Antimicrobial Resistance in Gram-Negative Pathogens: Crafting the Tools Necessary to Navigate the Long Ascent out of the Abyss

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(See the article by Johnson et al, on pages 900–5.)

The unrelenting increase in the prevalence of antimicrobial resistance is of great concern. The urgency of the problem is compounded by the recognition that fewer new antimicrobial agents are introduced each year [1]. Past efforts to curb antimicrobial resistance have been largely unsuccessful. It is important to note that what attention has been focused on emerging resistance has been primarily directed toward gram-positive organisms (eg, methicillin-resistant Staphylococcus aureus [MRSA] and vancomycin-resistant enterococci). Indeed, the few antibacterial agents introduced in recent years have targeted treatment of multidrug-resistant gram-positive organisms.

Despite strong evidence for person-to-person spread of MRSA, the optimal infection-prevention strategies to curtail the spread of this organism remain unclear. This gap in information has primarily been attributable to an historical lack of scientifically robust and generalizable data. Only very recently have more-rigorous studies been conducted to evaluate the role of specific strategies (ie, universal screening) for controlling MRSA, and even these studies have differed markedly in their conclusions [2, 3]. The impact of a weak foundation of scientific evidence is perhaps not surprising: forces external to the health care epidemiology community have increasingly imposed pressure for action. For example, despite the lack of clear evidence of the effect of universal screening for MRSA, an increasing number of US states have introduced or passed legislation mandating screening programs for MRSA.

What can this experience teach us about facing antimicrobial resistance among gram-negative pathogens? Unlike the 1980s and 1990s, the importance of gram-negative organisms as causes of health care–acquired infection may be resurgent [4, 5]. Furthermore, the breadth of resistant organisms continues to increase and now includes multidrug-resistant (MDR) Pseudomonas aeruginosa, extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, MDR Acinetobacter baumanii, and carbapenemase-producing Klebsiella pneumoniae. Therapeutic options for treating infection due to these organisms are few. Indeed, there are increasing numbers of organisms that should be considered to be extremely drug resistant (XDR) for which few—and sometimes no—therapies exist [6]. Not surprisingly, mortality rates among patients with infections due to these organisms are very high and are closely linked to delays in the initiation of adequate therapy [7, 8]. Unfortunately, “adequate therapy” is difficult to institute when the organism is resistant to all commercially available antimicrobials. Therapeutic options are unlikely to improve in the coming years, because no new agents active against MDR gram-negative organisms are currently in clinical stages of development.

Given the above considerations, it is imperative that we make every effort to preserve the agents that we have available now. The 2 primary components of the emergence of resistance are endogenous elaboration of resistance in the presence of selective pressure (eg, antibiotic use) and person-to-person spread. Clearly, interventions should be targeted preferentially at those processes thought to primarily underlie the emergence of resis-
tance for a given gram-negative pathogen. Unfortunately, these data do not currently exist.

It is against this backdrop that Johnson et al [9] conducted the study published in this issue of the *Journal*. The goal of this study was to characterize the importance of person-to-person spread in the emergence of imipenem-resistant *P. aeruginosa* (IRPA). The authors used as their study population all patients admitted to the medical and surgical intensive care units (ICUs) at the University of Maryland from 1 September 2001 through 1 September 2006. All such patients underwent perianal sampling at ICU admission, weekly thereafter, and at ICU discharge. Among those patients not colonized with IRPA at ICU admission, the authors assessed the incidence of new colonization with IRPA. Pulsed-field gel electrophoresis (PFGE) was used to assess the genetic relatedness of IRPA isolates. Furthermore, only those subjects with similar PFGE types whose hospitalizations overlapped by at least 1 day were considered to represent person-to-person spread.

Overall, 7071 patients were included in the study cohort. Compliance with perianal swabbing was 90%, with 17,656 perianal swabs being collected during the study period. A total of 151 subjects had culture results positive for IRPA colonization at ICU admission. There were 149 subjects who had culture results that were negative for IRPA at admission but who subsequently acquired IRPA during their ICU stay. Among these acquisitions, 46 (31%) had a PFGE pattern similar to that for another isolate. However, only 16 (11%) had both a similar PFGE pattern and an overlapping hospital stay. Of the 149 patients who developed new IRPA colonization during their ICU stay, 38 (26%) had an imipenem-susceptible *P. aeruginosa* isolate obtained from a culture sample at admission. Of these patients, 27 had resistant isolates that were identical by PFGE to their preceding susceptible counterparts.

