The Continuing Saga of MRSA

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In this issue of the Journal, there are 3 papers that expand our understanding of an old enemy, Staphylococcus aureus. They report changes in the prevalence of nasal colonization with S. aureus in the United States, explore the associations among host and bacterial genotypes and nasal carriage or skin infection, and question what defines a community-associated strain of methicillin-resistant S. aureus (MRSA), respectively [1–3].

Both scientific and public interest in MRSA have been heightened by a recent report estimating that MRSA infections were associated with death in 18,650 people in the United States, in 2005. Since 2001, the incidence of invasive MRSA infection has increased 1.7-fold in Atlanta and 2.9-fold in Baltimore [4]. These findings resulted in a spate of articles in the lay press that described MRSA as a “superbug” that had killed more people in the United States than did AIDS in 2005.

The frequency of methicillin resistance in S. aureus has increased in isolates recovered from individuals infected and/or colonized with hospital-associated and community-associated strains. Currently, in many hospitals over half of infections caused by hospital-associated S. aureus strains involve methicillin-resistant organisms and, in some communities, nearly half of the community-associated strains recovered from skin and soft tissue infections (SSTIs) are methicillin resistant. [5, 6].

Gorwitz et al. [1] inform us that, although the overall prevalence of nasal carriage of S. aureus in the US population has declined significantly when the period from 2001–2002 is compared 2003–2004, the proportion of methicillin-resistant isolates recovered increased from 2.5% to 5.2%, and the proportion of MRSA isolates that are of the pulsed-field gel electrophoresis (PFGE) types typical of community-associated MRSA (CA-MRSA) strains rose from 8% to nearly 20%. Colonization with MRSA, in turn, is associated with increased risk of infection with MRSA. The study is population-based and so is probably a fairly accurate reflection of the situation in the United States in 2004. These trends are likely to continue.

Emonts et al. [2] demonstrate that differences in several host inflammatory response genes probably contribute significantly to the propensity for both colonization and infection with S. aureus in an elderly study population. Polymorphisms in each of the genes the authors studied had previously been shown to interact with S. aureus in various ways, either in vitro or in vivo, to increase the severity of infection with S. aureus (interleukin [IL]-4 deficiency), to interact with staphylococcal protein A (C-reactive protein [CRP]; and tumor necrosis factor [TNF]-α, concentrations of which are controlled by the TNFA promoter region), or to respond to activation by CRP (complement factor H [CFH]). The investigators postulated that variants of some of these genes were likely to be overrepresented or underrepresented among individuals who were colonized or infected with S. aureus, and they were correct. A very large sample size (3851 participants), 678 (18%) of whom had persistent carriage of S. aureus and 1270 of whom had boils, as well as longitudinal design, conferred great statistical power on the study. Careful statistical analysis, which incorporated multivariate regression and controlling for confounding, further strengthened their findings of association.

The ILA−524 C/C host genotype, as opposed to the ILA−524 T allele, was associated with an increased probability of nasal carriage of S. aureus, irrespective of the strain’s genotype. In addition, persistent nasal carriage was associated with both the ILA−524 C/C genotype and certain S. aureus AFLP strain markers, suggesting the complexity of the interaction between host and microbe. The authors postulate that the C allele, which results in lower levels of IL4 serum concentration and mucin production, allows the increased frequency of nasal carriage because of decreased mucociliary clearance of the organism. Conversely, haplotype 2, the CRP (1184–2042–2911) C→G→C haplotype, was found more often in individuals...
without carriage, and CRP C-C-G haplotype 3 was associated with a decreased occurrence of boils. Homozygosity for the CFH 402Tyr variant was overrepresented among individuals who reported a history of boils. TNFA polymorphism was not associated with nasal carriage of S. aureus.

The findings of Emonts et al. [2] further illuminate the complex interaction between this pathogen and its reluctant human host. A picture emerges of a dynamic balance between host and pathogen, influenced by multiple features of each. Subtle differences in either the pathogen or the host lead to a greater or lesser risk of colonization or disease. We are just beginning to understand and catalogue these differences, and the final model of human–S. aureus interaction is likely to be exceedingly complex.

David et al. [3] ask whether the boundaries “hospital-associated” heretofore implied resistance to multiple antibiotics and carriage of staphylococcal cassette chromosome mec (SCC mec) type I, II, or III, and the label “community-associated” implied carriage of SCCmec IV and Panton-Valentine leukocidin (PVL) genes; the production of phenol-soluble modulin peptides (discussed further below); and comparatively limited antimicrobial resistance, a pattern that includes susceptibility to clindamycin and doxycycline. David et al. [3] ask whether the boundaries between these 2 categories have become so blurred that the terms “community-associated MRSA” and “hospital-associated MRSA” are no longer epidemiologically or clinically useful. They conclude that “association with the healthcare environment now has little predictive value for distinguishing patients with infection due to multiply resistant MRSA isolates from those infected by CA-MRSA isolates,” and that “defining CA-MRSA by the absence of risk factors for healthcare exposure greatly underestimates the burden of epidemic CA-MRSA disease” [3, p. 1235–43].

