Gram-Negative Bacterial Infections: Research Priorities, Accomplishments, and Future Directions of the Antibacterial Resistance Leadership Group

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Antimicrobial resistance in pathogenic gram-negative bacteria is one of the most pressing challenges in the field of infectious diseases and is one of 4 key areas of unmet medical need identified by the Antibacterial Resistance Leadership Group (ARLG). The mission of the Gram-Negative Committee is to advance our knowledge of these challenging infections and implement studies to improve patient outcomes. Studies have fallen primarily into 2 broad categories: prospective cohort studies and interventional trials. Among the observational studies, CRACKLE (Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae) has contributed seminal multicenter data describing risk factors and clinical outcomes of carbapenem-resistant Enterobacteriaceae (CRE) in sentinel US hospitals. Building on this success, CRACKLE II will expand the network to hospitals across the United States and Colombia. Similar protocols have been proposed to include *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (SNAP and POP studies). In addition, the CREST study (Carbapenem-Resistant Enterobacteriaceae in Solid Organ Transplant Patients) has provided pivotal data on extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae and CRE carriage among solid organ transplant recipients to inform management of this vulnerable patient population. Two clinical trials to define novel ways of using an existing antibiotic, fosfomycin, to treat ESBL-producing Enterobacteriaceae (one that has completed enrollment and the other in late protocol development) will determine the clinical efficacy of fosfomycin as step-down oral therapy to treat complicated urinary tract infections. Additional clinical studies and trials using immunotherapeutic or newly approved agents are also in the planning stage, with the main goals of generating actionable data that will inform clinical decision making and facilitate development of new treatment options for highly resistant gram-negative bacterial infections.

Keywords. gram-negative; antimicrobial resistance; observational studies; interventional studies; clinical trials.

Antimicrobial resistance in gram-negative bacterial pathogens has reached a critical level where treatment options have become extremely limited for some types of infections [1, 2]. Resistance of *Escherichia coli* to oral agents such as trimethoprim-sulfamethoxazole and fluoroquinolones has eroded the utility of these antibiotics, leaving few options for the treatment of urinary tract infections in healthcare and community settings. Furthermore, cephalosporin resistance due to production of extended-spectrum β-lactamase (ESBL) has become commonplace in *E. coli* [3]. Resistance to carbapenems, once reliable and safe options for the treatment of serious gram-negative infections caused by drug-resistant organisms, has increased in the last decade among healthcare-associated pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and other carbapenem-resistant Enterobacteriaceae (CRE). Systemic infections from these organisms carry unacceptably high mortality, as high as 50%, because of the lack of efficacious treatment regimens [4].

Antimicrobial resistance in gram-negative pathogens has implications beyond the immediate issues of morbidity and mortality. None of the advances of modern medicine such as complex surgery, transplantation, cancer chemotherapy, and intensive care are possible without reliable means to treat the infections that inevitably complicate them.

The Antibacterial Resistance Leadership Group (ARLG) provides a framework to prioritize and implement clinical studies to advance knowledge of the most challenging

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antimicrobial resistance problems and improve the clinical outcome of patients affected by antimicrobial-resistant infections. The long-term goals of the ARLG Gram-Negative Committee are to identify, design, and implement transformational clinical trials to improve outcomes of extensively drug-resistant (XDR) gram-negative infections and to minimize opportunities for further resistance to occur. Here, we review the ARLG's activities in the field of gram-negative infections over its first 3 years and discuss unmet needs and potential opportunities moving forward (Table 1) [5–15].

OBSERVATIONAL STUDIES

Carbapenem-Resistant *Klebsiella pneumoniae*

Carbapenem resistance, increasingly common in *K. pneumoniae*, represents a major threat to our population. Since the first carbapenem-resistant *K. pneumoniae* (CRKP) strain producing *K. pneumoniae* carbapenemase (KPC) was identified in 1996, the incidence of infections due to CRKP has increased dramatically [4]. The rise in resistance to colistin and tigecycline, agents of last resort with activity against CRKP, is particularly concerning [16].

