to ertapenem (defined as MIC ≥2 µg/ml via BD Phoenix® automatic susceptibility testing system and via confirmatory organism growth on ertapenem-infused agar) and was negative per CARBA-R test. Molecular characteristics and mechanisms of resistance were analyzed by whole genome sequencing.

Results: During the study period, 6 NCP-CRKP were obtained (43% of CRKP bloodstream isolates). The primary source of infection was intra-abdominal (n=3, 50%), urinary tract infection (n=2, 33%), and central-line associated (n=1, 17%). The majority of isolates (n=4; 67%) were also meropenem resistant based on phenotypic susceptibility; however, two isolates (33%) were meropenem susceptible. Infectious Diseases were consulted in 100% of cases. Empiric antibiotic selection prior to phenotypic results were meropenem (n=2; 33%), piperacillin-tazobactam (n=2; 33%), ceftriaxone (n=1; 17%), and eravacycline (n=1; 17%). Definitive therapy of NCP-CRKP was meropenem-vaborbactam (n=4; 66%), meropenem (n=1; 17%), and ceftriaxone (n=1; 17%). Median length of stay was 4.2 days (IQR 2.36 – 22.97). Thirty and 90-day readmission rate and 30-day mortality was 17% (n=1), 17% (n=1), and 50% (n=3), respectively. One patient had recurrent bacteremia with the same NCP-CRKP at 30- and 90-days. Resistance genes found among the isolates include *blaSHV*, *blaTEM*, *blaDHA*, *blaCTX-M*, and *blaOXA*. ESBL enzymes were found in all isolates, with a median gene copy number of 2.49 (range 1.13-3.24). Porin mutations were detected in 4/6 (67%) strains.

Conclusions: In NCP-CRKP isolates carbapenem-resistance was associated with a combination of acquired non-carbapenemase beta-lactamases and porin loss. Patients received a variety of definitive treatment options based on the available phenotypic results. Further investigation is warranted to determine the optimal treatment regimen for these organisms based on clinical outcomes and likely molecular mechanisms of resistance.

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Poster 4

Investigating The Potential of Bacteriophage to Limit Uropathogenic *E. coli* Colonization

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Background

Urinary tract infections (UTIs) are the second most common bacterial infection in the human population, affecting 404.6 million cases annually with 236,786 deaths. UTIs are common among women and ~50% women have ≥1 UTIs; ~25% face recurrent UTIs, requiring repeated antibiotics which increases the risk of multi-drug-resistant *E. coli*. Uropathogenic *Escherichia coli* (UPEC), the main etiological agent for UTIs, gains exposure to the urinary tract from mucosal reservoirs such as vaginal tract where UPEC is a common colonizer. Although FDA-approved antibiotics such as fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and β-lactams are available for the treatment of UTIs, the risk of recurrence and resistance to antibiotics underscores exploration of non-antibiotic approaches, especially phage therapy as an alternative and adjunctive approach to prevent/and or treat UTIs.

Hypothesis

We hypothesize that elimination of UPEC reservoirs such as the vaginal tract will reduce the incidence of UTI. UPEC-targeting (bacterio)phage/and or phage cocktails can serve as a non-antibiotic method to control UPEC vaginal colonization.

Methods

We have explored the potential of two lytic phage alone or as a cocktail in preventing UPEC using *in vitro* and *in vivo* models of UTIs. In the *in vitro* model, we have tested efficacy of lytic phages alone or as a cocktail against UPEC by measuring growth curves in bacteriological media. We have further tested whether bacteriophage can prevent cell attachment and invasion by UPEC in cell culture model utilizing human vaginal epithelial cells (VK2/E6E7). The infectious phage particles after adhesion and invasion to VK2 cells was determined using culture-based double agar overlay method. We have also assessed the efficacy of phages against UPEC in humanized microbiota mice (^{HMb}mice) *in vivo*.

Results

We found that phage alone or in cocktail inhibited UPEC growth in bacteriological media for 20 h. Similarly, pretreatment of VK2 cells with the lytic phage reduces adhesion and intracellular survival of UPEC compared with controls. During adhesion and invasion ~10^5 PFU/mL and 10^7 PFU/mL phage were recovered respectively, suggesting phage replication in presence of host during longer incubation. Further, the daily dose of phage causes significant reduction in UPEC vaginal burdens after 72h of phage treatment. UPEC dissemination was observed across multiple tissues including vaginal, cervical, uterine, kidney, but burdens were not different between phage and mock-treated groups after 7 days post-infection. Additionally, we observed that higher vaginal and cervical UPEC burdens were associated with dissemination to the kidneys. We have observed that although mono phage and phage cocktail demonstrate efficacy against UPEC *in vitro,* in murine models only mono phage treatment reduce UPEC burdens while phage cocktail were ineffective *in vivo* despite promising *in vitro* activity. Further studying ongoing to understand to bacterial-phage dynamics during *in vivo* infection that leads to diminished efficacy.

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Antimicrobial Peptides and Immunomodulatory Therapeutics to Combat Multidrug Resistant Priority Pathogens

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Bacterial resistance to antibiotics is a serious and escalating threat to healthcare systems in the United States as well as around the world. There are >2.8 million antimicrobial resistant infections in the United States alone, of which >35,000 are fatal. Studies have predicted that by 2050, deaths attributed to such infections could outnumber than those from cancer and diabetes combined. Further complicating factor is the lack of new classes of antibiotics being brought to the market. This is attributed to a considerable expense of antibiotic discovery programs and the unfavorable economics, as the resistance to new antibiotics can arise fairly quickly, limiting their use except in circumstances where they are the drug of last resort. Consequently, the interest has also grown to evaluate efficacy of non-antibiotic therapeutics. A variety of therapeutics fall into this category and include but not limited to: antimicrobial peptides, host-acting immunomodulatory drugs, and host-derived therapeutics on which antimicrobial resistance has little impact on treatment efficacy. Bactenecin 7 (Bac7) is a proline rich antimicrobial peptide isolated from bovine neutrophils that has broad efficacy against Gram-negative bacteria. It inhibits protein synthesis by binding to the ribosome within the 50S subunit but at location distinct from ribosome acting antibiotics, although most similar to macrolides. We have shown Bac7(1-35) to be effective at inhibiting bacterial replication *in vitro,* and is a protective therapy for several Gram-negative pathogens including respiratory infections caused by *Yersinia pestis* or *Klebsiella pneumoniae* as well as in a sepsis model of *Salmonella* Typhimurium infection. For all of these infections, ~70% survival of mice was observed. We have identified several other host-acting immunomodulatory therapeutics that could be used to treat both Gram-positive and Gram-negative infections. None of these therapeutics were identified to be directly inhibitory to bacteria. Treatment with Amoxapine, a tricyclic antidepressant, and other anti-psychotic drugs, used in patients with neurological symptoms were effective against *Y. pestis*, *K. pneuminiae*, *Clostridioides difficile*, *S.* Typhimurium, Mycobacterium *tuberculosis,* and *Acinetobacter baumannii* with similar treatment efficacies of 60-70%. Our studies indicate that amoxapine stimulates innate immune signaling through inflammasome and autophagy pathways. Amoxapine treatment also stimulates production of host antimicrobial peptides such as Reg3γ. Further investigation of the specific innate immune signaling could help identify pathways that other host-acting drugs can take advantage of to treat multidrug resistant bacteria. The third non-antibiotic therapy being investigated to treat multidrug resistant bacteria is by engineering chemokine decoys to limit damaging neutrophil responses during infection which can lead to tissue damage. The decoys prevent native chemokine signaling resulting in decreased neutrophil activation. Together, these non-antibiotic based treatment strategies provide promising new ways to combat multidrug resistant bacterial infections.

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Poster 64

Geospatial and Genomic Epidemiology of Clinical *Burkholderia pseudomallei* Isolates in Cambodia

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Burkholderia pseudomallei, the cause of melioidosis, is a soil-living gram-negative pathogen found ubiquitously across tropical and subtropical regions. Although the geographical range of disease is expanding, melioidosis remains understudied in highly endemic low-middle income countries where morbidity and mortality are high. We report the first genomic epidemiological study of *B. pseudomallei* in Cambodia. Between January 2021 and October 2022, positive blood cultures growing *B. pseudomallei* were prospectively collected at 6 participating hospitals across 5 Cambodian provinces. DNA libraries were prepared and sequenced. Genomes were analyzed. Multilocus sequence typing was performed using a 7-locus schema (PubMLST). Single nucleotide polymorphisms within the core genome were identified between all isolate pairs along with known antibiotic-resistance genes. Over 22 months, 203 patients with culture-confirmed bacteremic melioidosis were included for analysis. Patients were predominantly male (140/203; 69%) and frequently presented with pneumonia (79/203; 39%). Most isolates were obtained during the wet season of May to October (166/203; 82%). Among 111 sequenced isolates, clinical outcomes were available for 38 patients; 8/38 (21.1%) died before discharge. 85 unique sequence types (STs) were identified (Simpson's D 0.99). Twenty unique patients shared an identical ST with at least one other patient; these shared ST isolates differed by

25-52 nucleotides. Geographic distances between isolates ranged from 0 to 390 km, with slightly closer distances among shared ST (median 108 [6-316] km) versus unique ST isolates (median 127 [0-390] km). Cambodian isolates clustered with other South Asian isolates and were genomically distinct from isolates found in Australia. Two beta-lactamase genes, *bla*OXA-57 and *bla*OXA-59, were detected in 95% (106/111) of isolates and present exclusively and in nearly equal proportions across isolates (54/106 and 52/106, respectively), with no clear geographic distinction. Presence of *bla*OXA genes did not correlate with susceptibility to amoxicillin-clavulanate (89 susceptible of 97 isolates; 92%), ceftazidime (105/106 susceptible isolates; 99%), or meropenem (100% susceptible). Overall, isolates within this clinical cohort were highly diverse. Although shared sequence types existed at large geographical distances (>300 linear kilometers), there was a trend towards these STs existing in closer physical proximity to one another. Studies are ongoing to determine further genomic associations with clinical, geographic, and resistance phenotypes of *B. pseudomallei* in Cambodia.

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It Takes Two to Tango: Determining How Phage and Ciprofloxacin Interact to Combat AMR Pathogens

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Antimicrobial resistance (AMR) is an urgent and expanding threat, with AMR pathogens expected to kill as many as 10 million people annually by 2050. However, few new antibiotics have come to market as high cost and low profits disincentivize antibiotic development. This accentuates the need for additional methods to combat AMR. One promising tool is phage therapy – the use of bacteria-infecting viruses, called phage, to treat bacterial infections. Dozens of compassionate use cases of phage therapy have shown promising results. Phage is generally administered in combination with antibiotics, and phage-antibiotic interactions can occur in a synergistic, additive, or antagonistic manner. However, there are currently no rules that predict these interactions.

Ciprofloxacin (CPFX) is a fluroquinolone antibiotic that targets bacterial topoisomerases and can have synergistic or antagonistic interactions with phage depending on concentration. We aim to determine whether phage-encoded topoisomerase alters phage-CPFX interactions, and whether CPFX alters bacterial evolves of resistance to phage. To achieve this, we first conducted phage-CPFX interaction screenings on multiple strains of Extraintestinal Pathogenic *E. coli* (ExPEC) at a wide range of phage and antibiotic concentrations. We then developed a synergy score that compares the calculated additive effect of a phage and antibiotic to the observed combinatorial effect, and allows for display of these results in the form of a heat map. We found that CFPX-susceptible strains showed remarkably similar synergy scores, while CPFX-resistant strains differed from each other. Surprisingly, phage-antibiotic antagonism occurred independent of whether the phage encodes topoisomerase. However, we have not yet determined if phage-encoded topoisomerase alters this antagonism. This research will help determine factors impacting phage-antibiotic interactions, informing the rational selection of phage for therapeutic use.

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Poster 65

Situations Predisposing Primary Care Patients to Use Antibiotics Without a Prescription in the United States

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Background: Using antibiotics without medical guidance (non-prescription use) is a potential safety threat to individual and public health. Patients' situations can impact their decisions to use non-prescription antibiotics in the future (intended use). This study (1) explores the dimensionality of 13 predefined situations to identify summary variables (defined as 'situational constructs'), which include conceptually similar situations that influence patients' intended use of non-prescription antibiotics, and (2) identifies the sociodemographic predictors associated with these situational constructs.

Methods: A cross-sectional survey was conducted from January 2020 – June 2021 in the waiting rooms of six safety-net primary care clinics and two private EDs in Texas. We used Exploratory Factor Analysis (EFA) as a data reduction technique to identify each situational construct (Figure 1). Each patient was given a construct score based on how they answered the questions/items per situational construct (e.g., a patient would receive a score of '2' for construct 3 if they answered 'yes' to both items and a score of '1' if they answered 'yes' to 1 of the 2 items). Multivariate Linear Regression identified the sociodemographic factors (e.g., age, gender, race, education, insurance, healthcare system, language preference, birth country, and health literacy) associated with each situational construct.

	Situation/Item Factor Loading*		
Situation Construct and Situations/Items**	**1**	**2**	**3**
Construct 1: Barriers to a doctor visit and receiving a prescription			
You cannot take time off work.	0.92		
You have no time to go to the doctor because of family responsibilities.	0.94		
You cannot get to the doctor's office because of transportation problems.	0.93		
The doctor's office hours are not convenient for you.	0.94		
The doctor has no time to see you when you are sick.	0.93		
A visit with a doctor is too expensive.	0.80		
Construct 2: Convenience and accessibility of non-prescribed antibiotics			
You have leftover antibiotics at home from a previous prescription.		0.61	
Friends/relatives give you antibiotics.		0.83	
You can buy antibiotics without a prescription in the United States.		0.85	
You can buy antibiotics without a prescription in another country.		0.80	
Antibiotics are cheaper than over-the-counter cold and flu medications.		0.72	
Construct 3: Previous symptom relief with antibiotics			
You got better by taking this antibiotic before.			0.97
Your doctor prescribed you this antibiotic for the same symptoms before.			0.97
Cronbach Alpha	α = 0.96	α = 0.81	α = 0.95
Mean inter-item correlation	0.79	0.48	0.90

Figure 1: EFA results: situations and corresponding constructs

Results: Our EFA identified three situational constructs: (1) barriers to a doctor visit and receiving a prescription (α = 0.96), (2) convenience and accessibility of non-prescription antibiotics (α = 0.81), and (3) previous symptom relief with antibiotics (α = 0.95) (Figure 1). After controlling for gender, race, education, insurance, language preference, birth country, and health literacy, our multivariate regression results revealed that younger age (P<0.04) and the safety-net health system (P<0.001) were significantly associated with patients' intended use of non-prescription antibiotics for all three constructs. In addition, being born in the US was associated with patients' intended use related to construct 3, 'previous symptom relief with antibiotics' (P<0.001).

Conclusions: Our study revealed that younger patients and individuals receiving care from the safety-net clinics had an increased risk of intended non-prescription antibiotic use across all situational constructs. Future stewardship interventions should consider the types of situations that drive patients' decisions to use antibiotics without a prescription. Interventions aimed at

reducing barriers to healthcare (e.g., high costs and long waits associated with doctor appointments) and educating individuals on the risks associated with inappropriate antibiotic use while providing alternative (non-antibiotic) treatment options may reduce antibiotic use and antimicrobial resistance.

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Basis of Fidaxomicin Resistance in *Clostridioides difficile*: A Systematic Review and Meta-analysis

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Background: Fidaxomicin (FDX), an RNA polymerase inhibitor antibiotic, is guideline recommended therapy for *Clostridioides difficile* infection (CDI) resulting in selection pressure for resistance development. Recently the six key binding sites of FDX at the RNA polymerase were elucidated (Cao, *Nature* 2022). However, whether fidaxomicin resistance occurs at these key binding sites is unknown. The purpose of this project was to determine whether identified single nucleotide polymorphisms (SNPs) associated with fidaxomicin resistance occur at the binding pocket of RNA polymerase.

Method: A systematic literature search was done using the following terms in PubMed: “fidaxomicin” and “antimicrobial resistance”. Seven articles were included in the meta-analysis after applying inclusion and exclusion criteria. The analyses were performed using the published *C. difficile* RNAP published sequence (code 7L7B) on Protein Data Bank. Results were supplemented with three isolates from our collection with reduced FDX MIC (1 ug/ml).

Results: Twelve different amino acid changes associated with changes in FDX susceptibility were identified. Three of 12 (25%) SNP changes aligned with fidaxomicin binding key residues (D237Y, R236C, and R89G). Other frequent SNPs identified was a substitution of thymine (T) at position 3428, resulting in the following amino acid changes V1143D, V1143G and V1143F (25%). Significant increase in fidaxomicin MIC (≥ 64 mg/L) were associated with either nonsynonymous substitution that replaces the corresponding hydrophobic side chain amino acid with a negative charge side change (V1143D) or an amino acid that interfere with the cation-π interaction between β’ R89 and fidaxomicin macrolide C3-C5 double bond (R89G). All SNPs identified in three supplemented clinical strains from our collection were at novel base positions.

