Delineating the Epidemiology-Host-Microbe Relationship for Methicillin-Resistant *Staphylococcus aureus* Infection

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(See the major article by Rose et al on pages 1862–74.)

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of nosocomial infections and is associated with prolonged length of hospitalization, morbidity, and mortality [1]. Over the past 15 years, MRSA has emerged as an important cause of infection outside of healthcare settings, with infections due to so-called community-associated MRSA (CA-MRSA) now observed in community settings [2, 3]. Infections due to CA-MRSA were initially distinct from those due to traditional hospital-acquired MRSA strains in that they were noted to cause disease even in young, previously healthy individuals [2]. MRSA strains have long been recognized to express a variety of toxins and virulence factors that are felt to contribute to the high morbidity and mortality associated with MRSA infection [4]. With the emergence of CA-MRSA, additional questions have arisen as to which microbial factors may be most important for causing severe disease [5], especially given the fulminant manifestations that were reported early in the epidemic [6–8].

The most common CA-MRSA strain in the United States, as determined by pulsed-field gel electrophoresis, is USA300 [9], a member of clonal complex 8 (CC8). USA300 typically carries SCCmecIV and often expresses Panton-Valentine leukocidin (PVL), a cytotoxin that has been proposed by some to lead to increased virulence [10]. In hospital settings, USA100, which belongs to clonal complex 5 (CC5), has traditionally been the most prevalent MRSA strain; infections with USA100 largely affect individuals with significant comorbidities and prior healthcare exposures [11]. However, the epidemiology of MRSA has changed with the emergence of CA-MRSA. In addition to widespread reports from community settings [3], USA300 has been reported as a cause of nosocomial infections in the United States [12]. Although the most common clinical manifestation of USA300 MRSA is skin and soft-tissue infection [13], severe infections such as necrotizing pneumonia [14], necrotizing fasciitis [6], and overwhelming sepsis [7] have also been seen.

These severe USA300 MRSA infections, which often occur in populations distinct from those affected by traditional hospital-acquired MRSA strains, led to research into whether USA300 MRSA strains have added virulence factors. While one study observed that cases of invasive community-onset pneumonia due to the USA300 strain type were more likely to have early onset complications [15], several studies have demonstrated that the USA300 strain type is not associated with a higher mortality rate than non-USA300 strains [16]. It remains unclear why certain individuals develop overwhelming infection due to MRSA and which host or microbial factors may be responsible. A recent study by Calderwood et al [17] used genome sequencing to identify staphylococcal factors that predicted the development of bloodstream infection in individuals who were colonized with MRSA. After controlling for various host factors in their analysis, the authors observed that MRSA colonization with a strain carrying the staphylococcal enterotoxin P (*sep*) gene was significantly associated with development of a subsequent MRSA infection. The authors [17] and an accompanying editorial [18] noted the importance of incorporating host factors into an analysis of virulence factors and suggested that future work in this field should look at the combined effects of these factors to optimize prediction models for who will develop the most severe disease.

In this issue of *The Journal of Infectious Diseases*, Rose et al [19] investigate the association of various host and microbial
factors with clinical outcomes for individuals with nosocomial pneumonia due to MRSA. The authors analyzed respiratory MRSA isolates collected during a prior multicenter, double-blinded, randomized, controlled trial, the objective of which was to determine the efficacy of linezolid versus vancomycin therapy for the treatment nosocomial pneumonia. Given the previously noted challenges in determining the impact of individual bacterial factors on clinical outcomes, cytotoxicity was examined as a global measure of virulence. The authors defined high cytotoxicity as ≥90% killing of cells within 2 hours and analyzed this variable as dichotomous (ie, low or high cytotoxicity) and by quartiles. The authors included cytotoxicity of the MRSA strain, host factors, and clonal type in multivariate models to predict death or clinical cure.

