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Antimicrobial Resistance In Gram-Negative Pathogens: Crafting The Tools Necessary To Navigate The Long Ascent Out Of The Abyss

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The unrelenting rise in 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 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 (e.g., methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE)). Indeed, the few antimicrobial 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 spread of this organism remain unclear. This has primarily been due 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 (i.e., 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 healthcare 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 healthcare acquired infections may be resurging [4,5]. Furthermore, the breadth of resistant organisms continues to increase and now includes multidrug-resistant (MDR) *Pseudomonas aeruginosa*, extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, MDR *Acinetobacter baumannii*, and carbapenemase-producing *Klebsiella pneumoniae*. Therapeutic options for these organisms are few. Indeed, there are increasing numbers of organisms that should be considered extremely drug resistant (XDR) for which few, and sometimes no, therapies exist [6]. Not surprisingly, mortality rates for patients with infections due to these organisms are very high and closely linked to delays in 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 as 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 all efforts to preserve the agents we have available now. The two primary components of emergence of resistance are endogenous elaboration of resistance in the presence of selective pressure (e.g., antibiotic use) and person-to-person spread. Clearly, interventions should be targeted preferentially at those

processes thought to primarily underlie emergence of resistance for a given gram-negative pathogen. Unfortunately, these data do not currently exist.

It is against this backdrop that Johnson and colleagues conducted the study published in this issue of the *Journal of Infectious Diseases* [9]. 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 between September 1, 2001 and September 1, 2006. All such patients underwent peri-anal sampling on ICU admission, weekly, and upon ICU discharge. Among those patients not colonized with IRPA upon ICU admission, the authors assessed the incidence of new colonization with IRPA. Pulsed-field gel electrophoresis (PFGE) was used to assess genetic relatedness of IRPA isolates. Furthermore, only those subjects with similar PFGE types whose hospitalizations overlapped by at least one day were considered to represent person-to-person spread.

Overall, 7,071 patients were included in the study cohort. Compliance with peri-anal swabbing was 90% with 17,656 peri-anal swabs collected during the study period. One-hundred fifty-one subjects were positive for IRPA colonization on ICU admission. There were 149 subjects who were negative for IRPA on admission but subsequently acquired IRPA during their ICU stay. Among these acquisitions, 46 (31%) had a similar PFGE pattern to 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 on admission culture. Of these, 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 the sort are critical in helping better define the optimal approach to curbing 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. pneumoniae* (ESBL-KP) and ESBL-producing *Escherichia coli* (ESBL-EC) colonization. In these studies, Harris and colleagues found that while 52% of new ESBL-KP colonization was due to person-to-person transmission, only 13% of ESBL-EC was due to transmission [10, 11]. This series of papers suggests that while person-to-person transmission plays an important role in acquisition of antimicrobial resistant gram-negative organisms, its relative contribution to emergence of 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 and colleagues deserves further scrutiny. Most past studies have simply relied on molecular evidence (e.g., PFGE) to define transmission. This is obviously a low threshold in that if two 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 which required both similar PFGE patterns as well as 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 while 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 wide, 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 (e.g., 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 (e.g., duration of colonization, 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 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 methodologic 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 healthcare epidemiology practice? Should we be employing enhanced infection control approaches for IRPA? Perhaps a broader question is what proportion of resistant colonization must to be accounted for by transmission to warrant targeting person-to-person spread? 5%? 10%? 50%? 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 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 paper is how complex the emergence of resistance is and how little we really understand at this point. One of the historical limitations of the healthcare 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 swabs obtained. It is most encouraging that the importance of this type of work, while time and cost intensive is increasingly seen as a valuable investment by funding agencies.

In the future, two 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 in gram-negative pathogens represents an immense abyss into which we have continued to descend. Only through coordinated efforts across investigators and institutions within the healthcare 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.

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