Conclusion: Several SNPs that resulted in elevated FDX MIC were identified with the minority aligning with FDX RNA polymerase key binding sites. FDX resistance appears to be multifactorial with further work necessary to elucidate the mechanism of resistance.

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Rates of Resistance and Heteroresistance to Newer ß-lactam/ß-lactamase Inhibitors for Carbapenem-Resistant Enterobacterales

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Background: Heteroresistance (HR), the presence of antibiotic-resistant subpopulations within a primary susceptible isogenic population, may be an overlooked contributor to newer ß-lactam/ß-lactamase inhibitors (BL/BLI) treatment failure in carbapenem-resistant Enterobacterales (CRE) infections.
Objectives: To determine rates of susceptibility and HR to newer BL/BLIs including ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam in clinical CRE isolates.
Methods: The first CRE isolate per patient per year from two 500-bed academic hospitals from January 1, 2016 to December 31, 2021 were included. Reference broth microdilution (BMD) was used to determine antibiotic susceptibility, and population analysis profiling (PAP) to determine HR. Carba NP assays were used to determine carbapenemase production (CP).
Results: Among 327 CRE isolates, 46% were *Enterobacter cloacae*, 38% *Klebsiella pneumoniae* and 16% *Escherichia coli*. By BMD, 87-98% were susceptible, with incremental decreases in the activity of all three BL/BLIs over time. HR was detected for all antibiotic-bacteria combinations, with the highest rates of HR (28%) found in *K. pneumoniae* isolates and imipenem-relebactam. HR or resistance to at least one BL/BLI by PAP was found in 24% of CRE isolates and 65% of these HR-CRE had detectable CP.
Conclusion: A significant proportion of CRE isolates were either resistant or HR to newer BL/BLIs, with an overall decrease of ~10% susceptibility over six years to the BL/BLI tested. CP was detected in most CRE isolates resistant by BMD or HR/resistant by PAP. While newer BL/BLIs remain active against most CRE, these findings support the need for ongoing antibiotic stewardship and a better understanding of the clinical implications of HR in CRE.

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TABLE 1: Proportion of CRE isolates susceptible/intermediate to newer BL/BLIs by broth microdilution (BMD) but heteroresistant by population analysis profiling (PAP).

	Ceftazidime-avibactam		Imipenem-relebactam		Meropenem-vaborbactam	
CRE isolate species	S (BMD) n (%)	HR (PAP) n (%)*	S/I (BMD) n (%)	HR (PAP) n (%)*	S/I (BMD) n (%)	HR (PAP) n (%)*
E. coli (n=53)	50 (96)	1 (2)	46 (87)	0 (0)	50 (93)	1 (2)
K. pneumoniae (n=123)	116 (94)	15 (13)	109 (89)	30 (28)	115 (91)	2 (2)

E. cloacae (n=151)	148 (98)	13 (9)	149 (94)	9 (7)	150 (99)	3 (2)
Total (n=327)	314 (96)	29 (9)	297 (91)	38 (12)	315 (96)	6 (2)

*Percentage (%) calculated by dividing number of CRE isolates HR by PAP by number of CRE isolates susceptible by BMD; S= susceptible; I=intermediate; HR=heteroresistant

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Clostridium septicum and _C. difficile_ Compete for an Intestinal lipid-rich Environment Lacking in Naturally Evolved Antimicrobial Activity.

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Clostridium septicum is a gram-positive, toxin-producing bacterium known to cause gas gangrene. Infection is thought to involve hematogenous dissemination from the intestine, although colonization rates in humans remain poorly understood. To investigate susceptibility risks linked to *C. septicum* colonization, we conducted an extensive metagenomic survey of over 35,000 healthy and patient fecal specimens and observed that *C. septicum* in adults was exceptionally rare. However, intriguingly, this organism was commonly detected in infants. Furthermore, in-depth metagenomic characterization of the infant gut microbiome revealed a shared community representation between *C. septicum* and *C. difficile* colonization. Notably, the absence of shared taxa in this context conferred protection in experimental models of *C. difficile* infection. To substantiate the existence of a competitive gut niche shared by these diverse pathogens, we established an oral model of *C. septicum* infection. We demonstrated that asymptomatic carriage of *C. difficile* completely abrogated clinical disease caused by toxigenic *C. septicum*. Employing an integrated multi-omics approach, we identified a specialized intestinal niche, enriched in ceramides, sphingolipids, and sterols, that is commonly inhabited by these pathogens. Particularly, ceramides represent a key intermediate in sphingolipid biosynthesis known to facilitate host-pathogen interactions. Through comprehensive metagenomic comparisons and bioactivity-guided analysis of key microbiota taxa associated with pathogen decolonization, we successfully identified and elucidated the structure of hadromycin, a novel ether-class of sphingolipid possessing broad antimicrobial activity against *C. septicum* and *C. difficile*. Thus, sphingolipids have evidently evolved in the natural design of clostridial pathogen evasion during human development.

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Poster 46

The Large Tilting Motion of the Central Core in SERCA Couples the ATP Hydrolysis and Ca^{2+} Transport

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Abstract

The sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) transports two Ca^{2+} per ATP hydrolyzed from the cytoplasm to the lumen against a huge concentration gradient. The ATP hydrolysis in the three cytoplasmic domains drives the opening of the luminal Ca^{2+} pathway and Ca^{2+} release in the transmembrane domain remotely (~50Å). How the ATP hydrolysis couples Ca^{2+} transport remains unknown. The phosphorylated site by ATP and Ca^{2+} binding sites are connected by the central core (CC), which is made of the cytosolic extension of the M4/M5 (transmembrane helix) and the C-terminal part of the P domain. Based on the crystal structure analysis of the SERCA1a principal intermediates, we found that the large tilting motion of the CC is accompanied by the ATP hydrolysis and Ca^{2+} transport. We therefore hypothesized that the large tilting motion of the CC couples the ATP hydrolysis and Ca^{2+} transport. We observed that the large tilting motion of the CC was accompanied by the opening of the luminal Ca^{2+} pathway in the molecular dynamics (MD) simulation of the E1P-ADP-2Ca^{2+} R836A variant. After the protonation of the Ca^{2+} binding sites, the Ca^{2+} release process was observed in the MD simulation of the R836A variant with the open luminal Ca^{2+} pathway. We demonstrated that the large tilting motion of the CC drove the Ca^{2+} transport in the MD simulation of the R836A variant. This validated our hypothesis that the large tilting motion of the CC couples the ATP hydrolysis and Ca^{2+} transport. Therefore, we concluded that the ATP hydrolysis drives the large tilting motion of the CC, which drives the Ca^{2+} transport.

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Investigating Fitness Costs of Fidaxomicin-Resistant *Clostridioides difficile*

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Background: *Clostridioides difficile* infection (CDI) accounts for almost $5 billion in health care costs per year in the United States with a staggering number of cases reoccurring even after treatment with standard-of-care antibiotics, such as Vancomycin. The narrow-spectrum macrolide fidaxomicin (FDX) is also first-line treatment for CDI. Despite FDX targeting the β-clamp region of RNA polymerase (RNAP), resistance to fidaxomicin has been reported in the clinic.

Goal & Hypothesis: We aim to characterize the fitness costs associated with fidaxomicin resistance. We hypothesize that developing resistance will lead to a decrease in overall fitness and virulence of resistant *C. difficile*.

Methods: Paired isolates were obtained from the fidaxomicin Phase III trial hosted in Japan (NCT02179658). These paired isolates were obtained from patients before and after fidaxomicin therapy. Genetic relatedness was confirmed with multi-locus sequence typing. Both Sanger and whole genome sequencing identified mutations in RNAP. Growth rate assays, *C. difficile* cytotoxicity assay, pairwise fitness competition, and sporulation assays were used to characterize fitness defects. RNAseq was performed on paired strains FD282 (MIC=0.125µg/mL) and FD292 (MIC=128µg/mL) in early log, mid-log, and stationary phase. Differential expression was confirmed by qPCR.

Results: Each of the paired isolates had unique mutations associated with the target, RNAP. Strain FD77 (MIC=16µg/mL) had a Val1143Leu mutation in RpoB; strain FD292 exhibited a Val1143Asp mutation in RpoB; and strain FD131 (MIC=64µg/mL) acquired two mutations in RpoC: Arg89Gly and Arg326Cys. Growth rate assays revealed that FDX-resistant strains had variable defects, which varied with media conditions. Cytotoxicity assays indicated that both FD292 and FD131 produced a lesser amount of toxin compared to their respective paired FDX-susceptible strains. RNAseq revealed extensive remodeling of the transcriptome through differential regulation of transcriptional regulators, e.g. *fur*, *ccpA*, translation-related proteins (i.e. ribosomal proteins), and altering of central carbon metabolism. Within the >1000 differentially expressed genes, we observed downregulation of genes in the pathogenicity locus (i.e., *tcdA*, *tcdE*), which supports the phenotypic data. We observed discordant regulation of genes involved in sporulation, which is in agreement with the decreased sporulation that has been previously reported for FDX-resistant strains.

Conclusion: Overall, our findings suggest that the process of developing FDX resistance is associated with fitness costs, i.e. decreased toxicity, defects in fitness and sporulation. Future studies are warranted to determine the mechanism of these fitness costs.

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Poster 34

Basis of Commensal Bacillota Resistance to a Novel PolC-type DNA Polymerase III Inhibitor, Ibezapolstat, and the "Narrower" Spectrum of Activity towards *Clostridioides difficile*

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Background: Ibezapolstat (IBZ), a competitive inhibitor of the Bacillota PolC-type DNA polymerase III (PolC) completed phase 2 clinical trials. IBZ preserves the human gut microbiota through a narrower Gram-positive selective spectrum (GPSS). The purpose of this study is to elucidate the comparative structural basis of IBZ's "narrower" GPSS activity than anticipated for the treatment of CDI and preservation of the commensal Bacillota. We hypothesize that phylogenetically distinct point residue variants in the drug binding pocket confer reduced susceptibility in certain Bacillota families, specifically Lachnospiraceae, Oscillospiraceae (formerly Ruminococcaceae), and Coprobacillaceae (formerly Erysipelotrichaceae).

Methods: The methods of this study include bioinformatics sequence extraction using CLC Genomics Workbench (Qiagen), AlphaFold2 structural prediction (Google DeepMind), CB-Dock2 cavity detection, and AutoDock-Vina blind drug docking. Drug-target complex visualization was performed using Maestro (Schrodinger).

Results: The results of this investigation predict two polar "lysine hooks", Lys1148^{CdiPolC} and Lys1327^{CdiPolC}, *may* bind the IBZ 3,4-dichlorophenyl, a feature largely devoid from those IBZ-resistant commensal microbiota. Second, Thr1331^{CdiPolC} *may* bind the IBZ 2-methylamino, a feature conserved across most IBZ *susceptible* Bacillota but is variant across the IBZ *non-susceptible* commensal taxa. Third, the Thr1291^{CdiPolC} proximity to the IBZ central moiety is *nearly unique* to *C. difficile*.

Conclusion: We predict the mechanistic basis of the "narrower" GPSS activity of IBZ is due to phylogenetically conserved non-susceptibility via structural variations in the IBZ binding pocket of PolC across the families Lachnospiraceae, Oscillospiraceae and Coprobacillaceae. Further studies to confirm this hypothesis of comparative structural pharmacology are ongoing.

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Poster 48

Staphylococcus aureus Increases Staphyloxanthin Production In Response To Colonization On Human Nasal Organoids (HNOs)

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Preventing *S. aureus* nasal colonization is an effective strategy to prevent infections, and new nonantibiotic means are needed to prevent *S. aureus* nasal colonization. We used **h**uman **n**asal epithelial **o**rganoids (**HNO**s) to model *S. aureus* colonization and to identify *S. aureus* factors important for colonization. HNOs are a remarkably accurate model of human nasal epithelium, with a robust mucus layer and beating cilia. HNOs are differentiated from tissue-derived nasal stem cells in transwells with air apically and medium basally; they are nontransformed and nonimmortalized. We successfully monocolonized HNOs with 10^7 colony forming units (CFUs) of *S. aureus* strain JE2 (a methicillin-resistant derivative of the USA300 Lac strain) at 34°C with a median recovery of 10^4 CFU after 24 hours and notably, a resurgence to 10^8 CFU after 48 hours. This colonization pattern suggests partial clearance of *S. aureus* by 24 hours and *S. aureus* colonization recovery by 48 hours. Cytotoxicity, measured by lactate dehydrogenase release into basolateral medium (BLM), was comparable between colonized and uncolonized HNOs. Phenotypic variations in *S. aureus* colony color arise after 48 hours recovery from HNOs. After 24 hours of colonization *S. aureus* appeared like wild type; however, after 48 hours of colonization, we recovered three color morphotypes of *S. aureus* on Columbia blood agar medium: grey (matching the parental strain), yellow, and orange. Methanol extractions showed differential production of staphyloxanthin (STX), a known carotenoid pigment and virulence factor for *S. aureus.* STX is well described as advantageous to *S. aureus*: shielding it from reactive oxygen species and improving resistance to neutrophil mediated cytotoxicity. We have recovered *S. aureus* mutants with increased pigment from multiple independent experiments using 3 different HNO lines derived from genetically distinct donors. Colonies with increased STX production maintained this phenotype through multiple rounds of passaging. Using genomic sequencing, we determined that two of the yellow *S. aureus* mutants had SNPs in the *qox* operon. Based on these data, we hypothesize that increased STX pigment is important for the recovery of *S. aureus* viable numbers between 24 and 48 hours of colonization on HNOs. To test this, we will monocolonize HNOs with *S. aureus* mutants harboring transposon disruptions in *crtM*, *crtN*, *qoxA*, *qoxB*, *qoxC* and assay for potential differences in colonization success compared to the wild type. This project will determine whether STX affects *S. aureus* nasal mucosal colonization and identify new *S. aureus* gene targets for the prevention of nasal colonization and subsequent infection.

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Poster 35

Defining the Mechanisms by Which Phage -Encoded Peptides Inhibit Cell Division in Gram-Negative Bacteria: A Promising Gateway Towards Alterative Therapeutics of Bacterial Infections

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Bacterial antibiotic resistance is now a widespread threat to human health. Consequently, new antibiotic targets are needed. One very promising target is FtsZ, a homolog of eukaryotic tubulin and a keystone of the bacterial divisome. A large number of small molecules are known to bind FtsZ and perturb its essential function, indicating that it is a highly druggable target. Kil is a 47 amino acid peptide produced by Bacteriophage Lambda during lytic growth. It was previously shown that Kil inhibits *Escherichia coli* cell division by perturbing FtsZ ring assembly. This inhibition requires the FtsZ membrane tether ZipA, as cells lacking ZipA (but suppressed with an *ftsA** bypass allele) are more resistant to the action of Kil than *zipA*+ or *ftsA** *zipA*+ cells. Purified Kil peptide is sufficient to inhibit assembly of purified FtsZ *in vitro*, so the ZipA requirement *in vivo* suggests that Kil may bind to ZipA as well as FtsZ. As a first step to define Kil's molecular mechanism of action, we have used truncation mutants and molecular modeling to define the minimal residues of Kil needed for cell division inhibition activity. Molecular modeling predicts that a core segment of Kil folds into a helix-turn-helix (HTH) structure. Although deleting the C-terminal 11 or N-terminal 5 residues of Kil still retained the ability to inhibit *E. coli* cell division, removing both termini simultaneously nearly abolished its cell division inhibition activity, suggesting that a minimal region (6-36) with in the Kil HTH core is crucial to inhibit cell division. Based on the requirement of ZipA for Kil's inhibition of FtsZ, we hypothesize that the two helices in Kil's helix-turn-helix structure target ZipA and FtsZ independently. We are currently conducting *in vitro* experiments to test this model and also validating Kil's toxicity towards uropathogenic *E. coli* strains. Understanding how Kil and other phage-encoded peptides functions should shed light on how FtsZ normally interacts with its protein partners during bacterial cell division. This should lead to the identification of novel antimicrobial targets and discovery of more species-specific antimicrobial peptides for targeted therapies of bacterial infections.

