ARLG
Antibacterial Resistance Leadership Group

January 8, 2019
Q1 Newsletter

Welcome to the ARLG Newsletter! Here, you will receive important updates from ARLG regarding recent events, grants, publications, and the committees that help us work toward our mission: to prioritize, design, and execute clinical research that will reduce the public health threat of antibacterial resistance.

Get Involved with ARLG

ARLG continuously accepts proposals for clinical studies designed to prevent, diagnose, treat, or eradicate antibiotic-resistant bacterial pathogens. We also award grants and fellowships to qualified investigators. If you are interested in getting involved with ARLG, apply now or contact us for more information.

Apply for a Grant Contact Us

ARLG at IDWeek 2018^{tm}: An Opportunity to Share Knowledge, Learn from Colleagues, and Discuss Future Collaborations

The Antibacterial Resistance Leadership Group (ARLG) was in the spotlight at IDWeek 2018^{TM}, held October 3rd-7th in San Francisco, CA. ARLG leaders, researchers, or committee members moderated panels and presented lectures, posters, or abstracts at close to 300 sessions. On October 5th, ARLG collaborator **Thomas Holland, MD,** created a buzz with his presentation on strategies for treating *S. aureus* bacteremia. "We have to approach this topic with a bit of humility," he told the packed room. "There has been an increase in clinical trials…(but) we have a lot less data for these difficult and common scenarios than we would like."

ARLG at IDWeek 2018

A Meet-the-Professor morning session on October 6th focused solely on the ARLG. ARLG Co-Principal Investigator **Henry "Chip" Chambers, MD,** moderated the session: Updates from the Antibacterial Resistance Leadership Group.

ARLG researcher **Ephraim Tsalik, MD, PhD,** initiated the Meet-the Professor session with his talk, A Radical Departure: Host Gene Expression Diagnosis of Infection. Dr. Tsalik provided the attendees with an update on RADICAL studies, which are developing and testing a platform to measure gene expression in a clinically meaningful way. You can learn more about RADICAL and share this lay summary of results with your staff and patients.

Scott Evans, PhD, who directs the ARLG Statistics and Data Management Center, emphasized the need for pragmatic clinical trial approaches to address antimicrobial resistance in his talk: Making the Impossible, Possible: Pragmatic Clinical Trials. He discussed Sequential Multiple Assignment Randomized Trials for COMparing Personalized Antibiotic StrategieS (SMART-COMPASS) recently published in *Clinical Infectious Diseases*.

Beyond the podium lectures, posters and presentations, ARLG Project Leader **Maria Souli, MD**, received the SHEA William Jarvis Award for her manuscript entitled, "Reduction of Environmental Contamination with Multidrug-Resistant Bacteria by Copper-Alloy Coating of Surfaces in a Highly Endemic Setting." ICHE (2017), 38(7): 765-771. The editors of Infection Control and Hospital Epidemiology (ICHE) selected her manuscript for most outstanding international clinical study published in ICHE in 2017.

ARLG researcher **Deverick "Dev" J. Anderson, MD, MPH,** received the 2018 SHEA Antibiotic Stewardship Scholar Award for his contributions as an investigator and practitioner to antibiotic stewardship program and research.

The Infectious Diseases Society of America (IDSA) honored **Susanna Naggie, MD,** of Duke University with the Oswald Avery Award for Early Achievement. The award recognizes IDSA members or fellows age 45 or younger who have demonstrated outstanding achievements in an area of infectious diseases.

ARLG SPOTLIGHT

Sarah Doernberg, MD, MAS
Associate Professor
Medical Director of Adult Antibiotic Stewardship
University of California, San Francisco

About my role in ARLG

I consider my role in ARLG as a “Trialist in Training.” I have been involved in the development and execution of protocols for three studies:

1) MASTER GC: Performance of Nucleic Acid Amplification Tests for the Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in extragenital sites. This novel study involved collaboration with three manufacturers and input from the Food and Drug Administration (FDA) to evaluate performance of molecular diagnostic tests for extragenital gonorrhea and chlamydia. The primary goal was for the study results to support each company’s FDA application. This trial used the MASTERMIND (MASTER protocol for evaluating Multiple INfection Diagnostics) concept developed by the ARLG that is based on the following premise: One single participant can provide information and samples for the simultaneous evaluation of multiple diagnostics. The MASTER GC trial has completed enrollment of more than 2700 participants at nine sites. FDA submissions from the participating manufacturers and manuscripts from the scientists are underway.

2) RAPIDS GN: RAPid IDentification and phenotypic Susceptibility testing for Gram-Negative bacteremia. This randomized controlled trial is studying the impact of a platform that rapidly identifies and performs antimicrobial susceptibility testing on antimicrobial utilization and clinical outcomes in patients with Gram-negative bacillus bacteremia. The trial has just completed enrollment of 500 participants at two sites.

3) The third protocol consists of multiple, separate studies to improve *Staphylococcus aureus* bloodstream infection (BSI) trial design. These studies incorporate mixed methods to define a novel Desirability of Outcome Ranking (DOOR) endpoint as well as to develop a quality of life (QoL) measure for patients with *S. aureus* BSI. The DOOR endpoint was developed through a survey to infectious diseases clinicians. It has been used for the secondary analysis of two completed trials and disseminated widely at several international conferences. The *S. aureus* DOOR endpoint is now published in *Clinical Infectious Diseases*. We will continue to collaborate with other researchers on use of this innovative approach and anticipate using it in future ARLG trials. Manuscript development is underway from the first phase of the QoL substudy of patients with bloodstream infection, which will lay the groundwork for future studies and a validated measure of QoL for BSI.