The authors are to be commended on this important contribution to the literature. Their work represents by far the largest study to evaluate the role of person-to-person spread in the emergence of antimicrobial-resistant *P. aeruginosa*. Data of this sort are critical in helping to better define the optimal approach to curbing the further emergence of antimicrobial-resistant gram-negative organisms. Indeed, these data build on past work by this group [10, 11]. In these recent studies, Anthony Harris’ group has explored similar issues for ESBL-producing *K. pneumonia* (ESBL-KP) and ESBL-producing *Escherichia coli* (ESBL-EC) colonization. In these studies, Harris and colleagues found that although 52% of new ESBL-KP colonization was attributable person-to-person transmission, only 13% of ESBL-EC was attributable to transmission [10, 11]. This series of articles suggests that, although person-to-person transmission plays an important role in the acquisition of antimicrobial-resistant gram-negative organisms, its relative contribution to the emergence of drug resistance may differ across organisms. As such, infection-control interventions may need to be tailored to the specific organism.

The definition of person-to-person transmission employed in the study by Johnson et al [9] deserves further scrutiny. Most past studies have simply relied on molecular evidence (eg, PFGE) to define transmission. This is obviously a low threshold, in that if 2 patients are colonized with closely related strains but hospitalized months apart, little clinical epidemiologic evidence for person-to-person transmission exists. The current study used a more stringent definition that required both similar PFGE patterns and overlapping hospital stays. The impact of using this more stringent definition is evident in the results: 39% of subjects met the definition based only on PFGE results, whereas only 11% met the definition requiring both molecular and epidemiologic evidence of transmission.

So what is the “correct” definition? Using only molecular criteria casts the net widely but almost certainly classifies some events as person-to-person transmission when they are not. Subjects meeting the more stringent definition are much more likely to represent true transmission. However, this definition likely misses some transmission events if another source (eg, the hospital environment) serves as an intermediate step. More work is required to determine the impact of different definitions for transmission. Indeed, given different pathogen characteristics (eg, duration of colonization and viability on inanimate objects), the optimal definition may differ across organisms. Most importantly, we should strive for a standard definition across studies to optimize comparability of results.

Most studies of gram-negative organisms with resistance have focused primarily on organisms derived from clinical cultures. However, subjects identified only via clinical cultures represent a select subset of all patients colonized with the pathogen of interest. The importance of focusing on colonization in elucidating the epidemiology of antimicrobial resistance has been recently highlighted [12]. Furthermore, recent work has concentrated on specific methodological issues related to studying colonization, including carriage of multiple distinct strains in a given subject, the yield of different approaches to detecting colonization, and the utility of frozen fecal samples [13–17].

What are the implications of the current study for health care epidemiology practice? Should we be employing enhanced infection-control approaches for IRPA? Perhaps a broader question is what proportion of colonization with drug-resistant organisms must be accounted for by transmission to warrant targeting person-to-person spread? Five percent? Ten percent? Fifty percent? One might argue that, given the dire situation of antimicrobial resistance among gram-negative pathogens, even a small contribution from transmission should warrant intervention. If so, what should that intervention be?
Institution of contact precautions for patients colonized with the resistant organism? Universal screening? Screening targeted to specific high-risk populations? These decisions have important implications not only for the allocation of limited resources but also because implementation of infection-control isolation precautions has been increasingly associated with negative clinical outcomes and decreased patient satisfaction [18, 19].

One clear message of the Johnson et al [9] article is how complex the emergence of drug resistance is and how little we really understand at this point. One of the historical limitations of the health care epidemiology literature is that studies are often done with little or no financial support, often severely limiting the scope and quality of the work. This type of investigation requires considerable effort and resources, as evidenced by its length, the number of subjects enrolled, and the amount of swab samples obtained. It is most encouraging that the importance of this type of work, although time and cost intensive, is increasingly seen as a valuable investment by funding agencies.

In the future, 2 complementary needs are critical. First, given the recognized variability in the epidemiology of resistance across different centers and populations, multicenter studies of resistance are vital [20]. Only through such collaborative efforts can we hope to build the evidence base necessary to inform strategies for addressing these resistant infections. Second, additional resources must be made available. To this end, it is worth highlighting the recent introduction of congressional legislation to address a number of these issues; the Strategies to Address Antimicrobial Resistance (STAAR) Act seeks to strengthen federal antimicrobial resistance surveillance, prevention and control, and research efforts.

The problem of antimicrobial resistance among gram-negative pathogens represents an immense abyss into which we have continued to descend. Only through coordinated efforts across investigators and institutions within the health care epidemiology community and allocation of sufficient research funding to identify effective solutions can we hope to gain the foothold necessary to begin the long ascent.

References