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Poster 49

KPC Variants: From A Good Carbapenemase Towards an Ultraspecialized Enzyme For Ceftazidime Resistance

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Antibiotic resistance remains a global threat for treating bacterial infections. Bacteria produce beta-lactamase enzymes that hydrolyze beta-lactam antibiotics, rendering them inactive. Carbapenems are considered antibiotics of last resort because many beta-lactamases cannot hydrolyze them. However, enzymes capable of hydrolyzing carbapenems, such as KPC-2, have emerged and are distributed globally. Ceftazidime-avibactam therapy has been clinically employed; however, the rise of KPC mutants able to resist this combination is making therapy challenging. Mutations involved in ceftazidime-avibactam resistance are distributed along three hotspots represented by loops surrounding the active site of KPC β-lactamase: the Ω-loop (residues 164-179), the loop from residues 237 to 243, and the loop from residues 266 to 275; with D179Y, H274Y, T243M, and their combinations commonly implicated in ceftazidime-avibactam resistance. However, KPC-2 mutants leading to ceftazidime-avibactam resistance, often display reduced carbapenemase activity. In this study, KPC variants containg 1, 2, or 3 mutations (D179Y, T243M, and H274Y), that result in an enzyme conferring higher ceftazidime resistance at the expense of carbapenemase activity. Using steady-state and pre-steady state kinetics, we show that adding the D179Y mutation to variants harboring the T243M mutation exhibit reduced k_{cat} for all beta-lactams tested and the deacylation reaction becomes rate-limiting. Moreover, the addition of D179Y results in an increased MIC for ceftazidime and ceftazidime-avibactam and decreased MIC for ampicillin, cephalothin, and imipenem. The results demonstrate that the addition of these mutations convert KPC towards an ultraspecialized enzyme providing ceftazidime +/- avibactam resistance. Understanding why ceftazidime is so different compared to other beta-lactams remains challenging and necessitates considering the physiology of living bacterial cells containing the enzymes.

Poster 50

Exploring the Impact of Antibiotic Stewardship Programs on Pediatric Medicine

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Background

Antimicrobial resistance is a serious global health issue with an estimated 700,000 deaths per year from multidrug-resistant bacteria.[1] Antibiotics are the most common drug class prescribed for pediatric patients and the over/misuse of antibiotics is a leading cause of antibiotic resistance.[1] Antimicrobial resistant rates have been rising over time, making common infections challenging to treat, often with adverse consequences.[1] Antibiotic stewardship programs (ASPs) are dedicated to reducing inappropriate antibiotic use and targeting the appropriate spectrum of activity, dose, and duration of antibiotic therapy when necessary.[2] ASPs have become more prevalent in pediatric medicine over the years in efforts to control the increasing rates of multidrug-resistant bacteria among pediatrics patients.

Objective

The goal of this report is to review the current literature on antibiotic stewardship programs and their impact on pediatric medicine.

Methods

A database search was performed using the keywords “antibiotic stewardship program” and “pediatrics”. Studies that were not published within the last four years were excluded from the selection. Medical literature was selected to analyze the current information regarding antibiotic stewardship programs in pediatric clinical settings.

Results

After analyzing various studies, the results of this review demonstrate that ASPs often have a notable effect on reducing inappropriate antibiotic prescriptions in pediatric patients which, in turn, creates a cascade of beneficial effects. Several studies demonstrated a significant improvement in appropriate antibiotic prescription compliance after ASP implementation.[3,4,5] ASP’s goal of reducing inappropriate antibiotic use has helped improve overall clinical outcomes and reduced healthcare costs.

There are limitations on the study of ASPs in pediatric medicine. The implementation of ASPs is more common in inpatient units and more challenging to implement in outpatient clinics; however, antibiotics in pediatrics are more commonly prescribed in outpatient settings.[6] Therefore, more studies involving the impact of ASPs in outpatient settings are needed. Additionally, ASP programs have varying financial operational costs that limit access for some healthcare programs.

Conclusions

The implementation of ASPs in pediatric settings has been shown to provide an overall beneficial effect on the reduction of inappropriate antibiotic prescriptions for pediatric patients. While more research is needed to help determine the prospective long-term effects on reducing multidrug-resistant bacteria and trends of antimicrobial resistance, current studies have provided strong

evidence that ASP implementation may reduce the antimicrobial resistance threat in pediatric infections.

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Poster 51

ICU-based Infection and Colonization in Diabetic Cohort

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Background Patients with diagnosed Diabetes mellitus(DM) have elevated risks of infectious diseases, leading to higher morobidity and mortality rates. According to the CDC there are about 38.4 million people in the US who have diabetes leading many researchers and healthcare professionals to study the relationship between the gut microbiome and diabetes. This abstract seeks to highlight the prevalence of Infection and Stool Colonization amongst the patients enrolled in DYNAMITE study who have diabetes.

Methods This study comprised participants from the DYNAMITE study, encompassing individuals diagnosed with either Non-Insulin-dependent diabetes mellitus (NIDDM) or Insulin-dependent diabetes mellitus (IDDM). Within 24 hours of their admission to the Intensive Care Unit (ICU), these patients were enrolled and remained in their respective ICUs for up to 28 days. Throughout their participation, patients provided up to 2 stool samples and one blood/oral swab on a weekly basis. Stool samples were cultured on media to isolate Vancomycin-Resistant Enterococci (VRE) or Carbapenem-Resistant Enterobacteriaceae/Extended-Spectrum Beta-Lactamase (CRE/ESBL). Clinical cultures obtained during the patients' hospitalization were also included.

Results The cohort comprised 52(26%) DM patients, of which 18(35%) were diagnosed with NIDDM and 34(65%) with IDDM. Of these, 25 patients (48%) exhibited bacterial cultures meeting the criteria for infection outlined by the Centers for Disease Control and Prevention (CDC), totaling 72 bacterial cultures examined. Among these cultures, 20 were identified as colonization as per CDC criteria, while 52 were confirmed infections. Specifically focusing on the Medical Intensive Care Unit (MICU) subset, bacterial colonization was observed in 50% of patients, with 35 (67%)bacterial cultures classified as infections. Further analysis of stool colonization revealed that 23 patients in the cohort were colonized at some point with VRE, Gram-negative bacteria, C. difficile, or multiple organisms concurrently.

Conclusion In conclusion, this study highlights the significant impact of infectious diseases on individuals with diabetes mellitus, especially in ICU settings, elevating both illness severity and mortality rates. The identification of bacterial colonization and infections, including resistant strains, emphasizes the need for focused interventions. These findings reinforce the importance of investigating the gut microbiome's role in diabetes and suggest potential interventions to

manage infections in this population. Understanding and influencing these microbial relationships offers promise in preventing and treating infections among those living with diabetes.

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Poster 52

LiaF is an Activator of the LiaR-Mediated Response Against Daptomycin (DAP) in Multidrug-Resistant *Enterococcus faecalis* (*Efs*)

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Background: DAP is a first-line antibiotic used for the treatment of vancomycin-resistant enterococcal infections. Resistance to DAP in enterococci has been shown to be controlled by the *liaFSR* three-component regulatory system, that consists of a histidine kinase sensor (LiaS), a response regulator (LiaR) and a transmembrane protein of unknown function (LiaF). Mutations in *liaF* have been associated with activation of this system, with increased expression of the protein LiaX, and resistance to DAP in clinical isolates. However, it is unknown if LiaF plays a positive or negative regulatory role in *E. faecalis*. Here, we aim to evaluate the role of LiaF in regulating the LiaFSR response in both the presence and absence of antimicrobial stress with DAP.

Methods: Using OG117 (a laboratory strain of *Efs*) and the CRISPR-Cas9 system, we generated a derivative mutant in which four stop codons were added at position 11 to 14 in *liaF*, (OG117::*liaF*$_{11\text{-}14}$*), and a complemented strain *in cis* (OG117::*liaF*$_{11\text{-}14}$*::*liaF*). Mutant and complemented strains were confirmed by Whole Genome Sequencing (WGS) using Illumina. The lack of expression of *liaF* was confirmed by qRT-PCR (Log_2 fold change calculated by normalizing to *gyrB* expression) and absence of LiaF protein by western blot (using anti-LiaF polyclonal antibodies). In addition, to investigate the activation of the LiaFSR system we performed western blot targeting LiaR under non stress conditions (no DAP) and stress (DAP 4 μg/ml) using polyclonal anti-LiaR antibodies. The intensity of the bands was quantified using imageJ software and a ratio between the WT vs mutant and complement vs mutant was calculated.

Results: Loss of LiaF production in OG117::*liaF*$_{11\text{-}14}$* resulted in lower DAP MICs (1 μg/ml) compared to OG117 (4 μg/ml) and the complement OG117::*liaF*$_{11\text{-}14}$*::*liaF* (4 μg/ml). Transcriptional analyses indicated no expression of the *liaF* gene in the stop codon mutant and protein/western analysis showed no production of the LiaF in the OG117::*liaF*$_{11\text{-}14}$* while both the OG117 and OG117::*liaF*$_{11\text{-}14}$*::*liaF* showed a band of the expected size of 22 kDa. Based on the band intensity on western blot there was an increased expression of the LiaR protein (1.7X) in OG117 vs OG117::*liaF*$_{11\text{-}14}$* and (2.5X) in OG117::*liaF*$_{11\text{-}14}$*::*liaF vs* OG117::*liaF*$_{11\text{-}14}$* under non stress conditions. Similar results were seen in the induced (DAP 4) conditions with OG117 (5.6X) vs OG117::*liaF*$_{11\text{-}14}$* and OG117::*liaF*$_{11\text{-}14}$*::*liaF* (3.6X) vs OG117::*liaF*$_{11\text{-}14}$*, respectively.

Conclusions: These findings indicate LiaF positively regulates LiaR expression enhancing the LiaFSR response during exposure to DAP.

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Poster 70

In Vitro Evaluation of Using Ceftazidime/Avibactam against Carbapenem-Resistant *Acinetobacter baumannii*

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Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a global concern as effective treatments are very limited. We previously used a modified susceptibility testing approach to predict growth suppression in carbapenem-resistant Enterobacterales, but there are uncertainties about the generalizability of the model. The objective of this study is to verify if a similar approach can be extended to CRAB. A clinical isolate of CRAB resistant to ceftazidime/avibactam (CAZ/AVI, MIC=32/4 mg/L) was examined. CAZ susceptibility was determined using increasing concentrations of AVI (0-64 mg/L), and MIC reduction was characterized with a sigmoid inhibitory maximum effect (Emax) model. The effectiveness of CAZ/AVI was validated in a hollow fiber infection model (HFIM) over 72 hours, using simulated serum / epithelial lining fluid (ELF) exposures of 2.5 g over 2 hours every 8 hours. Baseline inoculum of approximately 5.5 log cfu/ml was examined. An AVI concentration-dependent reduction in CAZ MIC was observed (r^2=0.99). Ceftazidime MIC was dramatically reduced from 512 mg/L (no AVI) to 32 mg/L (AVI=4 mg/L), and further to 8 mg/L (AVI=16 mg/L). Pharmacokinetic simulations were satisfactory in the HFIM (r^2>0.96). Bacterial suppression was observed over 72 hours with the serum exposure, but not that from the ELF. Using multiple AVI concentrations within the clinically relevant range, our susceptibility testing approach could have better insights of treatment outcome for infections caused by CRAB. This could potentially lead to effective intervention(s) overlooked by conventional susceptibility testing method. In this case, the treatment outcome could vary based on site-specific drug exposures achieved.

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Poster 53

Discovery of Vancomycin Resistant *Clostridioides difficile* Isolate with *gdpP* deletion, Showing Survival in Physiological Vancomycin

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Background: *Clostridioides difficile* is a toxin producing opportunistic pathogen causing antibiotic associated diarrhea. Vancomycin is a preferred choice for treating C*. difficile* infection (CDI). Strains with reduced susceptibility to vancomycin has evolved (MIC > 2 µg/mL according to EUCAST breakpoint). Mutations in the *vanSR*-encoded two component system which leads to derepression of the *vanG* operon has been reported in both clinical and laboratory strains. However, fecal concentration of vancomycin (520 to 2200 µg/g stool) is considered to be high enough to inhibit these resistance strains. Nonetheless, genetic factors enhancing the survival of *C. difficile* in physiological vancomycin is poorly understood.
Herein, we characterized a vancomycin resistant clinical strain, JH248 that survive physiological vancomycin.

Methods: JH248 was whole genome sequenced and its susceptibility and tolerance to vancomycin determined by MIC and MBC testing. Autolysis to triton X-100 and c-di-AMP concentration were also determined as well as changes in its transcriptome.

Results: JH248 belong to sequence type 1 (ST1, RT027) of the hypervirulent clade 2 lineages. JH248 had Thr115Ala in VanR, a deletion of leucine 443 at the catalytic DHH domain of GdpP (c-di-AMP phosphodiesterase) and a deletion of Alanine 293 in SdaB (L-serine dehydrate). Compared to the vancomycin susceptible control strain R20291, JH248 survived in a vancomycin concentration of ≥ 256 µg/mL despite having an MIC of 4 µg/mL. JH248 also had reduced autolytic response and increased cellular concentration of c-di AMP. Increases in c-di-AMP have been shown to correlate with tolerance to cell wall acting antibiotics. To understand the contribution of *sdaB* to vancomycin resistance in JH248, an *sdaB* knockout mutant was generated using R20291. Deletion of *sdaB* resulted in a two-fold increase in the vancomycin MIC (2 µg/mL) as compared to the wildtype (1 µg/mL). The transcriptome of JH248 showed upregulation of genes (*glyA*, *cycA* and *opucA*) involved in glycine metabolism and transport.
Conclusion: Findings from this study uncovered a vancomycin nonsusceptible *C. difficile* strain with impaired GdpP function with increase tolerance to physiological concentrations of vancomycin. Using MBC rather than MICs, strains such as JH248 may be a cause for concern.

Poster 54

Iron Transporter: FeoB1, and Pyruvate Contribute to the Toxin Biosynthesis Pathway in Clostridioides Difficile

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Clostridioides difficile infection (CDI) is a major threat to public health, resulting in over 200,000 hospitalized cases per year and nearly 13,000 deaths according to the CDC. *C. difficile* colonizes the gut causing CDI when antibiotic induced dysbiosis occurs. *C. difficile's* virulence is governed by the toxins it releases, TcdA and TcdB. These deactivate host's Rho/Ras GTPases, which damages the gut epithelia and produces inflammation. The current standard of care for CDI relies on fidaxomicin and vancomycin, which may further damage the gut microbiome and increase the risk of *C. difficile* recurrence. Therefore, there is a need for microbiota-safe therapeutics that would disarm *C. difficile* without harming commensal gut microbes. We discovered that deletion of FeoB1, *C. difficile's* primary iron transporter, inhibits toxin production rendering it avirulent. This classifies FeoB1 inhibition as a potential approach for narrow spectrum therapeutics. Therefore, we sought to further investigate the basis for the effects of FeoB1 loss on toxin production, in order to identify other key players as well as additional drug targets. Our transcriptional and biochemical analyses identified that the loss of FeoB1 caused an accumulation of pyruvate. This warranted additional study because pyruvate accumulation has been known to decrease toxin production in *C. difficile*. Specifically, we have found that three genes governing the Krebs cycle were downregulated in our FeoB1 deletion mutant. We hypothesize that the failure of this cycle to metabolize pyruvate into downstream products is responsible for the accumulation of pyruvate and that this accumulation is causal to decreased toxin biosynthesis. Thus, we are continuing our investigation of these genes by genetically knocking them down and consequently reducing the expression of the enzymes they produce: pyruvate carboxylase, aconitase, and isocitrate/3-isopropylmalate dehydrogenase. The results of the pyruvate and toxin measurements in both antisense and deactivated-Cas9 knock-downs, inhibiting translation and transcription respectively, will be presented.

Acknowledgements: This project is supported by the National Institutes of Health (NIH).

Poster 38

Validation of the Modified Rapid Test for Detection of the Cefazolin Inoculum Effect (CzIE) in Bloodstream Methicillin-*Susceptible Staphylococcus aureus* from North and Latin America

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BACKGROUND

Staphylococcus aureus is a major bacterial human pathogen that causes a variety of potentially serious infections including BSI (bloodstream infection). Cefazolin is an alternative for severe deep-seated Methicillin-Susceptible *Staphylococcus aureus* (MSSA) infections, as it is safer, well-tolerated and with similar efficacy than isoxazolyl-penicillin. The CzIE is associated with therapeutic failures and mortality in MSSA infections. We recently developed a rapid-test for detection of the CzIE (rCT), subsequently this test has been modified using ampicillin disc. We perform a blind evaluation of the modified test in bacteremic isolates of MSSA from North and Latin-America.

METODOLOGY

Ninety-nine MSSA recovered from bloodstream infections in North-America (2019; n=69) and Latin-America (2011-2019; n=30), previously characterized for the presence of the CzIE, were included. Blind evaluation of the modified rCT was performed in a set of MSSA, in a central laboratory in Colombia. rCT was performed according to the published protocol, and modification of the use of ampicillin disc (10μg) placed in 1 mL of BHI-broth for induction. The researchers were blinded to the results of the gold standard to detect CzIE (broth microdilution using standard (ST) and high (HI) inocula and breakpoint $\geq 16\ \mu g/mL$). Diagnostic performance metrics were calculated and typing of BlaZ was performed using Whole-Genome-Sequencing data available of all strains.

