ARLG
Antibacterial Resistance Leadership Group

September 2019 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 a clinical trial site, please contact us.

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MASTER-GC Study Employs an Innovative Model to Test Diagnostics for Extragenital Gonorrhea and Chlamydia

Molecular diagnostic assays have transformed the field of infectious diseases, allowing for swift and sensitive detection of organisms previously challenging to diagnose, but it can be difficult to study how these new tests perform. In the MASTER-GC study, ARLG investigators collaborated with the National Institute of Allergy and Infectious Diseases (NIAID), the U.S. Food and Drug Administration (FDA), Cepheid, and Hologic to simultaneously test samples from a single patient's pharynx and rectum for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* on multiple diagnostic platforms.

Results from this simultaneous testing were incorporated into a reference, or gold standard, that could then be used to assess whether each of the diagnostic platforms correctly diagnosed extragenital gonorrhea and chlamydia. After establishing the reference standard, MASTER-GC enrolled more than 2,500 patients. The study tested a new design that allowed simultaneous evaluation of multiple diagnostics from different companies.

Prior to this study, there were no diagnostic tests approved by the FDA for determining the presence of extragenital gonorrhea, despite recommendations from the U.S. Centers for Disease Control and Prevention (CDC) for screening in certain populations. As a result, few laboratories offered testing and clinicians lacked an FDA cleared diagnostic test. Lack of testing can result in the continued spread of the bacteria that cause chlamydial and gonorrheal infections, including infections from drug-resistant strains.

"Accurate diagnostics that are more readily available will result in better detection and timely treatment, which could help to slow the rise of antibiotic resistance," said ARLG Co-Principal Investigator, Vance Fowler, MD. "Diagnosis is a major problem in antibacterial resistance, and gonorrhea has been identified by the U.S. Centers for

Disease Control and the World Health Organization as a concerning bacterium with rapidly emerging resistance."

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Update from the Pharmacokinetics Special Emphasis Panel

Chair, Pharmacokinetics Special Emphasis Panel
Thomas Lodise, Pharm D, PhD
Albany College of Pharmacy and Health Sciences
Professor, Department of Pharmacy Practice

The Pharmacokinetics Special Emphasis Panel (PK SEP) is dedicated to enhancing our current understanding of antimicrobial exposure-response relationships in patients with invasive infections. Similar to other ARLG special emphasis panels and committees, the PK SEP supports the mission of the ARLG by reviewing proposals, assigning scientific merit scores, and serving as a resource in prioritizing the network's scientific agenda. The panel's purpose is to ensure that state-of-the-art pharmacokinetic/pharmacodynamic (PK/PD) methods are used to design innovative pharmacologic strategies that optimize the utility of the existing antibacterial agents in our armamentarium for implementation into clinical practice.

The PK SEP concentrates on development of innovative dosing regimens for antibacterial agents prioritized by the CDC, FDA, and the National Institutes of Health (NIH) to combat antibacterial resistance. In addition, the PK SEP is most interested in identifying optimal dosing schemes for patient populations typically underrepresented in Phase III clinical trials, but likely to be encountered in clinical practice.

With support from the PK SEP, the ARLG is pioneering practice-changing research. Panel chair, Tom Lodise, PharmD, PhD, highlights three of these studies below:

PROVIDE: Prospective Observational Evaluation of the Association between Initial Vancomycin Exposure and Failure Rates among Adult Hospitalized Patients with MRSA Bloodstream Infection.

Recently published in Clinical Infectious Diseases, PROVIDE was a multi-center prospective study to evaluate the relationship between day-2 vancomycin exposure profiles and outcomes in patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.

Vancomycin is the most commonly administered antibiotic in United States hospitals and has been a mainstay for treatment of MRSA infections for decades, yet optimal dosing of vancomycin is unclear.

The PROVIDE study took place in 14 hospitals across the United States. The primary outcome was treatment failure, defined as 30-day mortality or a positive blood culture at ≥7 days. Secondary outcomes included acute kidney injury (AKI), defined as a ≥1.5-fold increase in serum creatinine.

A total of 310 patients were enrolled in the study. Overall, higher day-2 vancomycin exposures for patients with MRSA bacteremia were not associated with a lower incidence of treatment failure but were associated with higher rates of AKI. Patients with day 2 area under the curve (AUC) exposures ≤515 experienced the best global outcomes (no treatment failure and no AKI).

