ARLG
Antibacterial Resistance Leadership Group

January 2023
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 impact the prevention, diagnosis, and treatment of infections caused by antibiotic resistant bacteria.

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.

Submit a Proposal

Contact Us

News

Editorial by Henry Chambers, Vance Fowler Highlights Strategic One Health Approach to Address Antimicrobial Resistance

An editorial titled “Confronting Antimicrobial Resistance Together” by Henry Chambers, MD, and Vance Fowler, MD, was published in the November issue of the *American Journal of Physiology – Lung Cellular and Molecular Physiology*. The article reinforces the theme of World Antimicrobial Awareness Week 2022, “Preventing Antimicrobial Resistance Together,” and emphasizes the importance of One Health, a unified, transdisciplinary approach that aims to improve health outcomes by recognizing the interconnectivity of humans, animals, and our shared environments.

Drs. Chambers and Fowler use the COVID-19 pandemic as a key example of the need for a One Health approach to antimicrobial resistance (AMR). In 2020, COVID-19 deaths surpassed the number of deaths caused by the “Big Three” infectious diseases: tuberculosis (TB), HIV-AIDS, and malaria. The authors discuss how progress in the prevention and treatment of these illnesses was disrupted by the pandemic, and suggest that COVID-19 likely exacerbated AMR. Prescribing of antibiotics to patients without a bacterial infection, increases in hospitalizations, and overwhelmed diagnostic laboratories, among other factors, potentially could lead to increased rates of AMR.

Read more

ARLG Spotlight — Heather King

Heather A. King, Ph.D.
Research Health Scientist, Durham VA Health Care System, Health Services Research and Development, Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT)
Assistant Professor, Department of Population Health Sciences and Division of General Internal Medicine, Duke University School of Medicine

About my role in the ARLG

For more than six years, I have had the opportunity to lead several ARLG patient-reported quality-of-life (QoL) studies on bacterial infections alongside wonderful ARLG collaborators like Drs. Thomas Holland, Sarah Doernberg, and Jessica Howard-Anderson. I also feel privileged to be part of ARLG's Innovations Working Group under the leadership of Dr. Helen Boucher and to be a member of the Health-Related Quality of Life (HRQoL) Task Force. In addition, I provide expertise on study design and methodology to our U.S. and global colleagues.

About my work on QoL studies

We began our research in bloodstream infection and have expanded our work to address patient-reported HRQoL and its measurement across four major infectious syndromes which include complicated urinary tract infection (cUTI), acute bacterial skin and skin structure infection (ABSSSI), hospital acquired/ventilator associated bacterial pneumonia (HABP/VABP), and complicated intraabdominal infection (cIAI).

Why is this research important?

Engaging patients is crucial to developing treatments for bacterial infections. It is important to capture outcomes that reflect what matters most to patients as they recover.

Our work informs the measurement of patient-reported HRQoL in studies for new antibacterial agents. By incorporating these patient-reported outcome measures into clinical trials, we learn valuable information about the patients' perspectives on the effects of an intervention including how it influences function across a variety of life domains.

Read More

Helen Boucher Cites Progress and Perils Fighting Antimicrobial Resistance

ARLG investigator, Executive Committee Member, and Innovations Working Group Chair, Helen Boucher, MD, FACP, FIDSA, spoke with Contagion about current challenges and progress in combatting antimicrobial resistance (AMR). She sat for the video interview after delivering her Maxwell Finland Lecture, “Running to Stand Still: Progress and Perils with AMR” at IDWeek 2022. The Maxwell Finland Lecture is awarded annually to experts who have contributed to the areas of bacterial pathogenesis, antimicrobial agents, emerging infections, and hospital-acquired infections.

“It [AMR] affects every one of us—you, me, our children—and I think it’s still not really understood and really embraced by many as a problem that affects them today,” says Dr. Boucher. Limited awareness about AMR, lack of antibiotics, and a gap in surveillance data to understand the extent of AMR in the United States are some of her primary concerns.

Read more

ARLG Early Faculty Seedling Award Applications Are Open!

As part of our mission to mentor the next generation of researchers, ARLG offers the Early Faculty Seedling Award as a grant opportunity to help early stage investigators develop preliminary data and apply for additional external funding. Applications for this award are now open for submission.