RESULTS

Taking into the account the breakpoint of $\geq 16\mu g/mL$, the CzIE was detected in 71 out of 99 MSSA. Moreover, compared to the gold standard, the modified test showed a sensibility and specificity of 97% and 86%, respectively, and overall accuracy of 94%. NPV and PPV was 92% and 95%, respectively. Types C and A were the predominant BlaZ types in the 69.7% and 27.3% of the 99 MSSA. Furthermore, among the MSSA exhibiting CzIE (n=71), type C and A were the most frequent BlaZ types, in 47 and 21 of isolates, respectively. In the analysis of BlaZ type C isolates, the modified rapid test had a sensitivity of 96% and specificity of 82%, and accuracy of

91%. Whereas, in BlaZ type A isolates (n=27), the complete set of MSSA were correctly identified (sensitivity and specificity of 100%).

CONCLUSION

The modified test correctly detected the CzIE in bloodstream MSSA from different geographic areas, with a global accuracy of 94%. Notably, the accuracy of the test for BlaZ type C isolates was 91%. Further, the use of ampicillin disks proved to be practical, simplifying and speeding up the realization of the test.

Poster 68

Validation of the Modified Rapid Test for Detection of the Cefazolin Inoculum Effect (CzIE) in Bloodstream Methicillin-Susceptible *Staphylococcus aureus* from North and Latin America.

Lina Carvajal[1], Sandra Rincón[1], Diana Panesso[1,2,3], Sara Gomez[4,5], Kavindra Singh[2,3], Karen Jacques[2,3], Husna Malikzad[2,3], Dziadula J[3], William Miller[2,3], Cesar Arias[2,3], Jinnethe Reyes[1]

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Ninety-nine MSSA recovered from bloodstream infections in North America (2019; n=69) and Latin America (2011-2019; n=30), previously characterized for the presence of the CzIE, were included. Blind evaluation of the modified rCT was performed in a set of MSSA, in a central laboratory in Colombia. rCT was performed according to the published protocol, and modification of the use of ampicillin disc (10μg) placed in 1 mL of BHI-broth for induction. The researchers were blinded to the results of the gold standard to detect CzIE (broth microdilution using standard (ST) and high (HI) inocula and breakpoint $\geq 16\ \mu g/mL$). Diagnostic performance metrics were calculated and typing of BlaZ was performed using Whole-Genome-Sequencing data available of all strains.

Taking into the account the breakpoint of $\geq 16 \mu g/mL$, the CzIE was detected in 71 out of 99 MSSA. Moreover, compared to the gold standard, the modified test showed a sensibility and specificity of 97% and 86%, respectively, and overall accuracy of 94%. NPV and PPV was 92% and 95%, respectively. Types C and A were the predominant BlaZ types in the 69.7% and 27.3% of the 99 MSSA. Furthermore, among the MSSA exhibiting CzIE (n=71), type C and A were the most frequent BlaZ types, in 47 and 21 of isolates, respectively. In the analysis of BlaZ type C isolates, the modified rapid test had a sensitivity of 96% and specificity of 82%, and accuracy of 91%. Whereas, in BlaZ type A isolates (n=27), the complete set of MSSA were correctly identified (sensitivity and specificity of 100%).

The modified test correctly detected the CzIE in bloodstream MSSA from different geographic areas, with a global accuracy of 94%. Notably, the accuracy of the test for BlaZ type C isolates

was 91%. Further, the use of ampicillin disks proved to be practical, simplifying and speeding up the realization of the test.

Acknowledgements: Universidad El Bosque.

Poster 10

Transcriptional Expression of the Genes Associated to Amino Acid Biosynthesis and Virulence in Methicillin-Resistant *Staphylococcus aureus* (MRSA) USA300-LV is Modulating by Mercury.

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Environmental pollution by mercury has a large impact on ecosystems and is a particularly serious threat in developing countries, like Colombia where is the third mercury (Hg) emitting country globally. Bacteria have evolved efficient systems to cope with mercury but the actual impact of this heavy metal on the evolution of antibiotic resistance is unclear. Preliminary data suggest that a high number of clinical isolates of MRSA recovered in Latin American countries with high level of mercury pollution, harbor mercury resistance genes (*mer*ABR cluster). The most prevalent MRSA clonal lineage in Colombia called USA300-Latin American Variant (USA300-LV), contains a genomic island designated as the copper and mercury resistance (COMER) element and the genomics indicate that the *mer*ABR cluster is present in >50% of the genomes, particularly in isolates recovered from Colombia, Ecuador, Peru, Venezuela and Chile. For these reasons, we evaluated the impact of mercury on the USA300-LV MRSA that is poorly understood.

Thus, we determine the impact of sub-inhibitory concentrations of $HgCl_2$ (1.28 µM) on the transcriptome of a representative clinical isolate of the MRSA USA300-LV clone (CA-MRSA12) by RNA sequencing. We identify differentially expressed genes (DEGs) by EDGEpro software and DEseq2 R package (p-*value* ≤0.05) and the functional enrichment analysis was used to identify the metabolic pathways and biological processes significantly related to DEGs (p-*value* ≤0.05).

We found 115 DEGs. Functional enrichment analysis showed that 71 upregulated genes were enriched by multiple anabolism pathways related to amino acid biosynthesis, specifically Valine, Lysine, Leucine, and Isoleucine. These amino acids are important metabolites for the biosynthesis of peptidoglycan (Lysine) during cell-wall metabolism, and anteiso-fatty acids (Valine, Leucine, and Isoleucine) for permeability of the membrane in *S. aureus,* as an adaptive response to the environment. On the other hand, the same analysis with the 44 down-regulated genes showed a statistical significant enrichment of virulence and host immune system defense process related to crucial virulence factors of MRSA USA300-LV such as IgG-binding protein (Sbi) and Fibrinogen-binding protein.

Summarizing, our results suggest that mercury is stimulating the expression of genes associated with biosynthesis of key metabolites for remodeling cell envelope (membrane and cell wall) of the MRSA USA300-LV. Whereas, its virulence is reduced, possibly as an adaptive response to environments contaminated with heavy metal, as mercury. This would be a probable explanation to the success of this clonal lineage of *S. aureus* in Colombia.

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Poster 9

Phylogeny of Mercury Reductase Protein MerA in *Staphylococcus aureus* from Bloodstream Infections Recovered from Latin-America.

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MRSA belonged to USA300-Latin American-Variant (USA300-LV) is the clone stablished in hospitals of the northern region of South-America and has replaced previous successful MRSA clones. Moreover, we found that mercury resistance genes are enriched in USA300-LV isolates recovered from invasive infections in hospitals in this region. Among these genes, *merA* encodes the mercury reductase enzyme (MerA), the key protein of the Mer operon, a bacterial enzymatic system involved in the detoxification of mercuric compounds. We aimed to investigate the phylogenetic relationships of MerA in bloodstream *S. aureus* collected in Latin-American hospitals.

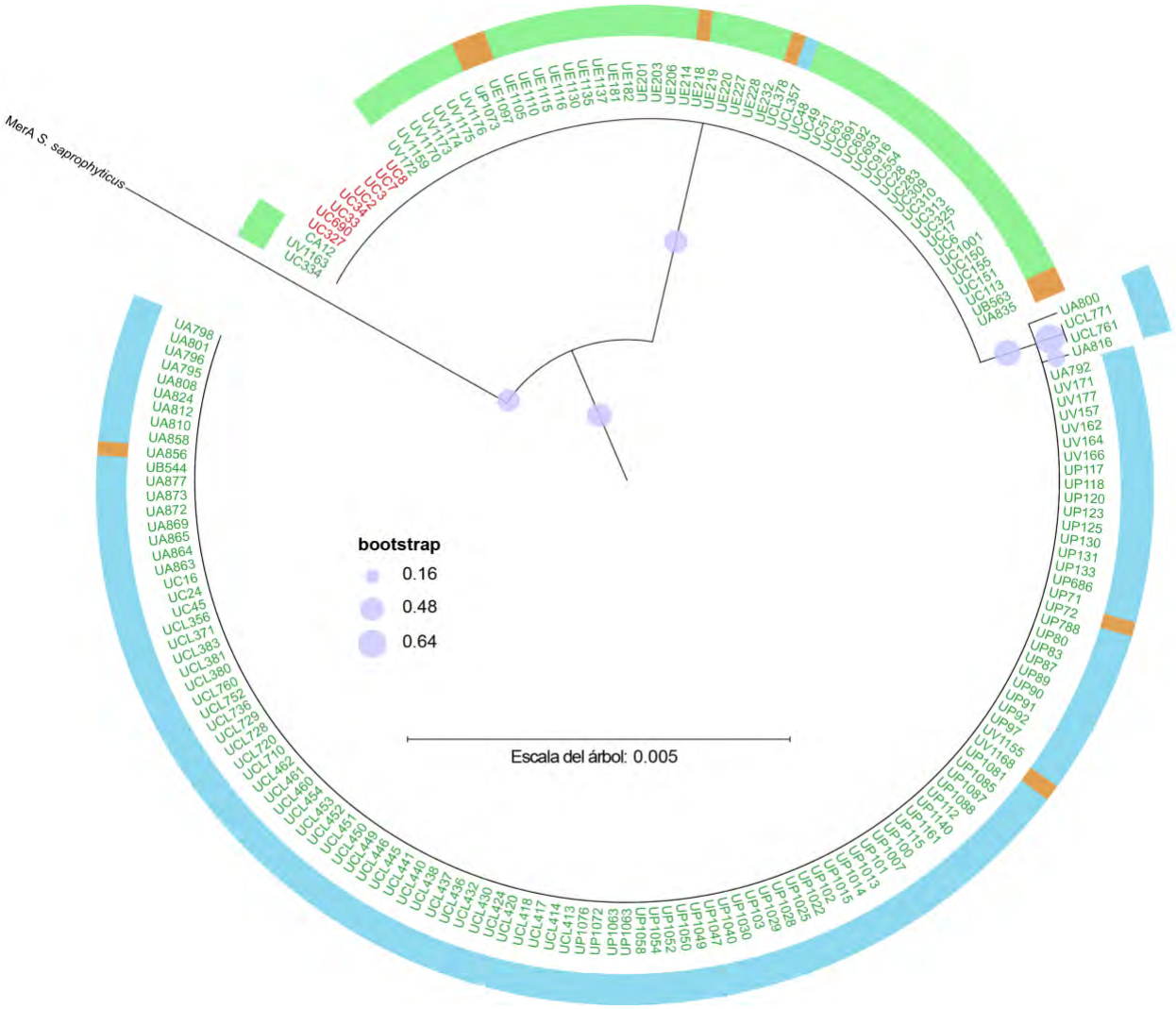
A total of 331 genomes from Latin American hospitals were included (2010-2014). 184 MRSA carrying *merA* belonged to USA300-LV (n=52), Chilean-Cordobes (n=123), and Brazilian (n=9) clones. *merA* was investigated by *in-silico* PCR in 147 MSSA. From the assembled genomes, *merA* sequence was searched based on the sequence of *merA* gene of the MRSA-USA300-LV CA12 strain (identity ≥90%, coverage ≥80). Amino acid deduced sequences were obtained using Expasy server. MerA protein sequences from MRSA and MSSA genomes including the sequence of *S. saprophyticus* (outgroup, GenBank:LR134089.1:c2520758-2519115) were aligned with the ClustalW algorithm and analyzed by phylogenetic inference using the Maximum-Likelihood method. Evolutionary distances were calculated using the WAG model (best model according to Bayesian information criterion), with 1000 bootstrap replicates. All positions containing gaps and missing data were eliminated, and the analysis was performed in MEGA software, v10. Furthermore, MIC determinations against $HgCl_2$ by broth-microdilution were performed in all the *S. aureus* isolates included in the phylogenetic analysis.

Only eight genomes out of 147 (n=5.4%) MSSA harbored *mer*A. Moreover, among 192 *S aureus* genomes included in the phylogenetic tree based on the amino acid sequence of MerA, we identified two main clades (Figure 1). The major clade grouped 125 MerA from genomes belonging mainly Chilean-Cordobes clone (122), as well as 3 sequences of Brazilian clone. The minor clade grouped 67 MerA sequences: 52 MerA of USA300-LV, 6 of Brazilian, one of Chilean-Cordobes clone along with 8 MerA identified in MSSA. Therefore, this is suggestive that the protein was highly related between MSSA, and different MRSA lineages evaluated (high identity >99% similar at amino acid level between these sequences). Further, Chilean-Cordobes and USA300-LV clones (two of the most successful clones in Latin-American hospitals) clustered into two separate but highly related clades (similarity > 99%). In addition, we found that *mer*A genes were functional, since all the isolates included in the phylogenetic analysis had a MIC of $HgCl_2 \geq$ 128μM/mL.

We found a high evolutionary relationship between MerA among the clones included. Moreover, small highly conserved differences (on average in 3 amino acids) were identified, that could impact on the diversification of the function of the protein in MRSA.

Acknowledgements: Universidad El Bosque (PCI-2023-0002)

Figure 1. Phylogenetic analysis of 192 *S. aureus* genomes based on the MerA protein sequence. Inner circle shows the isolates included in the tree (codes in green, MRSA; in red, MSSA). Outer circle shows different clones included in the analysis (green, USA300-LV clones; orange, Brazilian clone; blue, Chilean-Cordobes clone)



Poster 37

The Pre and Post-Occupancy Comparison of Environmental Microbiota in the Adult Intensive Care Unit of a High-Complexity Hospital from Colombia.

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The human microbiota is constantly changing, influenced by the exchange of microorganisms between the individuals and the environment, which facilitates the transmission of clinically significant bacteria. This phenomenon is especially relevant in the hospital setting. However, the understanding of the composition of the environmental microbiome in relation to space occupancy remain limited. We aimed to characterize the environmental microbiota of the adult Intensive Care Unit (ICU) of a high-complexity hospital in Colombia in the pre-occupancy context and four years after its opening.

In five of the 12 rooms comprising the adult ICU, 34 samples were taken from surfaces corresponding to bedrail, mattress, washbasin, monitor, nurse call bell, table, and corridor washbasin for the pre-occupancy period (2018). In the post-occupancy (2022) another 34 samples were taken from the same surfaces. The swabs were stored in DNA/RNA shield buffer and stored at - 80°C. Microbiome composition was determined by 16S rRNA sequencing (V4-region) using the MiSeq-Illumina platform. Amplicon sequence variants (ASVs) classification was performed using greengenes2 database. Simpson and Shannon indices were calculated to determine differences in microbiota diversity between periods, and Sankey's and SIMPER analysis to identify statistical differences in taxa abundance between periods.

Adult ICU surfaces showed differential microbiota composition between the pre-occupancy and the post-occupancy periods. In the pre-occupancy period, a predominance of Proteobacteria was found on bedrails and washbasins (abundance >80%), while on the other surfaces it was close to 50%, with the presence of Firmicutes, Bacteroidota, and Fusobacteriota. The most abundant genera were *Acinetobacter* and *Pseudomonas*. For the post-occupancy, an increase in the abundance of Bacteriodota, Firmicutes, and Actinobacteriota, and a reduction in Proteobacteria were observed, consistent with a higher abundance of *Prevotella*, *Staphylococcus*, *Corynebacterium*, and *Faecalibacterium*.

The only surfaces that showed differences in their alpha-diversity were bedrails and washbasins related to an increase in diversity in the post-occupancy period (Shannon and Simpson indices, p-value <0.05). In the bedrails, the abundance increased from 0.8% to 59% for Bacteroidota (Microscillaceae genera and *Prevotella* spp.), from 8% to 21% for Firmicutes (*Staphylococcus* spp. increasing, but declining of *Bacillus* spp.), while Proteobacteria decreased from 90% to 5%, associated with the reduction of *Acinetobacter* spp. and *Pseudomonas* spp. Similar changes were seen in the abundance of Phylum Bacteriodota, Firmicutes, and Proteobacteria in washbasins. Remarkably, only washbasins have an increment in the abundance of Actinobacteria in the post-occupancy period, related to the increase of *Corynebacterium* genus.

Occupancy is a major determinant of bacterial colonization within hospital environments. We identified changes potentially driven by hospital occupancy, with displacement of environmental microbiota by bacterial taxa associated with the human microbiota, particularly skin (i.e. *Staphylococcus* spp. and *Corynebacterium* spp.) and gastrointestinal (i.e. *Prevotella* spp. and *Faecalibacterium* spp.).