Despite the rapid spread of CRKP in the United States, the epidemiology, clinical impact, and longer-term outcomes of patients colonized or infected with CRKP remained unclear. To address this knowledge gap, CRACKLE (Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae) was launched in 2011 as a multicenter observational cohort of hospitalized patients infected or colonized with CRKP [17]. With the initial support of the Clinical and Translational Science Collaborative (UL1TR000439), 3 major healthcare systems in the Cleveland area began working together to gather clinical data and CRKP isolates from hospitalized patients in a standardized and prospective manner [5]. With support from the ARLG, 10 additional sites were added and enrollment was expanded to include all CRE. To date, more than 1100 admissions from over 800 patients have been included in the study. The key findings of CRACKLE that have been reported to date are summarized in Table 2 [2, 4–11]. Building on this success, a nationwide expansion is in process that will include 32 study sites throughout the continental United States and Colombia (CRACKLE II; Figure 1). Collaborations with the ARLG Laboratory Center [18], Statistical and Data Management Center (SDMC) [19],

Table 1. Antibacterial Resistance Leadership Group Studies Addressing Unmet Needs in Gram-Negative Bacterial Infections

Study	Title/Topic	Description	Status
Observational			
CRACKLE I	Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae I	Natural history of CRE infection/colonization	Completed [5–11]
CRACKLE II		Natural history of CRE infection/colonization; expanded to include all census regions	Ongoing
ESBL Bacteremia	Clinical outcome of ESBL bacteremia	Empiric therapy; clinical decision tree	Completed [12, 13]
CREST	Carbapenem-Resistant Enterobacteriaceae in Solid Organ Transplant Patients	Active surveillance of solid organ transplant patients to determine the impact of ESBL-E/CRE carriage on outcome	Completed
SNAP	Study Network of *Acinetobacter* as an XDR Pathogen	Natural history of XDR *Acinetobacter* infection/colonization	Planning stage
POP	*Pseudomonas* and Other Lactose-Non-Fermenting Pathogens	Natural history of MDR *Pseudomonas* infection/colonization	Planning stage
PRIMERS	Platforms for Rapid Identification of MDR Gram-Negative Bacteria and Evaluation of Resistance Studies	Rapid genotyping of drug-resistant gram-negative bacteria	Ongoing [14, 15]
Interventional			
PROOF	Pharmacokinetics, Pharmacodynamics and Safety/Tolerability of Two Dosing Regimens of Oral Fosfomycin Tromethamine in Healthy Adult Participants	PK/PD and safety/tolerability of 2 oral fosfomycin regimens in healthy adults	Ongoing
FOCUS	Phase IV Randomized, Double-Blind Trial to Evaluate the Efficacy of Fosfomycin Oral Versus Levofloxacin in Complicated Urinary Syndromes	Randomized, placebo-controlled, active control study of oral fosfomycin as a step-down therapy for cUTI	Planning stage
ACUMIN	Acute Care Unit Minocycline	PK/PD of intravenous minocycline among critically ill adults	Planning stage
PK^2	Pharmacokinetics of Plazomicin in Kids	PK/PD of plazomicin in adolescents, children, and infants	Planning stage
PROPEL	Pharmacokinetics of Plazomicin in the Epithelial Lining	ELF penetration of plazomicin in patients with VAP/HAP	Planning stage
GC MASTERMIND	Gonorrhea and Chlamydia Master Protocol for Diagnostics	Evaluate diagnostics for extragenital gonorrhea and chlamydia	Ongoing

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; cUTI, complicated urinary tract infection; ELF, epithelial lining fluid; ESBL-E, extended-spectrum β-lactamase–producing Enterobacteriaceae; HAP, hospital-acquired pneumonia; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

Table 2. Key Findings From CRACKLE

Finding
• Severe acute illness (median Pitt bacteremia score [2]) and underlying chronic comorbidities (median Charlson score [4]) were common in patients infected and/or colonized with CRE [5]
• Hospitalizations during which CRE are isolated tended to be prolonged (median length of stay, 9 days) and included an ICU stay in 51% of patients [5]
• Overall mortality = 18% ° Associated mortality highest in patients with CRE pneumonia (hospital mortality, 34%; aHR[a], 3.44) and bacteremia (hospital mortality, 38%; aHR[a], 2.59) ° No additional mortality was observed in patients with CRE UTI [5, 6]
• Readmissions during which CRE were again isolated occurred in 20% of patients within 90 days of discharge [7]
• Tigecycline use may lead to sequential tigecycline resistance, and stay in long-term care facilities was found to be a risk factor [8, 9]
• Common CRKP strain types included ST258A and ST258B [5, 10, 11]
• ST258A was associated with higher treatment failure rates in CRKP bacteriuria [10]
• Aminoglycoside was associated with improved outcomes and tigecycline was associated with worse outcomes in patients treated for CRKP bacteriuria [10]

