

ARLG Update

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Meet our Committees

Gram-Negative Bacteria

Outgoing Chair: Brad Spellberg, MD

The long-term goals of the ARLG are 1) to complete a superiority trial of antibacterials for drug-resistant Gram-negative bacterial infections; 2) to define shorter course, narrow-spectrum therapeutic regimens for common infections, as a principle means to support stewardship and reduce selective pressure; 3) to identify a more effective alternative to vancomycin for staphylococcal infections; and 4) to develop rapid diagnostics for antibacterial resistance to expedite clinical trials and inform appropriate drug therapy.



Dr. Brad Spellberg

New therapeutic strategies are desperately needed for treatment of infections caused by MDR-GNB, particularly strains that are extensively- or pan-drug resistant. With few effective agents and increasing incidence of these organisms, there is a critical need for innovative trial designs to identify better therapies to treat these infections. Improved diagnostic testing is needed to rapidly and accurately identify resistance in GNB, thereby offering the potential to spare the use of broad spectrum antibacterial agents in situations where narrower spectrum agents (or no antibacterial therapy) are sufficient for treatment. Long-term objectives are to identify and/or design transformational clinical trials to improve outcomes of MDR-GNB infections and to minimize opportunities for further resistance to occur.

The Gram-Negative Subcommittee is soliciting clinical studies to:

- Develop and test antimicrobial agents or strategies for Gram-negative infections in adults or children caused by multiple-drug resistance gram-negative bacilli including carbapenem-resistant, expanded-spectrum cephalosporin-resistant, or quinolone-resistant bacteria.
- Evaluate novel agents or strategies to prevent emergence of resistance during treatment of infections caused by Gram-negative bacilli.
- Optimize administration of antimicrobial agents for treatment of Gram-negative infections with respect to dose, dosing interval, and duration of therapy in adults or children.

For more information about the ARLG, its leaders, or its current projects, please visit arl.org

Committee Member	Institution
Brad Spellberg (Chair)	University of Southern California
Robert Bonomo	Case Western Reserve University
Yohei Doi	University of Pittsburgh
Scott Evans	Harvard University
David Hooper	Massachusetts General Hospital
Keith Kaye	Wayne State University
David van Duin	University of North Carolina at Chapel Hill



ARLG Project Spotlight CRACKLE

Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* (CRACKLE)

Principal Investigator: David van Duin, MD, PhD

Carbapenem resistance is increasingly common in *K. pneumoniae* isolates, and represents a major threat to our population. Since the first reported carbapenem-resistant *K. pneumoniae* (CRKP) was identified in 1996, the incidence of infections due to this multi-drug resistant (MDR) pathogen has increased dramatically. The rise in resistance to colistin, the antibiotic of last resort for serious CRKP infections, is extremely concerning, and deserves further study. In addition, tigecycline resistance is increasingly common in CRKP bloodstream infections. The impact of other CRKP infections, the epidemiology of CRKP infection and colonization, and the longer term outcomes of patients colonized with CRKP remain unclear.

The primary objectives of this project are 1) to determine whether CRKP strain type and/or OmpK35/36 porin expression is associated with hospital mortality in CRKP infections; 2) to evaluate the constellation of clinical and microbiologic factors associated with colistin and tigecycline non-susceptibility; and 3) to explore variation in treatment and outcomes of CRKP infections in various anatomical sites. To accomplish this, CRACKLE was designed as an observational study that utilized an existing CRKP consortium consisting of 20 hospitals that are part of 9 different health care systems and studied the outcome data for about 980 subjects. This project has resulted in 6 published papers, 2 papers under review, and 10 abstracts accepted by ICAAC or IDWeek. The extension and expansion of this consortium has been proposed and is in development as CRACKLE II.



Dr. David van Duin



Dr. Minh-Hong Nguyen



ARLG Project Spotlight CREST

Using novel molecular beacons to study the impact of carbapenem resistant Enterobacteriaceae carriage on the outcomes of solid organ transplantation (CREST)

Principal Investigators: M. Hong Nguyen, M.D. and Cornelius J. Clancy, M.D.



Dr. Cornelius J. Clancy

Carbapenem resistant Enterobacteriaceae (CRE) infections carry high mortality. Solid organ transplant (SOT) recipients are highly vulnerable to infections, especially within the first 3 months post-transplant. It is unknown if CRE carriage by SOT recipients and donors is a risk factor for CRE infections following transplant. There are reports of severe CRE infections among SOT recipients who were CRE-colonized prior to transplant. Although routine cultures are performed on donor organs, it is unclear if molecular assays will be more sensitive at detecting CRE.

The primary objectives of this project are 1) to determine CRE carriage rates among intestine, liver, lung, pancreas, kidney, and heart transplant donors and recipients at time of transplant, and among recipients post-transplant; 2) to follow transplant recipients for 3 months post-transplant for the development of CRE infections or colonization; 3) to determine associations between CRE colonization, CRE infections and outcomes like length of hospital stay, and rates of mortality, rejection and allograft failure; and 4) to compare sensitivity and turn-around times of molecular beacon- and culture-based CRE screening methods, using peri-rectal, duodenal, colon and lung swabs or bronchoalveolar lavage (BAL) fluid.

To accomplish this, CREST has been designed as a prospective, observational study to evaluate the natural history of CRE carriage in intestine, liver, lung, pancreas, kidney, and heart transplant donors and recipients from time of transplant through 3 months post-transplant. Planned enrollment is 150 subjects over the course of 12 months. Current enrollment is at 73 subjects.