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Poster 67

Potential Pathogenic Bacteria Identified on Inanimate Surfaces in Adult and Surgical Intensive Care Units From a High Complexity Hospital in Colombia

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Healthcare-associated infections (HAIs) constitute a public health problem that led to increase in mortality, hospital stay duration, and costs. The rise of antibiotic resistance and the presence of pathogens on environmental hospital surfaces are associated to HAIs and in intensive care units (ICU) represent high-risk areas for these infections. Moreover, pathogenic microorganisms are capable to persist and survive for long term periods on high-contact hospital inanimate surfaces (frequently touched surfaces by patients, hospital workers and visitors). In our country, studies focused on the assessment of microorganisms on environmental hospital surfaces are lacking. We aimed to identify microorganisms potentially pathogens on high-contact surfaces in two ICUs from Colombia. Samples were obtained from an Adult intensive care unit (AICU) and a surgical intensive care unit (SICU) belonged to a high complexity hospital in Bogota, capital of Colombia (each ICU had 12 rooms). Sampling was performed between September 2022 to March 2023. Surfaces swabs were collected from 5 rooms at 6 high-contact surfaces (sink in patient rooms, bed rail, mattress, side table, nurse call bell and monitor, for each room at each ICU), including 3 hallway sinks (32 surfaces per ICU). Microbiological screening was performed using CHROMagar™ Orientation and single colonies were sub-cultured on CHROMagar™-Staph aureus, CHROMagar™-Pseudomonas, CHROMagar™- Acinetobacter, and selective media (Manitol Salt Agar, Enterococosel agar). Specie-specific identification and antibiotic resistance genes were confirmed by PCR.A total of thirty-two bacterial isolates (n=21 and n=11 from SICU and AICU, respectively), were recovered from a total of 64 surfaces sampled from 5 rooms in each ICU. Gram-negative bacteria were predominant (20 out of 32 isolates recovered) vs 11 Gram-positive bacteria. Sink in patient rooms was the surface that showed high recovery rate of isolates for both ICUs 67%,14 out of 21 isolates for SICU, and 45%, 5 out of 11 isolates for AICU. Moreover, Enterobacterales were predominant among isolates recovered from SICU (n=9, 8 recovered from patient room sinks and 1 from mattress). Whereas *Staphylococcus* spp. was the most common genus isolated in different surfaces in SICU (monitor n=2; mattress n=2; side table n=1; and nurse call bell n=1). In AICU, Enterobacterales were the most frequent bacterial group recovered from patient room sinks (n=2), hallway sink (n=2) and mattress (n=1). Regarding to antibiotic resistant organisms, only one isolate was identified as Methicillin-Resistant *S. aureus* (MRSA from a bed-rail in AICU). Potential pathogenic bacteria were identified in surfaces in both ICUs. Our findings highlight the relevance of microbiological environmental hospital screening that can identify reservoirs of clinically important bacteria that may cause HAIs.

Acknowledgments: This work was supported by Universidad El Bosque (PCI-2022-11028).

Poster 39

Cefazolin Inoculum Effect in Commensal Methicillin Susceptible *Staphylococcus aureus* MSSA Recovered From Nasal Cavity of Patients in Intensive Care Units in Colombia

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Cefazolin is an alternative for the treatment of MSSA infections and recommended for surgical prophylaxis. The cefazolin inoculum effect (CzIE), the increase in MIC at high bacterial inocula, is associated to therapeutic failures and increased mortality in deep-seated MSSA infections. High prevalence rates of CzIE in clinical MSSA isolated from bacteremia and osteomyelitis in Colombian hospitals has been documented. However, despite of these studies, there is a lack of knowledge on the characterization of the CzIE in commensal MSSA from critically-ill patients or those requiring constant monitoring, as ICU patients. We aimed to investigate and characterize the CzIE in nasal commensal MSSA recovered from patients admitted to ICUs in Colombia. We evaluated thirty-three MSSA isolates recovered from nasal swabs of 29 ICU patients at six high-complexity Colombian hospitals (2019-2023). Cefazolin MIC determinations by broth microdilution using standard inocula, and high bacterial inocula (in biological triplicates) were performed. Nitrocefin-based rapid test to identify MSSA exhibiting the CzIE was performed and diagnostic performance metrics were calculated. WGS was carried out using Illumina platform to characterize BlaZ types and allotypes, Clonal Complexes (CC) and Agr types. The CzIE was identified in 54.5% (n=18 out of 33) commensal MSSA. Notably, among 29 patients that contributed with 33 MSSA isolates, 17 patients (59%) had nasal colonization with MSSA exhibiting the CzIE (11 on admission to the ICU and 6 during the follow-up period, range 1 to 7 days). Among 18 MSSA displaying the CzIE, BlaZ type A was predominant in 61% of isolates, and BlaZ-2 was the allotype predominant in 50% of MSSA with the CzIE. Whereas among 15 MSSA lacking the CzIE, BlaZ type C was the most frequent in 47% of isolates, being BlaZ-1 the allotype predominant in 40% of MSSA. Moreover, a high diversity of genetic lineages with eight CC (CC1,CC5,CC15,CC22,CC30,CC45,CC398 and a new CC) were detected among the 33 MSSA isolates. CC30 was the predominant clone in MSSA displaying the CzIE (44% isolates), while two lineages (CC5 and CC30, 27% each one) were the most common in MSSA without the CzIE. Agr-III and Agr-I were the predominant types, identified in 56% and 47% of MSSA with the CzIE and lacking the CzIE, respectively. Compared to the gold standard (broth microdilution Cz HI-MIC) the rapid test identified commensal MSSA showing the CzIE with a sensitivity 100%, specificity 93% and an overall accuracy of 97%. We found an unexpected high prevalence (59%) of ICU patients colonized by MSSA exhibiting the CzIE, showing similar genetic features to MSSA isolates with CzIE from invasive infections. Furthermore, our findings suggest that the nasal cavity of ICU

patients may represent a reservoir for the dissemination of these colonizing MSSA, highlighting the importance of surveillance screening.

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Poster 55

Abstract Title

The Role of β-lactamase Active Site Loop Conformation for Binding and Inhibition by the β-Lactamase Inhibitory Protein (BLIP)

Abstract

b-lactamase enzymes inactivate β-lactam antibiotics resulting in drug resistance. The b-lactamase inhibitory protein (BLIP) is a 17.5 kDa naturally occurring inhibitor of class A b-lactamases. BLIP binds and inhibits b-lactamases with inhibition constants (K_i) ranging from picomolar to micromolar. Recently, we showed that the potency of BLIP inhibition is dependent on the conformation of an active site loop in CTX-M b-lactamases. The widespread CTX-M-14 and CTX-M-15 β-lactamases have an 83% sequence identity. We showed that BLIP weakly inhibits CTX-M-14 but potently inhibits CTX-M-15. The structure of the BLIP/CTX-M-15 complex reveals that binding is associated with a conformational change of an active site loop of β-lactamase. The protruding loop (aa 103-106) found in class A b-lactamases contains a conserved Tyr at position 105 that forms a wall of the active site pocket. We showed that the loop toggles between two conformations and tight binding of BLIP to the CTX-M-15 enzyme is associated with a conformation that moves Tyr105 away from the wall of the active site, allowing access of a BLIP loop containing Tyr50 for binding the enzymes. Here, we determined the structure of a BLIP E73W variant that potently inhibits both CTX-M-14 and CTX-M-15 enzymes with an increase in inhibition potency by 60- and 20-fold respectively. The structure of BLIP E73W in complex with CTX-M-14 revealed an altered positioning of BLIP where Trp73 traps the CTX-M-14 protruding loop residue Tyr105 and allows access of the BLIP Tyr50 loop to bind to the β-lactamase active site. Based on this observation, we hypothesized that observed binding specific of BLIP to various β-lactamases is controlled by the position of the protruding loop residue Tyr105. This predicts that removal of the Tyr with an alanine substitution would result in tight binding of BLIP to both CTX-M-14, CTX-M-15, and other class A β-lactamases. Consistent with this hypothesis, we found that Y105A substitutions in class A β-lactamases result in potent inhibition by BLIP. Specifically, BLIP potently inhibited CTX-M-14 Y105A with an increase of 250-fold and CTX-M-15 Y105A with an increase of 50-fold when compared to wild type CTX-M. These studies shed light on the role of loop conformation not only for enzyme catalysis but also for inhibitor potency. Therefore, assessing active site loop conformations will be important for the design of potent β-lactamase inhibitors.

Poster 56

BamE Essentiality in *Pseudomonas aeruginosa* is Linked to Cyclic Nucleotide Signaling

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Surface-exposed proteins play an important role in bacterial physiology and pathogenesis in Gram-negative bacteria. These proteins are associated with the outer membrane (OM) and belong to two main classes: integral membrane β-barrel proteins (OMP), and peripheral lipoproteins (Lp) anchored to a membrane by a N-terminal lipid moiety. OMPs are inserted into the OM by the essential β-barrel assembly machinery (Bam), and the mechanisms behind Lp targeting to the cell surface are poorly understood.

Our lab discovered that the Bam complex plays a role in surface localization of the OMP-dependent lipoprotein RcsF in *E. coli*. BamE is the key player in the assembly of RcsF/OMP complex. While RcsF remains the only known substrate that requires BamE activity and is conserved in Enterobacteria, BamE is more widely conserved suggesting the presence of additional surface exposed Lp (SLp) substrates. The goal of the project is to identify new SLp substrates of the Bam complex and determine the function of BamE in Gram-negative bacteria.

In *Pseudomonas aeruginosa, bamE* was proposed to be essential based on various transposon sequencing (Tn-seq) experiments, but results remained inconclusive because the *bamE* gene contains a promoter region of an essential *fur* gene. Through genetic analysis and various complementation experiments, I demonstrated that *bamE* is indeed essential in *P. aeruginosa*.

To identify an underlaying reason for *bamE* essentiality, I generated a conditional *bamE* mutant, in which *bamE* expression is controlled by the rhamnose inducible promoter, and performed detailed phenotypic analysis, including growth curves, transcriptomics and proteomics. This analysis is consistent with a defective Bam complex, evidenced by upregulation of AlgU stress response regulon, and downregulation of several OMPs.

Surprisingly, however, our transcriptome analysis (RNA-seq) revealed that some of the most differentially regulated genes were related to the cyclic nucleotide signaling. Specifically, c-di-GMP regulated genes, including *pel* polysaccharide and *cdrAB* genes, were strongly upregulated. At the same time, cyclic-AMP genes, including *chp, pil, vfr* and virulence genes, were downregulated. Strikingly, I isolated four suppressors of *bamE* essentiality in the Chp/Pil chemotaxis-like system that regulates cyclic-AMP production. The nature of the suppressor mutations suggest that increased cyclic-AMP production improves survival of the *bamE* depletion strain in the absence of rhamnose.

These experiments clearly indicate that BamE plays a more important role in the viability of Gram-negative bacteria than we anticipated based on research in *E. coli,* and provides a new exciting link between envelope biogenesis and cyclic nucleotide signaling that we will explore in our future work.

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Poster 57

Tinidazole Salvage Therapy for Metronidazole-Resistant *Trichomonas Vaginalis* Characterized by Single Nucleotide Polymorphism in the ntr6Tv Nitroreductase Gene

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Trichomonas vaginalis (*T.vaginalis*) is the etiologic agent for trichomoniasis, which is the most common, non-viral, sexually transmitted infection worldwide. This infection is known to cause vaginitis and cervicitis in females, and urethritis, epididymitis, and prostatitis in males. Additionally, it is a risk factor for development of genitourinary malignancies, HIV infection acquisition, and poor infant health outcomes. The current gold standard treatment utilizes 5-nitroimidazole (5-NI) agents, with metronidazole (MTZ) being the standard therapy and tinidazole (TNZ) used in refractory cases. Occasionally, some infections of *T. vaginalis* persist through treatment or recur after initial resolution. This may be due to MTZ resistance attributed to reduced nitroreductase activity through single nucleotide polymorphisms (SNPs) in $ntr4_{Tv}$ and $ntr6_{Tv}$.

A previously healthy 27-year-old woman presented to the clinic for evaluation of refractory trichomoniasis, after previous diagnosis by positive nucleic acid amplification test (NAAT) four months ago. The first case was treated with oral MTZ. On follow-up, patient was asymptomatic, but test-of-cure NAAT remained positive, so patient received one-time 2000 mg of oral MTZ. On second follow-up, patient returned with mild symptoms with a positive test-of-cure NAAT, so a final one-time 2000 mg of oral MTZ prescription was initiated. Patient was compliant with recommended sexual abstinence and medication regimen; however, the infection did not resolve, and patient continued to experience symptoms. Based on the persistence of infection, the clinical team assumed resistance to the MTZ treatment from a possible genotypic mutation, and patient was placed on a new treatment course of oral tinidazole. Patient opted out of vaginal TNZ therapy. After modified regimen, patients' infection resolved and repeat NAAT was negative.

Persistent trichomoniasis infection is difficult to identify and treat. Often, many patients are started on the mainstay treatment, MTZ, since the 5-NIs are known to be effective in most of the patient population. Additionally, early identification of MTZ resistance can contribute to an increased treatment success rate. One possible method for this is identification of SNPs, as was identified in this patient in the nitroreductase genes $ntr4_{Tv}$ and $ntr6_{Tv}$. Only after failure of the infection to resolve is the patient placed on an alternative regimen. However, the literature has yet to elucidate an effective treatment regimen for MTZ-resistant strains of trichomoniasis. In this case, MTZ resistance was addressed utilizing tinidazole without intravaginal adjunct, and was successful.

Poster 40

Fusobacterium nucleatum Enoyl-ACP Reductase II (FabK): A Narrow-Spectrum Drug Target

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Fusobacterium nucleatum, a commensal-turned-pathogen native to the oral cavity, contributes to dysbiotic diseases such as periodontal diseases and gastrointestinal cancers. While *F. nucleatum* infections are susceptible to many broad-spectrum antimicrobials, such treatment can cause further disruption to the microbiome putting patients at risk for dysbiosis associated illnesses. Thus there is a clinical need for the development of narrow-spectrum therapeutics that will inhibit *F. nucleatum* without worsening the microbial imbalance. The enoyl-ACP reductase (ENR) is a promising target for the development of narrow-spectrum antimicrobials. ENRs catalyze the final step of the elongation cycle in bacterial fatty acid synthesis, and are known to be essential in key pathogens, including *Clostridioides difficile* and *Staphylococcus aureus*. There are four distinct ENR isoenzymes, FabI, FabK, FabL, and FabV, of these FabK is structurally and mechanistically distinct from the others. FabK is the only flavoenzyme, requiring FMN for its enzymatic activity. Previous studies have shown that FabK is a narrow-spectrum drug target in *Clostridioides difficile*. Analysis of the *F. nucleatum* genome revealed that *Fn*FabK (Fn0174) is the sole ENR, indicating that it is a potential target for narrow-spectrum antimicrobials. We were unable to delete *fabK* in *F. nucleatum* ATCC 23726 and observed a loss of growth upon expression of *fabK* targeting anti-sense RNA. Supplementation of exogenous fatty acids were unable to prevent growth inhibition caused by silencing of *fabK*. Together these findings indicate that FabK is essential to the growth of *F. nucleatum*. Additionally, we tested a panel of analogs to a known FabK inhibitor and identified compound 681 as a potent inhibitor of *Fn*FabK (MIC=0.39 µg/ml; IC50: 2.06 µM). Exogenous fatty acids were unable to protect *F. nucleatum* from inhibition by 681. Resistant mutants generated against 681 possess amino acid mutations within *Fn*FabK or mutations affecting the expression of genes associated with fatty acid biosynthesis. Importantly, compound 681 exhibited little activity against a panel of representative species from the digestive tract. While 681 did inhibit *Streptococci* species, supplementation of physiologic fatty acids partially restored growth. Our results demonstrate that FabK is essential to *F. nucleatum* and is a target for the development of narrow-spectrum antimicrobials.

