ARLG
Antibacterial Resistance Leadership Group

April 2019
Q2 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

The ARLG brings together the world's top investigators in antibacterial resistance to collaborate in a dynamic, innovative environment. If you are interested in participating in ARLG research studies as clinical trial site, please contact us.

Contact Us

MDRO Network Team Members Travel to Sites to Connect, Train, and Support Quality Worldwide

Members of the ARLG Multi-Drug Resistant Organism (MDRO) Network coordinating team visited sites around the world to assess training success in several regions and find ways to enhance partnerships and practices within the MDRO Network.

The MDRO Network has 57 sites in 11 countries. Under the oversight of MDRO Principal Investigator, David van Duin, MD, PhD, and in collaboration with regional leaders Cesar Arias, MD, PhD, David Paterson, MBBS, PhD, Minggui Wang, MD. Lead Clinical Research Associates (LCRAs) David Souto and Beth Evans conducted these site visits in accordance with the National Institutes of Health (NIH) regulatory compliance requirements. Souto traveled to Colombia and Argentina while Evans visited sites in China, Singapore, and Australia.

The purpose of these visits is to:

- Partner with the Regional Coordinator Center (RCC) coordinators to ensure and document that regional oversight is successfully established and fulfill the funding source NIH regulatory and quality compliance requirements;
- Determine the need or desire for additional training at the site, RCC, or Regional Central Laboratory (RCL) level;
- Ensure that region-specific developed processes and tools meet regional needs and are implemented successfully;
- Ensure that RCCs and RCLs are implementing Good Clinical Practices and Good Documentation Practices successfully;
- Discuss ongoing and future bi-directional collaborations;
- Share lessons learned, discuss efficiencies, and solicit feedback on how the ARLG/MDRO can better support our collaborators.

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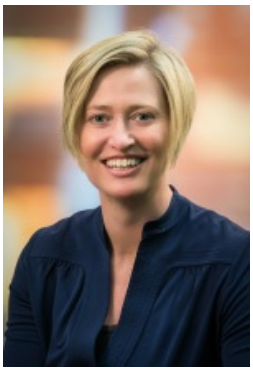
Visit our new Website



Update from the Diagnostics and Devices Committee

Kim Hanson, MD, MHS
Associate Professor
Director, Transplant Infectious Diseases and Immunocompromised Host Service
University of Utah and ARUP Laboratories

The Diagnostics & Devices Committee (DDC) was created to provide guidance and review study proposals in the areas of clinical microbiology and antimicrobial resistance (AMR). Additionally, the DDC works closely with other ARLG committees to identify unmet clinical needs and research gaps in content, study design and the execution of diagnostic related studies for infectious diseases. With support from the DDC, the ARLG has completed several groundbreaking diagnostic projects. Committee chair Kimberly Hanson, MD, MHS, highlights four studies below:

Blood Culture Identification (BCID): Few clinical studies of new diagnostics go beyond assessments of analytical and clinical test performance. In contrast, the Blood Culture Identification (BCID) study stands as one of the only randomized clinical trials of a molecular diagnostic test for infectious diseases. BCID was designed to evaluate the clinical impact of rapid bacterial identification directly from positive blood culture aliquots. This landmark study showed that antimicrobial use, particularly appropriate antibiotic de-escalation, was optimized by combining rapid testing with an active antibiotic stewardship intervention.