Abbreviations: aHR adjusted hazard ratio; CRACKLE, Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae; CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ICU, intensive care unit; UTI, urinary tract infection.
[a]CRE urinary colonization was used as the reference group.

and Leadership and Operations Center (LOC) [20] have also enabled expansion of database, operational, and laboratory and statistical analysis capabilities in CRACKLE II, including exploring direct electronic health record feeds. This follow-up study is specifically aimed at informing the designs of interventional diagnostic and therapeutic trials addressing CRE infections. The first patient was enrolled in CRACKLE II in July 2016.

ESBL-producing bacteria are a major driver of carbapenem use and are increasing in prevalence; yet the optimal empiric therapy for bacteremia caused by these organisms is not defined. With support from the ARLG, 2 studies have been conducted to address this question. In a large cohort of patients with ESBL bacteremia, comparison of empiric therapy with carbapenems and piperacillin-tazobactam showed that the former was associated with improved survival after adjustments [12]. Using the underlying cohort of bacteremia patients, a clinical decision tree was generated that has high positive and negative predictive values for ESBL bacteremia [13]. These findings should facilitate institution of early optimal therapy for this challenging infection.

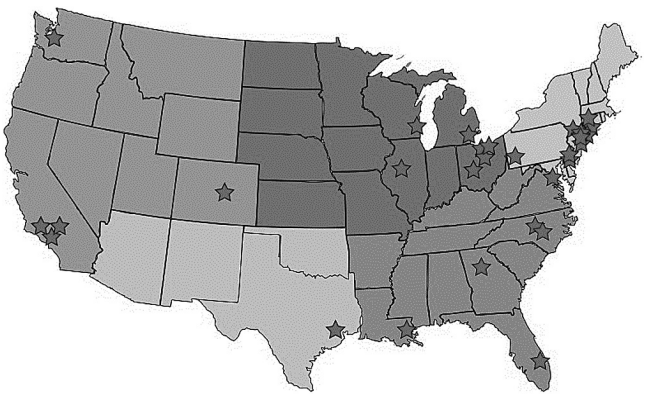

Figure 1. Locations of planned US study sites for CRACKLE II (Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae).

Solid organ transplant (SOT) patients constitute a special population that is vulnerable to ESBL-producing Enterobacteriaceae (ESBL-E) and CRE infection. Due to their profoundly immunocompromised status, outcomes of SOT patients who develop CRE infection remain suboptimal [21]. However, the natural history of ESBL-E/CRE colonization and subsequent infection after SOT remains unclear. CREST (Carbapenem-Resistant Enterobacteriaceae in Solid Organ Transplant Patients) is a longitudinal cohort study to better define risk of colonization and infection (lung, liver, and small bowel) in these patients. Enrollment is complete for CREST, and the full findings will be reported soon.

XDR *Acinetobacter* and *Pseudomonas*

Building upon the success of CRACKLE, similar natural history studies are in the planning stage for *A. baumannii* (Study Network of *Acinetobacter* as XDR Pathogen [SNAP]) and *P. aeruginosa* (*Pseudomonas* and Other Lactose-Non-Fermenting Pathogens [POP]). *Acinetobacter baumannii* and *P. aeruginosa* are highly problematic XDR pathogens, and treatment options are even more limited than for CRE. The goals of SNAP and POP are to elucidate the epidemiology, clinical presentation, and outcome of all XDR *A. baumannii* and *P. aeruginosa* infection/colonization cases at network hospitals, and to determine the molecular epidemiology of the isolates. These data will inform the design of future treatment trials.