The Early Faculty Seedling Award provides 50% of current salary support per year for protected research for up to two years and up to $25,000 in direct costs for

research over the next two years.

Who is eligible to apply?

- ID Fellows at the 4th or 5th year of fellowship
- MD or PhD (any discipline) with a faculty appointment of less than five years
- Applicants who work at a US domestic institution for the duration of the award irrespective of citizenship or visa status

The clinical research project may be conducted in the U.S. or internationally.

Learn more

COMBINE Study Summary Now Available!


SUMMARY OF RESULTS

COMBINE Antibacterial Resistance Leadership Group

The Antibacterial Resistance Leadership Group (ARLG) funds, designs, and conducts clinical research that will help prevent, diagnose, and treat infections caused by bacteria that are resistant to antibiotics.

The ARLG, along with the team of study doctors, scientists, and researchers, are pleased to describe the results from a study focused on antibiotic review strategies in community hospitals to prevent overuse of antibiotics.

WHAT IS THE STUDY TITLE?

Ceftazidime-Avibactam in Combination with Aztreonam (COMBINE)
Combination regimen of Ceftazidime-Avibactam with Aztreonam Hollow Fiber Infection Model against NDM-1-producing Enterobacteriaceae (COMBINE HFIM)

WHAT IS THE PURPOSE OF THE RESEARCH? WHAT IS THE PRIMARY ENDPOINT?

Doctors have few options for treating infections caused by antibiotic-resistant Gram-negative bacteria. Like many antibiotics, ceftazidime-avibactam (CZA) and aztreonam (ATM) do not work against some types of bacteria when used alone, but they do work when combined together.

CZA is made up of a β-lactamase inhibitor (avibactam) and an antibiotic (ceftazidime). ATM is another antibiotic treatment option. Both ceftazidime and ATM are β-lactam antibiotics that disturb the bacterial cell wall, which kills the bacteria.

Some antibiotic-resistant Gram-negative bacteria produce enzymes called β-lactamase, which stop β-lactam antibiotics from working. When ceftazidime and ATM do not work, the bacteria do not die.

β-lactamases called metallo-β-lactamases (MBLs) are very difficult to treat, because they inactivate all β-lactam antibiotics except ATM. ATM may not be stopped from working by MBLs, but it is stopped by other β-lactamases. However, ATM is protected by those other β-lactamases by the avibactam part of CZA.

Researchers wondered if combining CZA and ATM could become a new treatment option that is more effective and resilient against the MBLs made by antibiotic-resistant Gram-negative bacteria. CZA and ATM can be prescribed on their own, but doctors do not know when it may be safe to combine the two antibiotics or which doses may work best. To find out, researchers conducted the COMBINE and COMBINE HFIM studies. Researchers performed the COMBINE Hollow-fiber Infection Model (HFIM) Study to see which doses of CZA plus ATM would kill the most bacteria and prevent antibiotic resistance. The HFIM mimics the environment in the human body and allows bacteria to grow continuously. Using the HFIM, researchers can evaluate how different doses may show up in the blood.

Using the effective doses from the HFIM study, researchers performed the COMBINE Study to see how safe those doses were compared to ATM alone and CZA alone. They evaluated safety based on patients' vital signs, blood samples, and physical exams.

Researchers also looked for side effects. A known side effect from ATM is an increase in liver enzymes, which is a sign of liver damage. However, researchers did not know if CZA and ATM given together would cause further increases in liver enzymes compared to ATM alone.

WHEN DID THE RESEARCH TAKE PLACE?

The COMBINE HFIM study took place between January 2018 and February 2019. The phase I COMBINE Study occurred between July 9, 2019 and November 23, 2020.

HOW WILL THE RESULTS HELP PATIENTS AND DOCTORS?

Doctors will use the results to prescribe safe doses of a combination antibiotic that is resilient to antibiotic resistance. Patients may receive fewer antibiotic treatments and recover more quickly from bacterial infections.

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A lay summary of results has been posted for the Ceftazidime-Avibactam in Combination with Aztreonam (COMBINE) and Combination regimen of Ceftazidime-Avibactam with Aztreonam Hollow Fiber Infection Model against NDM-1-producing Enterobacteriaceae (COMBINE HFIM) studies.

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Events

ARLG at IDWeek OnDemand

Many of ARLG's top leaders were on hand at IDWeek 2022 discussing the latest AMR topics. The event in October featured 140 scientific sessions from ID experts on a variety of interesting subjects.