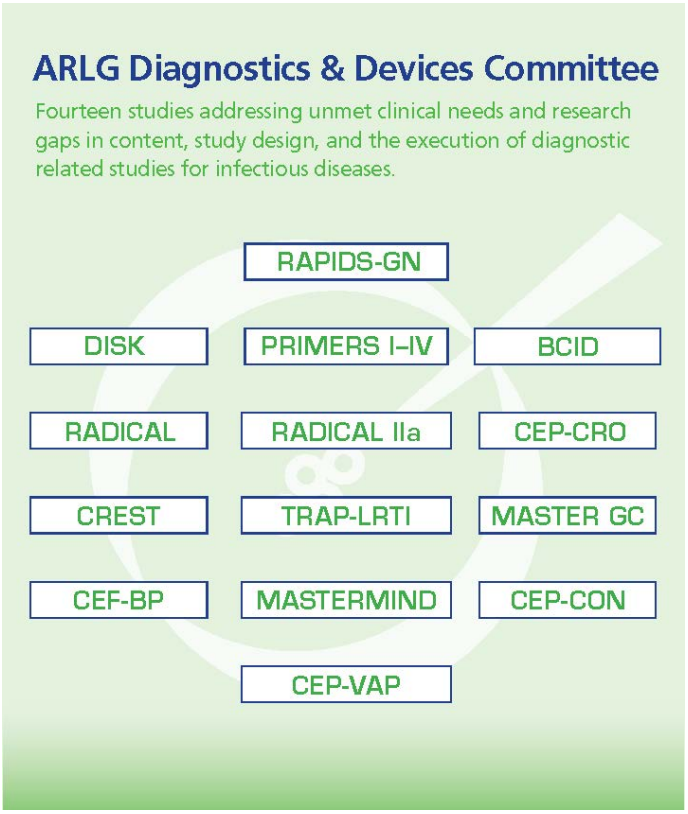
Rapid Diagnostics for Gram-Negative Bacteria in Blood (RAPIDS-GN): This ongoing study will build on BCID to prospectively compare outcomes derived from rapid organism identification and accelerated phenotypic antimicrobial susceptibility testing (AST) to standard culture and AST. Both groups in this trial will receive antibiotic stewardship.

Platforms for Rapid Identification of MDR-Gram negative Bacteria and Evaluation of Resistance Studies (PRIMERS): The ARLG also recently published a series of seminal articles defining the test performance of molecular methods for AMR detection. PRIMERS compared different molecular platforms for their ability to detect selected β-lactam resistance genes and illustrated the overall importance of resistance prevalence on test interpretation (i.e., the positive and negative predictive values of

genotypic testing).

In addition to studies targeting bacterial pathogens, the ARLG has also supported development of host gene expression profiling as a novel tool for differentiating viral from bacterial infections. **The Rapid Diagnostics in Categorizing Acute Lung Infections (RADICAL)** study aims to validate whole blood host immune response signatures as a rapid diagnostic for acute respiratory tract infection. RADICAL I enrollment has been completed. Primary RADICAL outcomes will assess the test characteristics of host gene expression as compared to other bacterial biomarkers using a panel of experts for case adjudication as the reference standard.

Going forward, additional cost-effectiveness, clinical outcome, and utilization studies in both inpatient and outpatient settings are needed to help determine the optimal use of diagnostic technologies with the aim of curbing AMR. Important variables to be assessed include impact on antimicrobial usage, effects on the emergence and spread of resistance, time to effective or optimal therapy, mortality and cost. The ARLG in collaboration with academic and industry partners are poised to conduct these studies and to continue to advance the practice of clinical microbiology.



ARLG SPOTLIGHT

Michael Woodworth, MD, MSc.
Assistant Professor, Division of Infectious Disease
Emory University

About my role in ARLG

I was awarded a two-year ARLG fellowship, which provides salary and tuition support for

my research activities. My research primarily focuses on the use of microbiome therapeutics like fecal microbiota transplantation (FMT) for the eradication of intestinal multi-drug resistant organism (MDRO) colonization. My main efforts are concentrated on patient recruitment, and regulatory work related to a clinical trial of the safety of FMT for MDRO decolonization in renal transplant patients after infection.

With support from the ARLG, I have also been able to:

- Experience hands-on wet-lab training in next generation sequencing
- Better understand data science approaches to analyzing sequencing data
- Complete a retrospective clinical outcome project for a cohort of more than 250 patients treated with FMT for recurrent *Clostridioides difficile* infection at Emory

Impact of ARLG research funding to my career

It is hard to overstate the impact that the ARLG fellowship has had on my career. Pursuing a research career as a junior physician scientist takes time to build a publication record and develop skills to grow a high impact translational research program. I have been able to successfully compete for a NIH Mentored Patient-Oriented Research Career Development (K23) award, which will allow me to continue to develop my research skills and experience over the next five years. This simply would not have been possible without the ARLG fellowship.

Read More

News

Two ARLG PI-Initiated, Laboratory-Based Trials Reached Database Lock

ARLG Principal Investigators Ritu Banerjee, MD, PhD of Vanderbilt University and Audrey Schuetz, MD, MPH, of Mayo Clinic have successfully led the RAPIDS-GN and DISK trials, respectively, to completion.