The results from PROVIDE have important implications for clinical practice and indicate

that clinicians should reassess the balance of benefits and risks of targeting higher day-2 exposures for patients with MRSA bacteremia. PROVIDE results heavily informed the draft vancomycin consensus guidelines by the American Society of Health-System Pharmacists. Based in large part on PROVIDE, the guidelines now recommend monitoring vancomycin AUCs vs. troughs in clinical practice.

ACUMIN: Acute Care Unit Minocycline

The ACUMIN study is examining the PK of intravenous (IV) minocycline in critically ill patients with Gram-negative infections in the intensive care unit (ICU). Minocycline is a tetracycline derivative first approved in the United States as both oral and IV formulations in the 1970s. A new IV formulation of minocycline became available in 2015 and is approved by the FDA for the treatment of patients with infections due to Gram-positive and Gram-negative pathogens, including *Acinetobacter baumannii*.

A. baumannii is a healthcare-associated pathogen and a major cause of pneumonia, bacteremia, and wound infection among critically ill patients. *A.baumannii* is intrinsically resistant to many commercially available antibiotics. It also has a remarkable capacity to develop resistance to commonly used antibiotics like carbapenems, aminoglycosides, and fluoroquinolones. As a result, the terms 'multi-drug resistant (MDR)' and 'extensively drug resistant' are often used to characterize the different patterns of resistance exhibited by *A. baumannii.* Infections due to MDR *A. baumannii* is a growing world-wide problem and is classified as a serious public health threat by the CDC. Fortunately, minocycline is highly active against *A. baumannii,* including MDR strains, and is well tolerated, making it a potential treatment option for MDR *A. baumannii* infections.

ACUMIN is designed to build a population PK model to describe the plasma exposure profile of minocycline in ICU patients following a single 200-mg intravenous infusion over 60 minutes. Results of ACUMIN will inform optimal dosing of minocycline in the critically ill patient population. More importantly, this study will determine if dosing adjustments for the approved FDA minocycline dosing regimen are needed based on weight and estimated renal function. ACUMIN enrollment is complete and data analyses will start in fall 2019.

COMBINE: Efficacy and Safety of Ceftazidime-Avibactam in Combination with Aztreonam

The COMBINE study focuses on the use of ceftazidime-avibactam in combination with aztreonam (ATM) for patients with metallo-β-lactamase (MBL) - producing Gram-negative infections. Metallo-β-lactamases are carbapenemases and have the ability to inactivate all β-lactams except ATM. Infections due to MBL-producing Gram-negative bacteria (GNB) are increasing worldwide and are a major public health concern as there are limited treatment options available. Furthermore, none of the recently approved antibiotics have notable activity against MBL-producing GNB. Several antibiotics with activity against MBL-producing GNB are being developed, but none are anticipated to be available until at least 2021. This underscores the demand of redeploying our existing agents in innovative ways to meet the needs of patients today.

One strategy that is serving as a "bridge" treatment for MBL-producing GNB infections is ceftazidime-avibactam (AVYCAZ) combined with ATM. Aztreonam is not inactivated by MBLs but many MBL-bearing GNB co-harbor extended spectrum beta-lactamases (ESBLs) that inactivate ATM. In the combination of ATM with AVYCAZ, AVI inhibits the ESBLs and other beta-lactamases that are often present in MBL-producing GNB, allowing ATM, which is unaffected by MBLs, to effectively bind to its target site of action (i.e., bacterial penicillin binding proteins).

The ARLG, in consultation with the PK SEP, designed an in-vitro PK/PD study to determine the optimal AVYCAZ combined with ATM treatment regimens that result in maximal bacterial kill and resistance suppression. The in-vitro PK/PD study is complete and the two combination regimens that showed maximal bacterial killing and resistance suppression over 7 days were:

- AVYCAZ 2.5 g IV as a 2-hour infusion every 8 hours combined with ATM 2 g IV as a 2-hour infusion every six hours, and

- AVYCAZ combined with ATM, each administered as a continuous infusion (CI) (AVYCAZ 7.5 g/day CI combined with ATM 8g/day CI).