As a reminder, you can still view any sessions, abstracts, or exhibits you may have missed with OnDemand access. The content is available now through March 2023.

Be sure to see this year's Maxwell Finland Lecture delivered by ARLG investigator, Executive Committee Member, and Innovations Working Group Chair, Helen Boucher, MD, FACP, FIDSA. Use the ARLG guide to find more exciting sessions and posters you will want to see before time runs out.

Learn more

Study Milestones

View recent ARLG study updates.

PHAGE	Study of the Safety and Microbiological Activity of Bacterio**PHAGE**s in Persons with Cystic Fibrosis Colonized with *Pseudomonas aeruginosa*	Enrolling
REPORT-ABC	Rapid **REPORT**ing of **A**ntimicrobial resistance from **B**lood **C**ultures	Published
SCENE	**S**creening for **C**olonization with Resistant **E**nterobacterales in **N**eutropenic Patients with H**e**matologic Malignancies	Closed
COMBINE	Ceftazidime-Avibactam in **Combin**ation with Aztreonam	Published

MDRO-SHREC	**S**tudy of **H**ighly **R**esistant **E**scherichia **c**oli	Published

Go to the ARLG Studies page for more milestones and updates!

Learn More

Recent Publications

View the following recent ARLG publications.

Patel R, Tsalik EL, Evans S, Fowler VG Jr., Doernberg SB. Clinically Adjudicated Reference Standards for Evaluation of Infectious Diseases Diagnostics. 20-Oct-22 Clin Infect Dis. Clin Infect Dis. 2022 Oct 20;ciac829. doi: 10.1093/cid/ciac829. Online ahead of print.

Chastre J, Francois B, Bourgeois M, Komnos A, Ferrer R, Rahav G, De Schryver N, Lepape A, Koksal I, Luyt C-E, Sanchez Garcia M, Torres A, Eggimann P, Koulenti D, Holland TL, Ali O, Shoemaker K, Ren P, Sauser J, Ruzin A, Tabor DE, Akhgar A, Wu Y, Jiang Y, DiGiandomenico A, Colbert S, Vandamme D, Coenjaerts F, Malhotra-Kumar S, Timbermont L, Oliver A, Barraud O, Bellamy T, Bonten M, Goossens H, Reisner C, Esser MT, Jafri HS; COMBACTE-MAGNET EVADE Study Group. Safety, efficacy, and pharmacokinetics of gremubamab (MEDI3902), an anti-Pseudomonas aeruginosa bispecific human monoclonal antibody, in P. aeruginosa-colonised, mechanically ventilated intensive care unit patients: a randomised controlled trial. 15-Nov-22. Crit Care. Crit Care. 2022 Nov 15;26(1):355. doi: 10.1186/s13054-022-04204-9.

Sivapalan P, Staehr Jensen J-U. Procalcitonin to reduce antimicrobial overuse in patients with lower respiratory tract infection: time for re-evaluation of our prescription culture? 13-Dec-22. Lancet Infect Dis. Lancet Infect Dis. 2022 Dec 13;S1473-3099(22)00757-5. doi: 10.1016/S1473-3099(22)00757-5.

Tsalik EL, Rouphael NG, Sadikot RT, Rodriguez-Barradas MC, McClain MT, Wilkins DM, Woods CW, Swamy GK, Walter EB, El Sahly HM, Keitel WA, Mulligan MJ, Tuyishimire B, Serti E, Hamasaki T, Evans SR, Ghazaryan V, Lee M, Lautenbach E, and the TRAP-LRTI Study Group, on behalf of the Antibacterial Resistance Leadership Group. Efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections associated with low procalcitonin: a randomised, placebo-controlled, doubleblind, non-inferiority trial. 13-Dec-22. Lancet Infect Dis. Lancet Infect Dis. 2022 Dec 13;S1473-3099(22)00735-6. doi: 10.1016/S1473-3099(22)00735-6.

Lopez S. Study Evaluates Biomarker to Help Curb Unnecessary Antibiotic Use: Placebo Worse Than Antibiotics After 5 Days, But Similar at Day 11. 13-Dec-22. DukeHealth. https://corporate.dukehealth.org/news/study-evaluates-biomarker-help-curb-unnecessary-antibiotic-use.

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