INTERVENTIONAL STUDIES

Oral Step-down Therapy for Urinary Tract Infections

Oral treatment options of urinary tract infections (UTIs) are increasingly limited due to worsening antimicrobial resistance among *E. coli* strains in the community. Oral agents that used to be first-line for the treatment of upper UTI (pyelonephritis) and lower UTI (cystitis), such as trimethoprim-sulfamethoxazole and fluoroquinolones, are no longer consistently reliable due to high resistance rates [22].

Fosfomycin is an old agent that remains active against most *E. coli* strains and can be taken orally [23]. In the United States, however, it is currently only approved for a single-dose treatment of uncomplicated lower UTI. Two sequential studies are being implemented and planned, respectively, to test efficacy of fosfomycin as a multiple-dose oral step-down for complicated UTIs. The first, a collaboration with the Pharmacokinetics Special Emphasis Panel and the ARLG SDMC and LOC, is PROOF (Pharmacokinetics, Pharmacodynamics and Safety/Tolerability of Two Dosing Regimens of Oral Fosfomycin Tromethamine in Healthy Adult Participants) to identify the optimal dosing schedule of oral fosfomycin to be tested for the treatment of pyelonephritis and complicated UTI. PROOF has enrolled healthy subjects who receive daily or every-other-day dosing of fosfomycin tromethamine 3 g by mouth in a randomized crossover study. One of these 2 regimens will be selected for FOCUS (Phase IV Randomized, Double-Blind Trial to Evaluate the Efficacy of Fosfomycin Oral Versus Levofloxacin in Complicated Urinary Syndromes), based on the steady-state pharmacokinetics and pharmacodynamics data obtained through PROOF. FOCUS will test whether fosfomycin tromethamine is as efficacious as levofloxacin as oral step-down therapy in treating complicated UTI, including pyelonephritis. Up to 3 days of prestudy therapy (expected to be mostly intravenous therapy in-hospital) will be allowed, followed by 5–7 days of study medication—a step-down study design that reflects clinical practice.

MINOCYCLINE PHARMACOKINETICS IN CRITICALLY ILL PATIENTS

Acinetobacter baumannii is a healthcare-associated pathogen characterized by its propensity for extensive drug resistance. Especially problematic is carbapenem-resistant *A. baumannii*, an important cause of pneumonia, bacteremia, and wound infection among critically ill patients for which very few treatment options are available [24]. A new intravenous formulation of minocycline made available in 2015 is approved by the US Food and Drug Administration for the treatment of infections due to *Acinetobacter* species, is active against the majority of XDR *A. baumannii* strains, and is well tolerated, making it a potential treatment option for XDR *A. baumannii* infections. However, the pharmacokinetic characteristics of minocycline in the critically ill are unknown. ACUMIN (Acute Care Unit Minocycline), another collaboration with the Pharmacokinetics Special Emphasis Panel, is a pharmacokinetic study designed to address this knowledge gap. ACUMIN will develop a population pharmacokinetic model for minocycline following a single 200-mg intravenous infusion over 60 minutes in up to 50 critically ill patients. The results of ACUMIN will inform optimal dosing of minocycline in the critically ill patient population most likely to receive this agent.

PLAZOMICIN PHARMACOKINETICS IN CHILDREN AND CRITICALLY ILL PATIENTS

Plazomicin is a novel aminoglycoside currently in phase 3 clinical development for the treatment of complicated UTIs, including acute pyelonephritis and serious infections caused by CRE. Plazomicin has activity against most CRE strains, including strains that are resistant to currently available aminoglycosides, and is active against KPC-producing *K. pneumoniae*, which accounts for most CRE identified in the United States [25]. Continuing the strong collaboration with the Pharmacokinetics Special Emphasis Panel, 2 pharmacokinetic studies are in the planning stage to inform dosing of plazomicin once it is approved for clinical use. PK^2 (Pharmacokinetics of Plazomicin in Kids) is a phase 1, open-label study to evaluate the pharmacokinetics of plazomicin in adolescents, children, and infants that will provide pivotal data supporting pediatric dosing of plazomicin from preterm infants to adolescents. PROPEL (Pharmacokinetics of Plazomicin in the Epithelial Lining) is a phase 1, prospective, multicenter, randomized study to evaluate the epithelial lining fluid penetration of plazomicin in patients with nosocomial pneumonia. Importantly, PROPEL will address lung penetration of plazomicin in the actual patient population likely to need this agent once approved, an important consideration for novel antibacterial agents.