Impact of these ARLG studies

Each study I have been involved with carries important contributions to the fight against antimicrobial resistance. The MASTER-GC study is novel in its ability to generate diagnostic performance data from a single sample that collaborating manufacturers can use to support their own FDA submissions. This design approach brings efficiencies and economies of scale that can be adapted for other infectious diseases studies of novel diagnostics.

The RAPIDS GN study takes a pragmatic approach to evaluate the impact of a novel diagnostic on clinical outcomes. Lessons learned from this study will be critical to inform future approaches to the implementation of the many diagnostics that are coming into the market. The studies for *S. aureus* BSI will contribute to a shift in how clinical trials for this condition are designed and analyzed resulting in more data to inform clinicians facing complex treatment decisions. All of these studies will advance our knowledge in the ability to detect and manage complex antimicrobial-resistant infections.

Impact of ARLG research funding to my career

Being a Trialist in Training and protocol clinician on several high-impact studies has been a transformative training experience, providing practical skills so I can progressively manage and lead future studies to advance ARLG’s mission. The mentorship and opportunities provided to me have been unparalleled and it is difficult to imagine how I would have gained the skills and knowledge in clinical trials without the ARLG. I am extremely grateful for the support that I have received.

Benefits of ARLG

The entire ARLG organization, from the operations team to the committee members and investigators, thrives on an innovative dedication to the vital challenge of addressing antibiotic resistance. The work being done by ARLG will influence and improve this problem for the generations to come.

News

World Health Organization (WHO) Report on Surveillance of Antibiotic Consumption 2016 - 2018 Early implementation

This report presents 2015 data on the consumption of systemic antibiotics from 65 countries and areas, contributing to our understanding of how antibiotics are used in these countries. In addition, the report documents early efforts of the WHO and participating countries to monitor antimicrobial consumption, describes the WHO global methodology for data collection, and highlights the

New ARLG Materials

The following ARLG materials are available on the website. Feel free to download, print, and share the fact sheets with your colleagues and the summary of results with your patients.

ARLG Fact Sheet

ARLG Laboratory Center Fact Sheet

PROOF Summary of Results

RADICAL Summary of Results

challenges and future steps in monitoring antimicrobial consumption.

Awards

Congratulations and best of luck to **Ephraim Tsalik, MD, PhD**, for his selection as one of five finalists in the Antimicrobial Resistance Diagnostic Challenge. This challenge is a federal prize competition funded by the National Institutes of Health and the Biomedical Advanced Research and Development Authority (BARDA), with each agency contributing $10 million. Dr. Tsalik's project, Host Gene Expression to Classify Viral and Bacterial Infection Using Rapid Multiplex PCR, is based on the ARLG-supported RADICAL studies. Each finalist will receive $100,000 to further develop their prototypes and supply them for testing to two CLIA-certified independent laboratories this spring, and up to three winners will be chosen in July 2020 to share at least $19 million.

Recent Publications

Check out the following recent ARLG publications since October 1, 2018.

Doernberg SB, Tran TT, , Davis JS, Paul M, Yahav D, Tong SYC, Leibovici L, Boucher HW, Corey GR, Cosgrove SE, Chambers HF, Fowler VG, Evans SR, and Holland TL. Good studies evaluate the disease while great studies evaluate the patient: Development and application of a DOOR endpoint for Staphylococcus aureus bloodstream infection. Clin Infect Dis. 2018 Oct 12. doi: 10.1093/cid/ciy766. [Epub ahead of print].

Jacobs MR, Abdelhamed AM, Good CE, Rhoads DD, Hujer KM, Hujer AM, Domitrovic TN, Rudin SD, Fouts DE, Richter SS, van Duin D, Kreiswirth BN, Bonomo RA. ARGONAUT-I: Activity of cefiderocol (S-649266), a siderophore cephalosporin, against Gram negative bacteria including carbapenem resistant nonfermenters and Enterobacteriaceae with defined extended-spectrum β-lactamases and carbapenemases. Antimicrob Agents Chemother. 2018 Oct 15. pii: AAC.01801-18. doi: 10.1128/AAC.01801-18. [Epub ahead of print].

Evans SR, Follmann D, Liu Y, Holland T, Doernberg SB, Rouphael N, Hamasaki T, Hiang Y, Lok JJ, Tran TTT, Harris AD, Fowler VG, Boucher H, Kreiswirth BN, Bonomo RA, van Duin D, Paterson DL, Chambers H. Sequential Multiple Assignment Randomized Trials for COMparing Personalized Antibiotic StrategieS (SMART-COMPASS). 2018 Oct 23. ePublication (preprint).

Anesi JA, Lautenbach E, Nachamkin I, Garrigan C, Bilker WB, Omorogbe J, Dankwa L, Wheeler MK, Tolomeo P, Han JH; CDC Prevention Epicenters Program. Poor clinical outcomes associated with community-onset urinary tract infections due to extended-spectrum cephalosporin-resistant Enterobacteriaceae. Infect Control Hosp Epidemiol. 2018 Oct 30:1-5. doi: 10.1017/ice.2018.254. [Epub ahead of print].

Golpisamy SN, Woodworth MH,Wang T, Carpentieri C, Friedman-Moraco R, Mehta A, Larsen C, Kraft C. The use of microbiome restoration therapeutics to eliminate intestinal colonization with multi-drug resistant organisms. 2018 11 01. ePublication (preprint).

van Duin D, Gu P, Dong J, Pfaff M, Arias RM, Evans B, Yu Y, Li L, Zhang F, Liu Z, Cao B, Fowler VG, Wang M. China-United States Research Collaborations in Antimicrobial Resistance. Clin Infect Dis. 2018 Nov 13;67(suppl_2):S142-S145. doi: 10.1093/cid/ciy694.