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High Throughput Screening Reveals β-Lactamase Synthesis Regulator / Muropeptide Transporter (*ampG*) as Involved in β-lactam Resistance in *Klebsiella pneumoniae*

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Abstract

Bacterial antimicrobial resistance (AMR) is a significant worldwide public health crisis that was associated with ~700,000-1,270,000 deaths worldwide in 2019. This includes *Klebsiella pneumoniae*, a major human pathogen that can develop resistance to most currently used β-lactam antibiotics including carbapenems. Although many mechanisms of carbapenem resistance in *K. pneumonae* are known, we utilized a high throughput screening (HTS) approach to identify new or underappreciated resistance mechanisms. 11 traditional antibiotics (cell wall synthesis inhibitors and protein translation inhibitors) were screened against a sub-library of 1667 transposon mutants derived from the *K. pneumoniae* outbreak strain KPNIH1. The sub-library of transposon mutants were selected for membrane associated genes from the primary library of approximately 12,000 transposon mutants. HTS was performed in 384 well plates containing 1/3rd MIC for any given antibiotic in Mueller Hinton-II broth with 0.4% DMSO and 25 mM of sodium bicarbonate. Transposon mutants were incubated for 18 hours at 37^{0}C after antibiotic treatment. The relative fitness ratio of transposon mutants compared to the MKP103 parental strain was determined from two independent experiments. The HTS identified 71 unique transposon mutants when analyzed against 11 antibiotics that demonstrated a significant fitness defect. *ampG* was one target which demonstrated a loss of function phenotype in the presence of tested β-lactams. The transposon mutant specific to β-lactamase synthesis regulator / muropeptide transporter (*ampG*) was found to be 2-fold more sensitive towards meropenem, meropenem / vaborbactam, and ceftazidime. Additionally, *ampG* transposon mutants were 4-fold more sensitive towards ceftazidime / avibactam and cefepime. The deletion of *ampG* demonstrated a similar trend of sensitivity towards β-lactams when compared to the transposon mutant. Overexpression of *ampG* in the mutant genetic background recapitulated the wild-type phenotype. To investigate the possible significance of *ampG* in clinical settings, we deleted *ampG* in a carbapenem-resistant clinical isolate. The deletion of *ampG* resulted in 4-fold more sensitivity towards meropenem. The overexpression of *ampG* in the deletion mutant partially complemented the wild-type phenotype. Our results indicate that *ampG* plays a significant role in resistance against β-lactams including carbapenems in the pathogen *K. pneumoniae*.

Poster 72

Epidemiology of Bacterial Infections Among Critically Ill Patients with Acute Kidney Injury: A Sub-study of The DYNAMITE Prospective Cohort

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The incidence of acute kidney injury (AKI) among critically ill patients is between 30-57%, and is associated with higher mortality. Severe infections and sepsis are among the most usual causes of AKI in the intensive care unit (ICU). This study aims to compare the microbiological epidemiology and clinical outcomes of patients with and without AKI. Data from this analysis is derived from DYNAMITE study. This is a prospective cohort of adults admitted to the ICUs in two Houston hospitals, conducted from 12/2020 to 11/2023. Subjects were recruited within their first 24 hours from ICU admission. Demographics, baseline characteristics and bacterial isolates were collected. Subjects were compared based on the presence of AKI within 24 hours of ICU admission. AKI was defined with the RIFLE classification. Bacterial cultures were collected as clinically needed. Repeated positive isolates from the same source or species were not counted. Data analysis was performed using RStudio and Jamovi v18. A total of 200 subjects were enrolled, most were male (52%), white (68%), and had a median age of 61 years old. Hypertension (60.5%), heart failure (36.5%) and liver disease (30%) were the most prevalent comorbidities. The main cause of ICU admission was respiratory disease (20%) followed by cardiovascular disorders (18.5%). Overall, 103 (51.5%) patients had AKI on ICU admission, and 48 (46.6%) of them required continuous renal replacement therapy (CRRT). A total of 178 positive bacterial isolates were collected from 85 subjects (52 AKI and 33 non-AKI). For the AKI group there were 101 positive bacterial culture vs 77 in the non-AKI counterparts. The most common source of isolation was blood 25 (24.7%) in the AKI group vs wound 26 (33.7%) in the non-AKI. Enterobacterales 65 (36.52%) including, *Escherichia coli* (27; 17.5%) and *Klebsiella pneumoniae* (16; 24.6%), were the most prevalent microorganism in both groups, followed by *Enterococcus* species (15; 14.85%), *Staphylococcus aureus* (14; 13.86%), in the AKI group vs *Pseudomonas aeruginosa* (11; 14.29%), Enterococcus species (9; 11.69%) in the non-AKI. The median hospital length of stay was 24 days (IQR 10-41) for the AKI group vs 20 days (IQR 13-36) in the non-AKI group (p 0.556). Hospital mortality was similar between the AKI and non-AKI groups (23.3% vs 18.6%, p 0.410). Despite the inherent differences between the ICUs the incidence of AKI and Enterobacterales infections were high. Further studies should assess causal links between Enterobacterales and AKI.

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Poster 36

Identification of A Novel ST307 Sub-clade in Third Generation Cephalosporin Resistant *Klebsiella Pneumoniae* Causing Invasive Infections in the United States

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Third generation cephalosporin resistant *Enterobacterales* (3GC-R-E) are among the multi-drug resistant (MDR) bacteria considered to be a serious public threat. After *Escherichia coli*, *Klebsiella pneumoniae* is generally the 2nd most common species causing 3GC-R-E infections. However, there is a dearth of current molecular epidemiology regarding 3GC-R *Klebsiella pneumoniae* (3GC-R*Kp*) in the United States despite its marked clinical impact. We sought to analyze 3GC-R*Kp* bacteremia rates between March 2016 and May 2022 at a tertiary care cancer center in Houston, TX using review of the EPIC electronic health record. We performed whole genome sequencing of 3GC-R*Kp* bacteremia isolates using Illumina and Oxford Nanopore Technologies platforms. A comprehensive comparative genomic analysis was performed to dissect population structure, transmission dynamics, and pan-genomic signatures of our *K. pneumoniae* population. During the study period, we identified 194 index (*i.e.,* first infection for a given patient) 3GC-R*Kp* bacteremias. There was no significant difference in the total rates of 3GC-R*Kp* bacteremia rates over the study period (Mann-Kendall trend test *P*-value> 0.05); however, higher rates of 3GC-R*Kp* infections occurred during the last six months of each calendar year compared to the first 6 months (0.67 vs. 0.45 bacteremias per month per 1,000 patient admissions respectively; Student's t-test *P*-value < 0.001). Among the 126 index 3GC-R*Kp sensu stricto* isolates sequenced, the population was highly genetically diverse with a total of 52 different sequence types (STs). However, 28 isolates of ST307 and ST29 backgrounds were sufficiently closely related (*i.e.,* < 25 single nucleotide polymorphisms separation from their nearest neighbor) to be considered likely to have resulted from nosocomial transmission. ST307 was by far the most common ST (37 isolates, 29%), and we found that only 4 of these 37 strains belonged to the "Texas lineage" of ST307 strains previously identified as prevalent in the Houston area. Rather 33/37 strains were part of the "global lineage" of ST307, which prior to this study, was rarely identified in Houston. Eighteen of the isolates formed a newly identified ST307 sub-clade predicted to have emerged around 2010 and characterized by chromosomal possession of $bla_{\text{SHV-205}}$ and unique accessory genome content relative to other ST307 strains. We identified 24 strains belonging to the new ST307 sub-clade recently submitted to NCBI from diverse United States geographic locations. We conclude that a new ST307 sub-clade is a leading cause of 3GC-R*Kp* bacteremia in our hospital in Houston, TX and has recently been isolated throughout the United States. Our study highlights the shifting population dynamics of 3GC-R*Kp* causing invasive infections and the necessity to continue AMR surveillance in order to identify emerging high-risk populations.

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Poster 73

Understanding Antimicrobial Resistance through the Lens of the Ocular Microbiome

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The human microbiome, a dynamic ecosystem shaped by host factors and the environment, holds critical insights into microbial communities across various bodily regions. This study focuses on the ocular microbiome, employing 16S rRNA gene sequencing on samples from 30 individuals, encompassing both healthy and diseased states.

Our analysis revealed over 150 taxa. Prominent among these is the prevalence of *Acinetobacter* in more than half of the samples, with 85 taxa appearing uniquely. Distinct microbial compositions characterize conditions such as dry eye disease, marked by elevated levels of *Solirubrobacterales*, *Acinetobacter*, and *Enterococcaceae*. In contrast, healthy eyes exhibit a unique profile, including the presence of *Streptococcus* and *Pedobacter*. Crucially, our findings hint at potential antimicrobial resistance, particularly with the identification of *Staphylococcus* and *Streptococcus* in the ocular microbiome. Beyond these, genera such as *Enterococcus*, *Acinetobacter*, and certain *Proteobacteria* members (e.g., *Pseudomonas*) are recognized for their association with antibiotic resistance. Our study highlights the translational potential of microbiomics, emphasizing the role of the ocular microbiome in understanding and addressing antimicrobial resistance, thereby contributing to advancements in ocular health and therapeutics.

Keywords: microbiome; 16S rRNA sequencing; ocular diseases

Poster 71

Characterization of Pre-Resistance Mechanisms Enabling Carbapenem Resistance in High-Risk *Escherichia coli* Lineages

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Escherichia coli is a leading cause of human infection and a major contributor to the epidemic of antimicrobial resistant (AMR) bacteria. AMR *E. coli* infections that are resistant to carbapenems, which are considered as last-resort antibiotic treatments, are among the most challenging to resolve in hospital settings. Despite extensive research on carbapenem resistant *E. coli* mechanisms, there remains a knowledge gap of how high-risk *E. coli* lineages, such as sequence type (ST) 131, adapt to initial antibiotic exposure, which can be conceptualized as a 'pre-resistant' phase.

We employed a combination of a novel micro-fluidics system along with standard batch culture passaging to analyze the adaptive strategies of the carbapenem-susceptible, *bla*$_{\text{CTX-M-15}}$-positive ST131 strain, MB1860, to increasing amount of carbapenems over time. Daily aliquots of MB1860 isoforms were subjected to whole genome sequencing including copy number variation assessment using the CONVICT computational biology tool. RNA-seq was performed on a subset of daily MB1860 populations from both experimental evolution platforms. Targeted analyses of porin presence were assessed using Western immunoblots. Relative mutational frequency and mutant ertapenem MIC fold changes were measured for 14 ST131 ESBL positive isolates from different cladal backgrounds.

MB1860 developed carbapenem resistance significantly faster (~11 days) in standard batch culture relative to the micro-fluidics system (~52 days). In both systems, we identified that MB1860 rapidly responded to carbapenem exposure by increasing the copy number of the β-lactamase encoding genes *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{OXA-1}}$ which are co-located on the chromosome in the setting of transposable elements capable of mediating gene amplification. Differential expression analysis of MB1860 daily population isolates exposed to ertapenem (ETP) 0.5× found that both systems had transposase and beta-lactamase activity significantly upregulated as compared to passage controls. Additionally, in both systems, we found by Western blot down-regulation of outer membrane porin, OmpC, which would be predicted to reduce carbapenem entry into the *E. coli* cell. Importantly, these changes occurred prior to fixed genetic mutations in porin encoding genes that were ultimately detected in fully carbapenem-resistant strains. When analyzing the carbapenem mutational capacity of the 14 ST131 strains from diverse backgrounds, we identified the capacity of all ESBL positive strains to develop increased carbapenem non-susceptibility as measured through mutational frequency and ETP MIC fold changes. Using complementary strategies, we have identified that *E. coli* initially adapts to carbapenem exposure through amplification of non-carbapenemase β-lactamase encoding genes, increased expression of those aforementioned genes, and down-regulation of porin production through non-fixed genetic mechanisms. These findings challenge the current dogma that strains with pre-existing mutations in porin encoding genes are selected for during carbapenem exposure.

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Poster 75

Absence of LiaF Increases Daptomycin Activity against *E. faecalis* in a Rat Model of Infective Endocarditis

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Background: Daptomycin (DAP) is a lipopeptide antibiotic currently used in the treatment of vancomycin-resistant enterococcal infections. The enterococcal LiaFSR three-component regulatory system plays a major role in DAP resistance. Prior work has suggested the absence of LiaF in *E. faecalis* impairs activation of LiaFSR, leading to increased susceptibility to DAP. The aim of this study was to evaluate the efficacy of DAP against *E. faecalis* lacking a functional LiaF in a rat endocarditis model.

Methods: Three strains were used in this study: wild-type *E. faecalis* OG117, a strain lacking functional *liaF* via addition of four stop codons at amino acid positions 11-14 (OG117*liaF**$_{11-14}$), and a complementation of wild-type LiaF in its chromosomal location (OG117*liaF**$_{11-14}$::*liaF*). Each strain was evaluated with a previously published endocarditis model using male Sprague-Dawley rats. Subcutaneous DAP was administered for 3 days (45.3 mg/kg every 24 hours) to mimic human dosing (6 mg/kg). Bacterial colony-forming units per gram of vegetation (CFU) were determined for baseline controls prior to therapy (*t*=0) and at 24 hours after the last DAP dose. Geometric means of bacterial CFU per gram were log-transformed for statistical analysis using unpaired *t*-tests. The animal protocol (IS00006793) was approved by CMP, HMRI, Methodist Hospital, Houston TX.

Results: The ID_{90} values for OG117, OG117 *liaF**$_{11-14}$, and OG117 *liaF**$_{11-14}$::*liaF* were 7.9×10^3, 7.8×10^4, and 7.3×10^4 CFU/g, respectively and bacterial burden at *t*=0 were similar between each group of animals. All strains showed a significant reduction in CFU with DAP therapy (**Table 1**). Notably, rats inoculated with OG117*liaF**$_{11-14}$ had significantly lower CFU as compared to OG117 ($P < 0.015$) and OG117*liaF**$_{11-14}$::*liaF* ($P < 0.005$). Among animals inoculated with OG117 *liaF**$_{11-14}$ and treated with DAP, 43% exhibited sterile vegetation, whereas none in the OG117 and OG117 *liaF**$_{11-14}$::*liaF* groups did.

Conclusion: Loss of functional LiaF resulted in increased efficacy of DAP in a rat model of endocarditis. Targeting and preventing activation of the LiaFSR stress response may be a viable strategy to overcome DAP resistance.

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Table 1. Summary of results from the rat endocarditis model.

Test Bacteria and inoculum/rat used for DAP therapy experiments	DAP MIC (µg/ml)	Infective Dose 90 (ID_{90}s)	GM CFU (log10) ± SD at time 0 (*t* = 0) (*n*)	GM CFU (log10) ± SD after 3 days of DAP therapy than *t* = 0	*P* value vs *t* = 0 or between therapy groups
WT *E. faecalis* OG117	4	7.9×10^3	6.5 ± 0.7 (n=4)	3.7 ± 1 (n=7)	$P < 0.001$ vs $t = 0$ $P < 0.015$ vs *liaF**

1.2×10^7/rat					
OG117*liaF**$_{11\text{-}14}$ 1.5×10^7 /rat	1 - 2	7.8×10^4	6.2 ± 1 (n=3)	1.6 ± 1 (n=7)	$P < 0.002$ vs $t = 0$
OG117*liaF**$_{11\text{-}14}$::*liaF* 1×10^7 /rat	4	7.3×10^4	5.5 ± 0.8 (n=4)	3.9 ± 0.7 (n=7)	$P < 0.01$ vs $t = 0$ $P < 0.005$ vs *liaF**

Poster 76

Ceftriaxone to Cefepime Susceptibility Discordance in Viridans Group Streptococci Bloodstream Infections at a Comprehensive Cancer Center

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Patients with hematologic malignancies are at risk for infections resulting from prolonged neutropenia complicated by mucositis. Bacteremia caused by translocation of oral and gastrointestinal pathogens such as Viridans group streptococci (VGS) is common. VGS is a serious cause of sepsis with a mortality rate of 18-30%. The National Comprehensive Cancer Network (NCCN) guidance for patients with febrile neutropenia (FN) recommends empiric therapy with an anti-pseudomonal antibiotic, such as cefepime (FEP). When VGS is isolated in neutropenic patients, de-escalation from FEP is challenging due to the need to maintain anti-pseudomonal coverage during FN. Recent observations at our institution suggested that concordance between FEP and ceftriaxone (CRO) susceptibilities are inconsistent. This study aims to further characterize the susceptibility patterns of VGS isolates at our institution.

A total of 173 VGS isolates from blood cultures between August 2020 and July 2023 were identified. Twenty-one polymicrobial cultures and 7 cultures with incomplete susceptibility data due to non-viable strains were excluded. Historical CRO and FEP susceptibility data were available for 81 isolates. Isolates missing FEP susceptibilities were recovered from a frozen banked supply and underwent gradient strip testing for both CRO and FEP. Comparison of CRO susceptibility to historical susceptibility was done to validate the organism's antimicrobial profile. Four isolates that were CRO discordant between the two testing methods by more than one doubling dilution were excluded. Minimum inhibitory concentrations (MIC) were interpreted using Clinical Laboratory and Standards Institute (CLSI) M100 guidelines.

After exclusions, 143 isolates were included for analysis. The most common VGS organisms isolated were *Streptococcus mitis/oralis* (73%) followed by *Streptococcus sanguinis* (10%). Overall, ceftriaxone was susceptible (CRO-S) in 128 isolates (89%) and cefepime was susceptible (FEP-S) in 102 isolates (71%). Concordant CRO and FEP susceptibility (CRO-S/FEP-S) was seen in 101 isolates (71%), while concordant non-susceptibility (CRO-NS/FEP-NS) was seen in 14 isolates (9.8%). CRO and FEP discordance (CRO-S/FEP-NS) was seen in 27 isolates (19%). Discordance was associated with a 2 to 6 times higher FEP MIC.