UNMET NEEDS AND OPPORTUNITIES

Resistance of gram-negatives is at the forefront of the current crisis of antibiotic resistance with major challenges in prevention, diagnosis, and treatment of infections caused by these organisms. A key mission of the ARLG Gram-Negative Committee is to advance knowledge of gram-negative bacterial infections, especially those with XDR pathogens, and conduct studies to test novel diagnostic and treatment options that will improve clinical care and patient outcome. Currently, the priority XDR pathogens include CRE, *A. baumannii*, and *P. aeruginosa*. Several new treatment options are becoming available for CRE, but options for other organisms continue to be extremely limited and will be the focus in coming years.

Numerous challenges in conducting clinical trials addressing infections from XDR pathogens include difficulty in identifying and enrolling patients in the target population, changes in epidemiology, delay in diagnosis, concomitant or polymicrobial infection, and baseline illness (Table 3). A deeper understanding of the natural history of these infections is essential for designing and implementing feasible clinical trials. CRACKLE II is designed specifically to collect typical inclusion and exclusion criteria of interventional trials and document the outcome of CRE infections to allow for early assessment of trial feasibility. Similar natural history studies are being conceived for *A. baumannii* and *P. aeruginosa*. These studies provide an opportunity to significantly facilitate design and conduct of randomized clinical trials.

Table 3. Unmet Needs and Opportunities in Gram-Negative Bacterial Infection

Need or Opportunity
Key challenges
• Extremely limited treatment options for XDR pathogens, especially *Acinetobacter* and *Pseudomonas*
• Lack of pharmacokinetic data for the patient populations in need of optimal therapy
• Difficulty in identifying changing epidemiology and target populations for interventional trials
Opportunities
• Testing of novel diagnostic and treatment options that will improve clinical care and patient outcome
• Conducting pharmacokinetic studies of novel therapies in ICU and pediatric populations
• Conducting natural history studies that inform design and implementation of interventional trials
• Expanding public–private partnerships to synergize expertise and resources

Abbreviations: ICU, intensive care unit; XDR, extensively drug resistant.

An emerging opportunity is the role of ARLG in public–private partnerships. Several studies taking advantage of such partnerships are in the planning stages and more are under consideration for the treatment of gram-negative infections. These partnerships provide platforms to synergize the expertise and resources to conduct studies that may not be conducted otherwise to inform clinical practice. Whereas preclinical and early clinical studies for new treatments have in the past been almost exclusively conducted in the private sector, we anticipate that the combined expertise and resources of the public, private, and academic sectors will establish new paradigms to advance the field and facilitate antibiotic drug development.

CONCLUSIONS

The ARLG has implemented and is planning multiple studies addressing unmet needs posed by gram-negative pathogens and infections. These include natural history studies, pharmacokinetic and pharmacodynamic studies, and interventional trials, each designed to address gaps in knowledge. The ARLG continues to prioritize observational and interventional studies in the field of gram-negative resistance, with the goal of generating information that will directly and positively impact management of patients with infections caused by these organisms.