The primary objective of RAPIDS-GN is to evaluate the impact of rapid identification and antimicrobial susceptibility testing (AST) on the time to first antibiotic modification in the first 72 hours after randomization. RAPIDS-GN enrolled 500 subjects in two sites over 1 year. Database lock occurred in March 2019. Dr. Banerjee expects to present the preliminary results at the American Society for Microbiology (ASM) Microbe meeting in June 2019.

The primary objective of the DISK trial is to evaluate the performance of a rapid disk diffusion test performed using positive blood culture broth (BCB) as the inoculum, read at 16-18 hours of incubation. The project enrolled 500 subjects across five sites over 7 months. Database lock occurred in February 2019. Dr. Schuetz expects to present preliminary results at the Clinical & Laboratory Standards Institute (CLSI) meeting in June 2019.

Congratulations to both ARLG PIs and study sites on this accomplishment. We are looking forward to the results for answering these important questions.

Upcoming Meetings

Connect with your colleagues at these upcoming meetings. If you are presenting on you ARLG work, please email us so we can promote your presentations in this newsletter.

April 13 – 16, 2019
Amsterdam, Netherlands

Support your ARLG colleagues who will be

presenting at the 29th European Congress of Clinical Microbiology & Infectious Diseases (ECCMID).

June 20 – 24, 2019
San Francisco, California, USA

Awards

Congratulations to **Michael Woodworth, MD, MSc,** for being selected as a recipient of the Southern Society for Clinical Investigation (SSCI) Research Scholar Award. This award provides funding for physician-scientists with innovative research projects related to internal medicine and its subspecialties. Dr. Woodworth will use the award to provide additional project funding for the ARLG ongoing pilot clinical trial of fecal transplantation for MDRO eradication in renal transplant patients.

Recent Publications

Check out the following recent ARLG publications since January 1, 2019.

Holland TL, Chambers HF, Boucher HW, Corey GR, Coleman R, Castaneda-Ruiz B, Fowler VG Jr. Considerations for Clinical Trials of Staphylococcus aureus Bloodstream Infection in Adults. Clin Infect Dis. 2019 Feb 15;68(5):865-872. doi: 10.1093/cid/ciy774.

Anesi JA, Lautenbach E, Nachamkin I, Garrigan C, Bilker WB, Omorogbe J, Dankwa L, Wheelter M, Tolomeo P, Han JH. The role of extended-spectrum cephalosporin-resistance in recurrent community-onset Enterobacteriaceae urinary tract infections: a retrospective cohort study. BMC Infect Dis. 2019 Feb 14;19(1):163. doi: 10.1186/s12879-019-3804-y.

Cheng YW, Phelps E, Ganapini V, Khan N, Ouyang F, Xu H, Khanna S, Tariq R, Friedman-Moraco RJ, Woodworth MH, Dhere T, Kraft CS, Kao D, Smith J, Le L, El-Nachef N, Kaur N, Kowsika S, Ehrlich A, Smith M, Safdar N, Misch EA, Allegretti JR, Flynn A, Kassam Z, Sharfuddin A, Vuppalanchi R, Fischer M. Fecal microbiota transplantation for the treatment of recurrent and severe Clostridium difficile infection in solid organ transplant recipients: A multicenter experience/ Am J Transplant. 2018 Aug 7. doi: 10.1111/ajt.15058. [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 Dec 21;63(1). pii: e01801-18. doi: 10.1128/AAC.01801-18. Print 2019

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Luterbach CL, Boshe A, Henderson H, Cober E, Richter SS, Salata RA, Kalayjian RC, Watkins RR, Hujer AM, Hujer KM, Rudin SD, Domitrovic TN, Doi Y, Kaye KS, Evans S, Fowler VG, Bonomo RA, van Duin D. The Role of Trimethoprim/Sulfamethoxazole in the Treatment of Infections Caused by Carbapenem-Resistant Enterobacteriaceae. Open Forum Infect Dis. 2018 Dec 14;6(1):ofy351. doi: 10.1093/ofid/ofy351. eCollection 2019 Jan.

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 Dec;39(12):1431-1435. doi: 10.1017/ice.2018.254. Epub 2018 Oct 30.

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. Infect Dis. 2018 Nov 13;67(suppl_2):S142-S145. doi: 10.1093/cid/ciy694.

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. Am J Med Sci. 2018 Nov;356(5):433-440. doi: 10.1016/j.amjms.2018.08.015. Epub 2018 Aug 29.

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