Cefepime susceptibility was overall consistent with ceftriaxone susceptibility when cefepime was susceptible. Discordant susceptibility occurred (CRO-S/FEP-NS) at nearly a 20% rate, however, the clinical significance and impact on antimicrobial therapy selection remain uncertain. This rate of discordance suggests an assessment of current FEP breakpoints for VGS may be needed.

Poster 77

A Novel Integron (In2051) Carrying *bla*$_{IMP-62}$ Surrounded By a Complex Genetic Environment In a Hypervirulent XDR *P. aeruginosa* Strain

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Background: The IMP-type enzymes compose a versatile group of acquired MβLs usually encoded as gene cassettes inserted into class 1 integrons. Regardless of the diversity of IMP enzymes, there are relatively few studies that aimed to characterize their genetic background and mechanisms of mobilization. The aim of this study was to characterize the genetic environment of a novel In2051 carrying *bla*$_{IMP-62}$ integron in a hypervirulent *P. aeruginosa* (P-14.182) strain from Brazil by whole genome sequencing (WGS).

Methods: In 2017, as part of a surveillance study, a carbapenem-resistant *P. aeruginosa* strain (P-14.182) was recovered from a urine culture of a 44-year-old female patient hospitalized at a tertiary hospital located in the city of São Paulo, Brazil. Species identification was performed by MALDI-TOF MS and antimicrobial susceptibility testing was performed by broth microdilution. WGS was performed using both short paired-end reads sequencing by Illumina® MiSeq and long-read sequencing by Oxford Nanopore MinION.

Results: The P-14.182 *P. aeruginosa* strain showed high MICs for piperacillin/tazobactam (>256 mg/L), ceftazidime (>256 mg/L), cefepime (>256 mg/L), meropenem (>256 mg/L), imipenem (>32 mg/L), aztreonam (32 mg/L), ciprofloxacin (>32 mg/L), gentamicin (>256 mg/L), and amikacin (>256 mg/L). Only polymyxin B (1 mg/L) showed some *in vitro* activity against the P-14.182 strain. The *bla*$_{IMP-62}$ gene was found inserted as unique gene cassette of In2051, which exhibited an Δ*orf5* truncated with IS*6100* at 3'-CS region (**Figure 1**). Additionally, In2051-IS*6100* was flanked upstream by IS*Pa7*-In0-*attI1*Δ-ΔIS*Aba125*-*aph(3')*-*VI*-ΔIS*Aba125*-ΔIS*Vsa3* genetic structure and downstream by *orf2*-*merRTPADE*. A 25-bp inverted repeats (IRi) and inverted repeats transposon (IRt) from Tn*402*-like adjacent to 5-bp direct repeats were found flanking IS*Pa7*-IS*6100*, indicating the presence of a composite transposon. An intriguing region was found upstream to Tn*Pa7*-*6100*. Other two copies of operon *merRTPADE* were also detected in the P-14.182 genome, being one of them nearby a transposable element composed by IS*Pa7*-In2021-*tniAB*-*sulP*-*uspA*-*dksA*-*sdiA*-IS*Pa7*. Although no plasmid was identified in P-14.182 genome, two regions of 24-kb/33.6-kb, separated by 125-kb, were identified nearby the Tn*Pa7*-*6100* harboring the partial conjugation machinery composed by *traDCGI*-12 TIGR genes and *traG*-*trbBCDEJLFGI*, respectively. Finally, the cytotoxins encoding genes *exoT*, *exoY*, and *exoU* belonging to T3SS were identified in P-14.182 genome, which has been associated with unfavorable prognosis in invasive *P. aeruginosa* infections.

Conclusions: This study unveils a novel integron (In2051) carrying *bla*$_{IMP-62}$ within a complex genetic environment in a hypervirulent extensively drug-resistant (XDR) *P. aeruginosa* strain belonging to ST167.

(A)

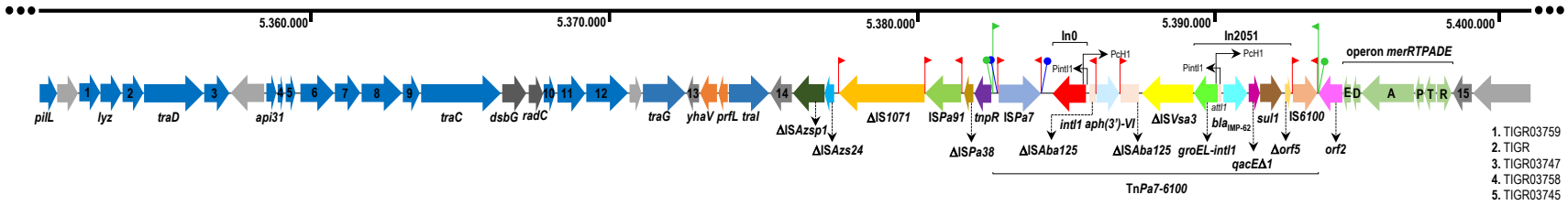

Figure 1. Schematic representation of genetic surrounding regions of In2051 carrying *bla*$_{\text{IMP-62}}$ (cyan arrow).

Poster 5

Different Mutations in the Rifampin Resistance-Determining Region (RRDR) of RpoB Cause Distinct Phenotypic Changes in *Enterococcus faecium*

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Vancomycin-resistant *Enterococcus faecium* (VREfm) is a primary cause of bloodstream infections (BSI) in hospitalized and immunocompromised patients. As enterococci are well adapted to the GI tract, to successfully colonize the bloodstream, VREfm-BSIs must evolve separate beneficial traits. Investigating these bloodstream-adapted changes can help us understand how VREfm is able to cause such persistent and deadly infections.

Preliminary studies of VREfm-BSI isolates in our hospital system revealed mutations in genes involved in transcription and translation as promising candidates for further investigation, as mutations to these machineries can lead to activation of stress tolerance pathways. Previous studies showed that mutations in *rpoB*, usually correlated with rifampicin resistance, also impact broad-spectrum cephalosporin resistance in enterococci. However, the effect of mutations in *rpoB* on general enterococci gene expression remains to be explored.

To explore the phenotypic consequences of mutations in *rpoB,* we plated an *E. faecium* clinical isolate onto media containing rifampin and isolated five isogenic mutant strains that each had a single nonsynonymous mutation in the rifampin resistance-determining region (RRDR) of *rpoB*. These mutations were S419L, Q473K, G482D, G482V, and H486Y. We performed phenotypic testing on the wild type parent strain and the five *rpoB* mutants to measure various phenotypic changes.

In testing the growth rate, we found that the isolate with the S419L mutation had a significantly longer doubling time, while the other four mutants had comparable doubling times to the wild type isolate. We next tested the wild type and mutant isolates against six antibiotics: rifampicin (RIF), vancomycin (VAN), daptomycin (DAP), meropenem (MEM), ceftriaxone (CRO), and ampicillin (AMP). As expected, all mutant isolates had higher RIF MICs compared to the wild type isolate. Interestingly, we found that when compared to the other four mutations, the impact of the G482D mutation on RIF MIC was much lower (64-fold vs >128-fold increase). In addition, we found distinct *rpoB* allele-specific effects on AMP MIC. Although occurring in the same position, the G482V and G482D mutations had notably different AMP MIC fold changes when compared to the wild type, with an 8-fold decrease and a 2-fold decrease, respectively. The other three isolates had a 4-fold decrease in their AMP MICs compared to the wild type isolate. While mutations in *rpoB* did not have a significant impact on VAN, DAP, MEM, or CRO MICs, we did observe differences in isolate growth rates in the presence of sub-inhibitory concentrations of some of these agents. Finally, we found that mutations in *rpoB* did not impact the isolates' ability to form biofilm.

Overall, we found that despite occurring in the RRDR region of *rpoB*, the different mutations we studied resulted in different phenotypic effects in an allele-specific manner, highlighting the diversity of possible phenotypic consequences of mutations in *rpoB*.

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Poster 78

Hi-C Metagenomic Characterization of the Host-antimicrobial Resistome in *Clostridioides difficile* Infection.

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Objective: This study employed Hi-C metagenomics to investigate clinically significant features in *Clostridioides difficile* infection (CDI) and corresponding antimicrobial resistance (AMR) profiles. Our primary goal was to characterize the genetic composition of gut microbiome communities, with specific attention paid to identifying mobile genetic elements (MGEs) and their associated AMR genes, utilizing the Hi-C metagenomic approach.

Methods: Fecal specimens from 10 pediatric subjects, including 5 CDI cases with prior antibiotic treatment and 5 healthy age-matched controls, underwent comprehensive analysis using the ProxiMeta™ Platform. In addition to ProxiMeta, widely used metagenome assembled genome (MAG) tools such as bin3c, MetaBAT2 and MetaPhlan4 were employed for comparative analysis. Marker gene detection involved BLAST searches, followed by network analyses utilizing Hi-C connectivity graphs. The identification of AMR genes and plasmids was conducted using AMRFinder Plus and BLAST against the RefSeq plasmid database. Our integrated approach linked plasmid, AMR, and virus contigs to genome clusters, while taxonomic summaries provided insights into host microbiome interactions.

Results: ProxiMeta2 successfully recovered a total of 304 complete MAGs (>95% completeness; <10% contamination). Taxonomic profiling revealed discernible shifts in the gut community structure of CDI samples, characterized by a reduction in Lachnospiraceae and Ruminococcaceae, and the prevalence of Enterococcaceae. AMR analysis identified up to 132 resistance genes per sample, with CDI samples exhibiting higher abundance, highlighting the pivotal role of plasmids in the dissemination of AMR. Host taxa predominantly linked with AMR genes included Clostridiales and Bacteroidales. Distinctive profiles in a CDI sample (bf12_860557) also indicated potential adaptation to environmental pressures, showcasing the versatility of AMR genes. Moreover, our study identified a significant connection between Enterobacteriales and resistance genes against heavy metals and disinfectants, as well as unveiling pathogenicity loci in *C. difficile* and virulence factors in *S. aureus*.

Conclusion: Hi-C metagenomics is emerging as a transformative new tool to define the specific role of select gut taxa in maintaining and propagating a diverse AMR landscape. Further, our studies highlight the significant role of Enterobacteriales-derived plasmids in transferring resistance genes in response to environmental selective pressures.

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Poster 79

Reduction in Vancomycin-Associated Acute Kidney Injury with Montelukast

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Vancomycin is the most common antimicrobial used for the treatment of serious infections implicated by β-lactam resistant Gram-positive bacteria, but it has been associated with acute kidney injury (AKI) in up to 43% of cases. Reduction in nephrotoxicity associated with antibiotics has been reported in a rat model with adjuvant zileuton. However, it is unclear if this protective effect could be translated to improve patient outcomes. The objective of this study was to ascertain if montelukast is correlated with reduced vancomycin-associated AKI. We conducted a retrospective study of adults (≥18 years) who received intravenous vancomycin at our institution between 01/2020-08/2023. Patients were included if they met these criteria: vancomycin therapy ≥3 days and baseline serum creatinine (SCr) <1.5 mg/dL. Patients with cystic fibrosis were excluded. Patients who received concomitant montelukast (intervention) were compared to those without (control). The primary outcome was the incidence of AKI (rise in SCr ≥0.3 mg/dL or ≥1.5x baseline) as defined by Kidney Disease Improving Global Outcomes. The primary outcome was compared using the Fisher's exact test while the duration of vancomycin therapy was compared by the Student's t test. Of 710 patients screened, 101 patients were included in the intervention arm and 108 in the control. Patients received vancomycin for similar durations (mean ± standard deviation, 5.3 ± 4.2 vs 6.3 ± 3.6 days, respectively; p = 0.07). The intervention cohort experienced 5.0% AKI compared with 13.9% in the control (p = 0.03). This pilot study suggests that montelukast may be protective against vancomycin-associated nephrotoxicity, which may reduce healthcare costs and patient harm. Additional studies with a larger patient cohort will be conducted to corroborate these findings.

Acknowledgements: None.

Poster 80

Impact of the Ampicillin-Susceptible, Penicillin-Elevated Phenotype in *Enterococcus faecalis* Isolates from Bloodstream Infections

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Background: *Enterococcus faecalis* accounts for a majority of enterococcal isolates associated with invasive infections. Historically, *E. faecalis* species that are susceptible to ampicillin (AMP) are routinely reported as susceptible to penicillin (PCN); however, there has been an increasing prevalence of ampicillin-susceptible, penicillin-elevated (ASPE) *E. faecalis* isolates. Limited data suggests poor clinical outcomes in patients with ASPE isolates, and significantly elevated MICs to β-lactams, particularly piperacillin (PIP) and ceftriaxone (CRO). The ASPE phenotype has been associated with a promoter mutation (A88 deletion) that leads to increased expression of the relatively-penicillin resistant PBP4 of *E. faecalis*. The aim of this study was to evaluate the impact of PBP4 promoter mutations on the activity of AMP+CRO, and define a cohort to examine the clinical outcomes of infection due to ASPE *E. faecalis*.

Methods: We selected 10 representative clinical strains of *E. faecalis* with different PBP4 promoters. Susceptibility of β-lactams was done by broth microdilution. Time-kill assays were performed to assess efficacy of AMP+CRO using the following conditions: sub-inhibitory AMP concentrations ($^2/_3$X MIC) and fC_{max} concentration of CRO. Bactericidal activity was defined as ≥3 $\log_{10}$ reduction in CFU/ml after 24 h. The clinical cohort will be a retrospective, observational study conducted within the Houston Methodist health system from January 1, 2017 to July 30, 2023. The primary endpoint is the 30-day mortality rate or discharge of patients treated with penicillin-based antimicrobial therapy versus non-penicillin-based antimicrobial therapy. Secondary endpoints include the incidence of ASPE MIC isolates, repeat blood culture clearance, infection-related readmission rates, relapse rates, and length of stay. Adult patients will be included if they have at least one positive *E. faecalis* blood culture with a follow-up blood culture and if they were treated with ampicillin, vancomycin, piperacillin-tazobactam, ampicillin-sulbactam, daptomycin, linezolid or imipenem-cilastatin.

Results: All strains were susceptible to AMP (≤ 2 µg/ml) along with elevated MICs to PCN (range 2 – 16 µg/ml) and PIP (range 4 – 128 µg/ml). The laboratory control *E. faecalis* strain OG1RF and 6 clinical *E. faecalis* strains demonstrated bactericidal activity. However, strains with ΔA88 PBP4 promoter variant did not respond to AMP plus CRO (change -0.7 to -2.24 $\log_{10}$ CFU/ml at 24 h). For the clinical cohort, 943 patients with positive *E. faecalis* blood cultures have been screened for study inclusion, with 545 patients fulfilling preliminary inclusion criteria. Clinical outcomes in patients that had an *E. faecalis* isolate with an PCN MIC of >4 and <16 will be compared to outcomes in those with an MIC ≤4.

Conclusion: *E. faecalis* strains with ΔA88 *pbp4* gene promoter variant demonstrated decreased efficacy of dual β-lactams compared to other *pbp4* variants. Clinical outcomes of *E. faecalis* treated with β-lactams, alone or in combination, need to be evaluated.

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Poster 81

Real-World Outpatient Use of Omadacycline for Bone and Joint Infections

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Background: Omadacycline (OMC) is approved for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. OMC is used in outpatient parenteral antimicrobial therapy (OPAT), with increased use in bone and joint infections (BJI). Data regarding this real-world use of OMC are limited. We present a multicenter observational review of OMC use in OPAT for treatment of BJI. Methods: Medical records were reviewed of patients receiving intravenous OMC from 2019 to 2022 for treatment of BJI. Data included demographics, diagnosis, medical history, microbiology, OMC regimen, adverse events (AEs), clinical outcomes, and 12-month follow-up. Clinical success was defined as complete or partial symptom resolution at completion of OMC with oral antibiotics continued if needed. Persistent and recurrent infection were deemed non-success. Indeterminate outcomes were excluded from outcome assessment. Patients with no recurrence at 12 months were identified as continued success. Results: Overall, 35 patients (mean age 62±11 yrs; male 71%) were treated in 8 infectious disease outpatient centers nationally; 66% (n=23) had OMC initiated in the outpatient setting with no prior hospitalization. The cohort was highly comorbid with a mean Charlson index of 5.3 ±2.7, diabetes in 66% and hypertension in 74%. BJI diagnoses were complicated osteomyelitis and prosthetic joint infections, detailed in Table 1. A total of 61 pathogens were identified; 63% of patients had polymicrobial infections. Prior treatment with other agents was provided in 63% of patients (n=22) and 17% (n=6) received concomitant IV antibiotics. Median duration of OMC therapy was 41 days (IQR, 22-51). Overall clinical success was achieved in 83% of patients (n=29). Non-success due to worsening infection was reported in 6% (n=2) of patients with osteomyelitis. Four (11%) patients were indeterminate for outcome. Mild to moderate AEs potentially related to OMC were reported in 12 (34%) patients. None required discontinuation of OMC. Continued success at 12 months was seen in 72% (21 of 29) of patients with initial success. Conclusion: These real-world provide promising results in the use of OMC in treatment of complex and difficult to treat patients with osteomyelitis and prosthetic joint infections.