To assess the safety and PK of these combination regimens, a Phase I study using healthy volunteers was launched at the Duke Early Phase Clinical Research Unit (DEPRU). The Phase I study includes six dosing cohorts and is evaluating the safety and PK of the AVYCAZ combined with ATM combination regimens relative to its standalone counterparts. Safety is being closely monitored using daily assessments of adverse events, vital signs and clinical laboratory safety tests. Serial blood and urine samples are being collected for PK evaluation. The target completion for enrollment is December 2019 with data analysis completed in early 2020.

Future Plans

As ARLG moves forward, the PK SEP will continue to support the mission of the ARLG by reviewing proposals, assigning scientific merit scores, and serving as a resource in prioritizing the ARLG scientific agenda. The panel will continue to ensure that the best PK/PD methods are used to derive optimal treatment strategies with maximal efficacy and safety for implementation into clinical practice. The PK SEP will also work to ensure the populations most likely to be encountered in clinical practice are included when designing future studies.

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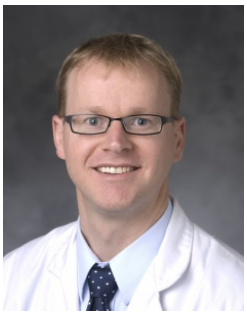
ARLG SPOTLIGHT



Thomas L. Holland, MD, MSc
Associate Professor
Department of Medicine, Division of Infectious Diseases
Duke University

About my role in ARLG

I joined the ARLG in a role that might be best described as an early-career trialist. Over the years, my role has grown and evolved as I have been involved in more studies and part of the Gram-positive committee. These efforts include:

- A set of projects around *Staphylococcus aureus* bloodstream infections. These infections are common and potentially deadly, but few trials have been done to try to determine the best treatment strategies for them. The ARLG has developed novel endpoints that improve trial feasibility and interpretation, including the desirability of outcome ranking (DOOR) and partial credit methods. Developed from a clinician survey and a patient-centered quality of life endpoint, we will use these endpoints in an upcoming interventional trial to test new treatment strategies.

- I had the opportunity to work with Tom Lodise, PhD, on the PROVIDE study. Results from this study will have a meaningful impact on how vancomycin, the antibiotic studied, is used.

Impact of ARLG research funding to my career

There is no equivalent opportunity to get involved in the design and execution of multi-site clinical trials, particularly with the mandate to rethink and improve how we design

these trials. I cannot imagine a better structure to learn how to ask and answer meaningful questions through clinical trials with antibiotic-resistant pathogens. My primary mentor has been Vance Fowler, MD, and I have benefited tremendously from his leadership of the ARLG. I'm biased, to be sure, but I think this is the ultimate training ground for an early-career investigator with an interest in clinical trials that can address the crisis of antibacterial resistance.

For Individuals who are not familiar with ARLG, is there one piece of information you would like to share with them?

The ARLG is an organization that is dedicated, from top to bottom, to innovating and moving the science forward. We never lose sight of the fact that these are real pathogens that cause infections in real people, and you won't find a more dedicated group of people, motivated by this opportunity to make things better for all our patients.

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Announcements

ARLG Leaders Recognized as Experts in *Staphylococcus aureus* and Bacteremia by Expertscape

Congratulations to the ARLG's co-principal investigators, Vance Fowler, MD, MHS, Duke University, and Henry "Chip" Chambers, MD, UCSF, as well as a number of other ARLG investigators who have been recognized as world experts in *Staphylococcus aureus* by Expertcape.

In addition, Dr. Fowler was recognized as the number one world expert in bacteremia by Expertscape. Other ARLG leaders, such as Robert Bonomo, MD, David Paterson, MD, Ralph Corey, MD, and Tom Holland, MD, ranked high on the list.

Connect with your ARLG Colleagues at IDWeek 2019

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ARLG at IDWeek 2019

Recent Publications

Check out the following recent ARLG publications since April 2019.

Anderson DJ, Watson S, Moehring RW, Komarow L, Finnemeyer M, Arias RM, Huvane J, Bova Hill C, Deckard N, Sexton DJ. Feasibility of Core Stewardship Interventions in Community Hospitals: a multicenter, historically-controlled study with crossover design: JAMA Netw Open. 2019 Aug 2; 2(8):e199369. doi: 10.1001/jamanetworkopen.2019.9369.

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