Rose et al observed that strains with low cytotoxicity that did not carry the SCCmecIV element—strains often seen in hospital settings—were associated with higher mortality, an effect observed for patients treated with vancomycin or linezolid. Upon further examination, Rose et al found that strains with low cytotoxicity more often were isolated from individuals with medical comorbidities, particularly diabetes, cardiac disease, and renal disease. In another observation, the authors reported high cytotoxic activity in CC8 strains. While univariate analysis revealed no significant association between infection with a CC8 strain and higher mortality, once cytotoxic activity was adjusted for in multivariate analysis, infection with a CC8 strain was associated with a higher odds of death. In contrast, cytotoxic activity did not appear to influence clinical cure of nosocomial pneumonia. The presence of SCCmecIV, the presence of PVL, or being in the CC8/299 lineage was associated with worse clinical outcomes at the end of the study.

The study by Rose et al [19] is notable in that it attempts to separate the effects of the host and the pathogen in predicting clinical outcomes and mortality resulting from MRSA pneumonia. Their finding of an inverse relationship between cytotoxicity and mortality once again underscores the importance of including host qualities in an assessment of MRSA disease. Although the study found that diabetes, cardiac disease, and renal disease were associated with increased mortality and may represent important host variables to consider when predicting who will have the most-severe MRSA infection, Rose et al cite a possible unmeasured host factor to explain why certain individuals, even when infected with a MRSA strain with low cytotoxic capability, still had a high risk of death. A better understanding of host characteristics and host response to MRSA infection may be of value to guide interventions to improve clinical outcomes of patients with MRSA pneumonia.

In addition to unmeasured host factors, we propose that epidemiologic factors be considered when developing a framework for preventing acquisition of MRSA and development of MRSA infection, as well as for identifying the patients who will have the most severe disease. For example, certain epidemiologic exposures (eg, incarceration, illicit drug use) [20, 21] may facilitate colonization with particular MRSA strains (eg, USA300 MRSA), but the impact of infection by the strain depends on the health of the host (eg, immune status) and bacterial factors such as those examined by Rose et al. The relative importance of epidemiologic, host, and bacterial factors in determining who will acquire MRSA colonization and who will develop severe illness or death due to MRSA infection remains to be elucidated.

A potential limitation of the study by Rose et al is that it is restricted to clinically diagnosed nosocomial MRSA pneumonia. Individuals with nosocomial pneumonia are often undergoing mechanical ventilation and in intensive care units; these patients may represent a unique subset of the population that develops MRSA infections. Thus, results of this study may not be generalizable to other MRSA infections, such as bloodstream or necrotizing skin infections, both of which are common and can lead to severe illness and death. Nevertheless, the approach taken by Rose et al to disentangle host and bacterial factors that increase the risk of severe MRSA infection and lead to worse clinical outcomes likely still holds and can inform future research into these other infection types.

Another important concept put forth by Rose et al is that patients infected with MRSA strains with low or high cytotoxic activity are intrinsically different. In a clinical trial, these differences may lead to nonuniform effects of bacterial factors or treatments across populations, making interpretation of outcomes more challenging. Balancing study arms to account for the factors or conducting stratified analyses may be necessary to best understand responses in these diverse populations.

The study by Rose et al highlights several important areas of future research. First, it remains unclear why some individuals develop overwhelming infections due to MRSA, whereas others have minor disease. This study underscores the potential role of host factors that predispose to severe disease and how future work should integrate bacterial and host factors for identifying which patients may develop the most severe MRSA infections. Second, creating an epidemiology-host-bacterial framework may be useful for informing prevention efforts aimed at reducing MRSA infections. Finally, the authors demonstrate the complexities involved with trying to delineate the relative contributions of the host and pathogen for predicting who will develop severe illness due to various MRSA strains. Expansion of their work to other types of MRSA infections will be of value to understand the range in severity of illness that MRSA can cause. While these investigations are ongoing, our continued vigilance in optimizing infection control and infection prevention for multidrug-resistant organisms is essential.
Notes

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