Acknowledgements: The study was supported by a research grant from Paratek Pharmaceuticals, Inc.

Table 1. Bone and Joint Infection Diagnosis Specifics

Diagnosis	n (%)	Polymicrobial n (%)
Osteomyelitis	**31 (89%)**	
Diabetic Foot Infection	18 (51%)	17 (49%)
Acute Osteomyelitis	4 (11%)	2 (6%)
Chronic Osteomyelitis	4 (11%)	1 (3%)
Vertebral Osteomyelitis	3 (9%)	2 (6%)
Mastoiditis	2 (6%)	-
Prosthetic Joint Infection	**4 (11%)**	
Hip Replacement	3 (9%)	-
Knee Replacement	1 (3%)	-
Total Bone and Joint Infections	35	22 (63%)

Poster 6

LiaR-Dependent Gene Expression Contributes to Antimicrobial Responses in *Group A Streptococcus*

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Bacterial pathogens have mechanisms to sense and counter antimicrobial peptide (AMP) activity. Some mechanisms involve the activity of two-component systems (TCS) that sense AMPs and activate regulatory pathways controlling the bacterial cell's responses. Alongside TCSs, bacteria coordinate cell division proteins, chaperones, cell wall sortases and secretory translocons at discrete locations within the cytoplasmic membrane, referred to as functional membrane microdomains (FMMs). In Group A *Streptococcus* (GAS), such an FMM dubbed the "ExPortal" coordinates protein secretion, cell wall synthesis and sensing of AMP-mediated cell envelope stress via the LiaFSR three-component system. Previously we showed GAS exposure to lipid II-targeting AMPs activates the LiaFSR system by disrupting LiaF and LiaS co-localization in the ExPortal, leading to increased LiaR phosphorylation, expression of the transcriptional regulator SpxA2, and altered GAS virulence gene expression. The mechanisms by which LiaFSR integrates cell envelope stress with responses to AMP activity and virulence are not fully elucidated. We hypothesize that members of the LiaR-dependent regulon contribute to GAS tolerance to killing by AMPs. Using RNA and chromatin immunoprecipitation sequencing (RNAseq, ChIP-seq) analyses we determined that the regulon under the direct control of LiaFSR in GAS is comprised of SpxA2 and three membrane-associated proteins: a PspC domain-containing protein (PCP), the lipoteichoic acid-modifying protein LafB and the membrane protein insertase YidC2. Our data show that phosphorylated LiaR induces transcription of these genes via a conserved operator. Disruption of the LiaR operator sequence increases susceptibility to AMPs in a manner primarily dependent on differential expression of SpxA2. Specifically, mutations that reduce LiaR phosphorylation or disrupt the LiaR operator of the *spxA2* promoter increase GAS susceptibility to killing by lipid II-targeting (bacitracin, human neutrophil peptide 1 -hNP1-) and anionic lipid-targeting (polymyxin B) antimicrobials. Furthermore, mutations that dysregulate of LiaR phosphorylation or disrupt the LiaR operator all attenuate GAS *ex vivo* fitness. Future work will investigate the GAS transcriptome associated with increased expression of the SpxA2 transcriptional regulator, as well as the contribution of the other members of the LiaR regulon to GAS fitness and virulence in response to cell envelope stress. Our work expands understanding of the LiaFSR regulatory network in GAS and identifies targets for further investigation of cell envelope stress tolerance mechanisms contributing to GAS pathogenesis.

Poster 82

Comparing Different Susceptibility Methods for Cefiderocol

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Background: Infections caused by multidrug-resistant (MDR) bacteria have continued to increase globally throughout the years. Cefiderocol was recently approved as a new antibiotic for treatment of MDR bacterial infections. The reference susceptibility testing method is broth microdilution in iron-depleted Muller Hilton broth (ID-MHB), but this method is time-consuming. The objective of the study was to compare the minimum inhibitory concentration (MIC) of cefiderocol determined by alternative methods to the reference method.

Methods: Nine *Pseudomonas aeruginosa* (PA) clinical isolates and one laboratory reference were used. The isolates' clonality was determined using Fourier-transform infrared spectroscopy (FTIR). Cefiderocol MICs determined by e-test, ComASP, and broth microdilution in regular MHB were compared to the reference method. Correlations to the reference MIC were assessed using linear regression and log-2 transformed MIC values.

Results: The cefiderocol MICs ranged from 0.06 and 32 mg/L; one of the isolates was resistant. Most of the isolates were clonally unique. For PA, e-test demonstrated a reasonable correlation with the reference method ($R^2 = 0.85$), while the other alternative methods demonstrated a weak correlation ($R^2 < 0.5$).

Conclusions: Overall, the current results suggest that the e-test was mostly in agreement with the reference MIC for PA isolates. Additional studies are needed to ascertain the utility of these alternative susceptibility testing methods.

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Poster 83

Targeting the Host Transcriptional Response for COVID-19 Therapeutic Intervention

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has taken an unimaginable toll on the global human population. Therapeutic options directed at the virus itself are limited, with only a handful of druggable targets available, such as the main protease (M^{pro}) and RNA-dependent RNA polymerase (RdRp). Unintended consequences of SARS-CoV-2 antiviral medications have been observed, such as increased mutagenesis with molnupiravir and virologic rebound with nirmatrelvir-ritonavir. The host response offers an orthogonal approach for the search of therapeutics addressing severe COVID-19. Using the peripheral blood transcriptomes of hospitalized COVID-19 patients and healthy controls, we trained a random forest classification model to predict infection status. The model's performance was validated on three independent COVID-19 datasets and shows high accuracy and good generalizability. Features (genes) important for discerning infection status were determined using Shapley additive explanations and used for pathway analysis and querying drug databases. Future studies include screening drug candidates for inhibition of cytopathic effects in Betacoronavirus 1 strain OC43, followed by SARS-CoV-2.

Poster 84

Rapid Genomic Characterization of High-Risk, Antibiotic Resistant Pathogens Using Long-Read Sequencing to Identify Nosocomial Outbreaks

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Abstract:
Large-scale analyses of antimicrobial resistant (AMR) pathogens using Illumina-based sequencing have identified significant numbers of genetically related strains suggesting transmission in the healthcare settings. Recent advancements in the accuracy of long-read sequencing made by Oxford Nanopore Technologies (ONT) suggest that stand-alone ONT sequencing might be used in real-time to identify such transmission. We sought to establish a validated ONT sequencing pipeline, aiming to elevate the efficiency and precision of outbreak detection and cluster identification within healthcare settings. Using the EPIC electronic health records, we identified potential healthcare acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and carbapenem-resistant gram-negative rods. Bacterial genomic DNA was directly extracted from clinical microbiology lab plates. Sequencing was conducted with the ONT MinION sequencer and R10.4.1 flow cell. The Nanopore fast5 data was converted to fastq raw data using the Guppy-v6.4.6 basecaller. Genome assembly was achieved through the Flyest package. MINTyper for SNP calling and Ridom SeqSphere+ for core genome MLST were used in genetic analyses. We validated the accuracy of our stand-alone ONT approach by comparing our ONT data to data we had previously generated using the same organism through Illumina. The comparison showed a core genome SNP distance of ≤ 5. The genomic DNA extraction and ONT sequencing of the same bacteria strains from both a fresh subbed plate and a one-week-old plate resulted in a pairwise SNP difference of 0. We also optimized resource utilization by reusing flow cells for up to three runs while maintaining an average genome coverage in excess of the 40x needed for highly accurate genetic comparisons. The weekly workflow, from sample collection to data analysis, averaged 2.2 days (range: 1 to 4 days). Since starting in August 2023, we have sequenced a total of 142 bacterial isolates from 127 unique patients. The isolate sources were blood (45%), tissue/wound/body fluid (20%), urinary tract (17%), respiratory tract (15%), and rectal swab (3%). Three suspected clusters of ST117 vancomycin-resistant *Enterococcus faecium* (VR*Efm*) and four genetically related ST633 *Pseudomonas aeruginosa* isolates were identified. The three ST117 VR*Efm* clusters involved 12 unique patients, distributed as 2, 3, and 7 patients in each group (pairwise SNP difference = 20, 11, 9). Patients within the same clusters exhibited epidemiological links through overlapping admissions and temporally shared ICU stays. The four ST633 *P. aeruginosa* isolates displayed genetic relatedness (pairwise SNP difference = 40.5), with each patient having potential epidemiological links through overlapping admission times, despite the absence of identified shared spaces. We conclude that our stand-alone ONT pipeline was able to rapidly and accurately detect genetically related AMR pathogens, aligning closely with epidemiological data. Our pipeline has the potential to assist in the efficient detection and deployment of preventative measures against healthcare-associated infection transmission.

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Poster 85

Cytotoxic Rhamnolipid Micelles Drive Acute Virulence in *Pseudomonas aeruginosa*

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Pseudomonas aeruginosa is an opportunistic human pathogen that has developed multi- or even pan-drug resistance towards most frontline and last resort antibiotics, leading to increasing infections and deaths among hospitalized patients, especially those with compromised immune systems. Further complicating treatment, *P. aeruginosa* produces numerous virulence factors that contribute to host tissue damage and immune evasion, promoting bacterial colonization and pathogenesis. In this study, we demonstrate the importance of rhamnolipid production in host-pathogen interactions. Secreted rhamnolipids form micelles that exhibited highly acute toxicity towards murine macrophages, rupturing the plasma membrane and causing organellar membrane damage within minutes of exposure. While rhamnolipid micelles (RMs) were particularly toxic to macrophages, they also caused membrane damage in human lung epithelial cells, red blood cells, Gram-positive bacteria, and even non-cellular models like giant plasma membrane vesicles. Most importantly, rhamnolipid production strongly correlated to *P. aeruginosa* virulence against murine macrophages in various panels of clinical isolates. Altogether, our findings suggest that rhamnolipid micelles are highly cytotoxic virulence factors that drive acute cellular damage and immune evasion during *P. aeruginosa* infections.

Acknowledgements: This study was supported by the National Institutes of Health, Cystic Fibrosis Foundation, and American Heart Association.

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Evaluation of Perioperative Antimicrobial Use in Ventricular Assisted Device (VAD) Placement

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The optimal regimen for antimicrobial prophylaxis after ventricular assisted device (VAD) placement is currently unknown. Despite consensus guidelines recommending short duration and single-agent antimicrobial prophylaxis, there continues to be wide variability in antimicrobial regimens across implantation centers. This is a retrospective, descriptive study to assess the use and duration of perioperative antimicrobials in patients who underwent a VAD placement. Twenty-four patients who underwent a VAD placement from September 2020 to May 2023 were included. The purpose of the study is to assess overall perioperative antimicrobial use and VAD-associated infections, including VAD-specific and VAD-related infections occurring in the post-operative period. VAD-specific infection was defined as infection involving the pump, cannula, driveline, or pocket. VAD-related infection was defined as endocarditis, mediastinitis, bloodstream infection, or ICD lead infection. Non-VAD related infection was defined as involving the urinary tract or lungs or *Clostridioides difficile* infection.
Most patients were White (50%) or African American (50%) males (83%) with a median age of 49 years (range: 27 to 77) who received a HeartMate3 VAD (91.7%). The most common antimicrobial prophylaxis regimen utilized for VAD placement was a three-drug regimen consisting of fluconazole, vancomycin, and piperacillin/tazobactam for a duration of approximately 4 days. Six patients (25%) developed VAD-associated post-operative infections, with one developing both a VAD-specific (driveline) and VAD-related-ICD infection. Among the 7 VAD-associated infections, 3 were VAD-specific (12.5 %) driveline infections, and 4 were VAD-related (16.6%) including endocarditis, bloodstream, surgical site, and ICD lead infections. There were 7 non-VAD related infections including pneumonia and urinary tract infections. Secondary outcomes included incidence of delayed chest closure (4.2%) or re-operation for any reason (25%), 30-day mortality (12.5%), and 30-day readmission (20.8%). Results of this descriptive study will be used to update, optimize, and protocolize antimicrobial prophylaxis in VAD placement.

Poster 87

Bacteriophage Resistance Results in Urinary Environment Fitness Defects for Uropathogenic *E. coli*

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The estimated 7 million urinary tract infections (UTI) occurring annually in the United States represent the most common cause of outpatient antibiotic prescriptions. These infections disproportionately impact women and are primarily caused by uropathogenic *E. coli* (UPEC). Growing rates of antibiotic resistance amongst urinary pathogens, coupled with the growing knowledge of the negative impact that antibiotics have on the healthy microbiota, necessitate the development of alternative UTI treatments. Bacteriophages (phages), viruses that infect bacteria, are appealing alternatives due to their specificity for bacterial hosts, ubiquity, and safety. Yet, as with antibiotics, bacteria can become resistant to phage. Frequently, this resistance develops through mutation of outer membrane proteins that phage use to adhere to and infect the bacteria.

Our group hypothesized UPEC would become resistant to a previously described lytic phage frequently used in our lab through genomic changes leading to mutations in outer membrane proteins, but that this resistance would negatively impact bacterial fitness in the urinary environment. We isolated phage-resistant UPEC and, through sequencing, identified that resistance was associated with mutations in genes important in lipopolysaccharide biosynthesis. These phage-resistant bacteria display attenuated growth in urine and are sensitized to some membrane-interacting antibiotics. In addition, they poorly colonize the bladder *in vivo*. We are currently studying the mechanisms underlying these growth and colonization defects.

While resistance to phage may arise during treatment, the incurred fitness costs may render UPEC more susceptible to environmental conditions or antibiotics. This susceptibility could be exploited to develop novel antibiotic-phage combinations for treating UTI. Future work seeks to identify mechanistic causes underlying this decreased fitness, assess the ability of phage-resistant bacteria to generate recurrent UTI, and identify the immune response to phage and phage-resistant bacteria.

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January 18, 2024 *(excerpted from Dec 11 and Nov 2,s 2023 Press Releases*)*

Acurx Pharmaceuticals is a late-clinical stage biopharmaceutical company focused on developing new antibiotics for difficult to treat infections. The Company's approach is to develop antibiotic candidates with a Gram-positive selective spectrum (GPSS®) that blocks the active site of the Gram+ specific bacterial enzyme DNA polymerase IIIC (pol IIIC), inhibiting DNA replication and leading to bacterial cell death. Its R&D pipeline includes antibiotic product candidates that target Gram-positive bacteria, including *C. difficile*, *methicillin-resistant Staphylococcus aureus* (MRSA), vancomycin resistant Enterococcus (VRE) and drug-resistant Streptococcus pneumoniae (DRSP).

Acurx recently announced: Positive Phase 2b Results Showing 100% of Patients Who Had Clinical Cure with Ibezapolstat Also Had Sustained Clinical Cure

- All 15 ibezapolstat-treated patients in Phase 2b who achieved Clinical Cure (CC) at end of treatment (EOT) remained free of *C. difficile* Infection (CDI) recurrence through one month after EOT, for a Sustained Clinical Cure (SCC) rate of 100%
- 2 of 14 patients treated with standard of care, oral vancomycin, experienced recurrent infection within one month after EOT for a SCC of 86%
- 100% of the 25 ibezapolstat-treated patients in Phase 2 (Phase 2a and 2b) who had CC at EOT remained cured through one month after EOT

The Company previously reported (November 2, 2023) that the overall observed Clinical Cure rate in the combined Phase 2 trials in patients with CDI was 96% (25 out of 26 patients), based on 10 out of 10 patients (100%) in Phase 2a in the MITT population, plus 15 out of 16 (94%) patients in Phase 2b in the PP population, who experienced Clinical Cure during treatment with ibezapolstat; and that ibezapolstat was well-tolerated.

Further analyses will be forthcoming as data become available, regarding other endpoints from the Phase 2b trial, including comparative effects vs vancomycin on the gut microbiome and Extended Clinical Cure (ECC) data up to 94 days

- *Preparation underway for meetings with FDA, EMEA and other global regulatory agencies for advancement to international Ph3 clinical trials*

*Please see complete Dec 11 and Nov 2, 2023 press releases www.acurxpharmaceuticals.com; Ibezapolstat is not currently approved for marketing by any regulatory authority

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