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References

1. World Health Organization. Antimicrobial resistance—global report on surveillance. **2014**. Available at: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf. Accessed 3 July 2016.
2. Review on Antimicrobial Resistance. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Available at: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf. Accessed 3 July 2016.
3. Flamm RK, Sader HS, Farrell DJ, Jones RN. Ceftazidime-avibactam and comparator agents tested against urinary tract isolates from a global surveillance program (2011). Diagn Microbiol Infect Dis **2014**; 80:233–8.
4. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis **2011**; 53:60–7.
5. van Duin D, Perez F, Rudin SD, et al. Surveillance of carbapenem-resistant *Klebsiella pneumoniae*: tracking molecular epidemiology and outcomes through a regional network. Antimicrob Agents Chemother **2014**; 58:4035–41.
6. Hauck C, Cober E, Richter SS, et al; Antibacterial Resistance Leadership Group. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. Clin Microbiol Infect **2016**; 22:513–9.
7. Messina JA, Cober E, Richter SS, et al; Antibacterial Resistance Leadership Group. Hospital readmissions in patients with carbapenem-resistant *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol **2016**; 37:281–8.
8. van Duin D, Cober ED, Richter SS, et al. Tigecycline therapy for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bacteriuria leads to tigecycline resistance. Clin Microbiol Infect **2014**; 20:O1117–20.
9. van Duin D, Cober E, Richter SS, et al. Residence in skilled nursing facilities is associated with tigecycline nonsusceptibility in carbapenem-resistant *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol **2015**; 36:942–8.
10. van Duin D, Cober E, Richter SS, et al. Impact of therapy and strain type on outcomes in urinary tract infections caused by carbapenem-resistant *Klebsiella pneumoniae*. J Antimicrob Chemother **2015**; 70:1203–11.
11. Wright MS, Perez F, Brinkac L, et al. Population structure of KPC-producing *Klebsiella pneumoniae* isolates from midwestern U.S. hospitals. Antimicrob Agents Chemother **2014**; 58:4961–5.
12. Tamma PD, Han JH, Rock C, et al; Antibacterial Resistance Leadership Group. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis **2015**; 60:1319–25.

13. Goodman KE, Lessler J, Cosgrove SE, et al; Antibacterial Resistance Leadership Group. A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamase-producing organism. Clin Infect Dis **2016**; 63:896–903.
14. Evans SR, Hujer AM, Jiang H, et al; Antibacterial Resistance Leadership Group. Rapid molecular diagnostics, antibiotic treatment decisions, and developing approaches to inform empiric therapy: PRIMERS I and II. Clin Infect Dis **2016**; 62:181–9.
15. Evans SR, Hujer AM, Jiang H, et al. Informing antibiotic treatment decisions: evaluating rapid molecular diagnostics (RMDs) to identify susceptibility and resistance to carbapenems against *Acinetobacter* spp. PRIMERS III. J Clin Microbiol **2016**. doi:10.1128/JCM.01524-16.
16. Kazmierczak KM, Biedenbach DJ, Hackel M, et al. Global dissemination of blaKPC into bacterial species beyond *Klebsiella pneumoniae* and in vitro susceptibility to ceftazidime-avibactam and aztreonam-avibactam. Antimicrob Agents Chemother **2016**; 60:4490–500.
17. Neuner EA, Yeh JY, Hall GS, et al. Treatment and outcomes in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. Diagn Microbiol Infect Dis **2011**; 69:357–62.
18. Manca C, Hill C, Hujer AM, et al. Leading antibacterial laboratory research by integrating conventional and innovative approaches: the Laboratory Center of the Antibacterial Resistance Leadership Group. Clin Infect Dis **2017**; 64(Suppl 1):S13–7.
19. Huvane J, Komarow L, Hill C, et al. Fundamentals and catalytic innovation: the Statistical and Data Management Center of the Antibacterial Resistance Leadership Group. Clin Infect Dis **2017**; 64(Suppl 1):S18–23.
20. Cross HR, Harris A, Arias RM, et al. Transforming concepts into clinical trials and creating a multisite network: the Leadership and Operations Center of the Antibacterial Resistance Leadership Group. Clin Infect Dis **2017**; 64(Suppl 1):S8–12.
21. Clancy CJ, Chen L, Shields RK, et al. Epidemiology and molecular characterization of bacteremia due to carbapenem-resistant *Klebsiella pneumoniae* in transplant recipients. Am J Transplant **2013**; 13:2619–33.
22. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis **2011**; 52:e103–20.
23. Sastry S, Doi Y. Fosfomycin: resurgence of an old companion. J Infect Chemother **2016**; 22:273–80.
24. Doi Y, Murray GL, Peleg AY. *Acinetobacter baumannii*: evolution of antimicrobial resistance-treatment options. Semin Respir Crit Care Med **2015**; 36:85–98.
25. Landman D, Babu E, Shah N, et al. Activity of a novel aminoglycoside, ACHN-490, against clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* from New York City. J Antimicrob Chemother **2010**; 65:2123–7.