First, some attempt at clarifying the definitions of commonly used terms involving MRSA is in order. There are a bewildering array of terms applied to the classification and description of MRSA strains. With regard to the spectrum of antimicrobial susceptibility, MRSA can be resistant to methicillin alone (MRSA), to one or more additional antimicrobials (or classes of antimicrobials) used to treat staphylococcal infections (e.g., clindamycin, tetracyclines, quinolones, rifampin, trimethoprim-sulfamethoxazole, and/or aminocyclitols), or to multiple antimicrobial classes (multidrug-resistant MRSA [MDR-MRSA]). Most hospital-associated strains are resistant to several classes of antimicrobial agents and most community-associated strains are susceptible to clindamycin, as well as to tetracyclines and other classes of antimicrobials.

In the past 10–15 years, the causes of colonization and/or infection with MRSA have also increasingly been divided into strains presumed to be healthcare-associated in origin or healthcare-acquired in terms of exposure (HA-MRSA) or strains that are community-associated in origin or community-acquired in terms of exposure (CA-MRSA). This distinction has been most useful for monitoring the rise of community-associated strains over the past decade, during which an increasing proportion of MRSA isolates appear to be of community origin and transmitted in the community [3].

The term “acquired” implies that there is strong epidemiologic evidence and evidence from a patient’s clinical history indicating that colonization and/or infection occurred after acquisition of the organism from exposure to the healthcare environment, or conversely, from an exposure that occurred in the community. The term “associated” is more commonly used to denote distinct strain types that, historically, were first seen in large numbers in hospitals or, more recently, to describe distinctive strains of MRSA recovered from the community. Thus, we suggest that “associated” refers to S. aureus strains, whereas “acquired” refers to the location of the exposure that led to colonization and/or infection.

Community-associated strains have historically had the following traits: they are predominantly of PFGE type USA300, carry their mutant penicillin-binding protein 2a (PBP2a) on mobile genes classified as SCCmec type IV, are resistant to a few limited classes of antibacterial agents, and harbor genes encoding for PVL, a putative virulence factor for pneumonia but perhaps not for SSTI [7, 8]. Recently, Wang et al. [9] have described a new class of secreted, short staphylococcal peptides that are associated with the virulence of SSTI caused by community-associated strains of MRSA, which are called phenol-soluble modulin peptides. These peptides recruit, activate, and lyse neutrophils, the main human defensive response against S. aureus. On the other hand, hospital-associated strains were generally found to be resistant to a broader spectrum of antimicrobial agents; to be more heterogeneous with respect to PFGE type; to carry SCCmec types II and III; and often to lack PVL genes and, probably, phenol-soluble modulin peptides as well.

However, confusion arises because, more recently, the onset of colonization and/or infection with a community-associated or hospital-associated strain of MRSA can result from either a healthcare-related exposure or a community exposure. Thus, a “hospital-associated” strain, originally acquired by one person as a result of contact with the healthcare environment, could be transmitted by to another person in the community who has had no formal contact with the healthcare environment. The organism would be accurately labeled a hospital-associated strain, but it was acquired as a result of community exposure and, epidemiologically, would be labeled community acquired. Conversely, a person who has had a history of exposure to the healthcare environment could acquire a strain that has laboratory characteristics similar to those historically associated with CA-MRSA, as David et al. point out in their article [3].

Although David et al. [3] provide a great deal of useful data on the characteristics of MRSA in Chicago, where the sit-
ulation with respect to endemic CA-MRSA is relatively mature, we are not convinced that the Centers for Disease Control (CDC) definition of CA-MRSA based on the “absence of healthcare-associated risk factors” is no longer epidemiologically or clinically useful. Among the isolates studied by David et al. [3] that were recovered from patients who met the CDC’s “lack of healthcare exposure risk factor” criterion and were, therefore, likely to CA-MRSA (212 of 616 MRSA isolates), >80% of the isolates were clindamycin susceptible, and >80% of the patients from whom the isolates were recovered had SSTI. From an epidemiological standpoint, the CDC criteria identified 34% of the MRSA isolates as community-associated MRSA, among which >90% were SCCmec IV*, non-MDR, and PVL+. This group of patients and isolates certainly meets our expectations for community-associated MRSA in an epidemiologic sense and can be used for epidemiologic studies of CA-MRSA.

Of the 404 isolates recovered from patients who did not meet the “lack of healthcare exposure risk factor” criterion and might, therefore, have been classified as HA-MRSA, approximately 170 (42%) had laboratory parameters that we generally associate with CA-MRSA. The patients from whom the isolates were recovered might well have been misclassified as being infected and/or colonized with HA-MRSA by the presence of the CDC’s healthcare associated risk factors criterion when, in reality, the isolates were probably acquired in the community by people with an incidental finding of a healthcare-associated risk factor. David et al. [3] state that these were probably acquired in the community because very few of the infections were the result of nosocomial transmission, based on a criterion of being isolated from specimens obtained <48 hours after admission. This leaves 234 isolates that were classified as healthcare-associated by both the risk factor criterion and laboratory parameters.

Thus, the CDC criterion performed reasonably well at identifying isolates as community-associated that met both the risk factor criterion and possessed laboratory characteristics consistent with CA-MRSA, and the CDC criterion accurately identified most of the isolates that might have been healthcare-associated. These patients and isolates remain useful for epidemiologic studies of risk factors for infection and/or colonization with community-associated MRSA, as well as studies to collect other related data. The real value of the David et al. article [3], we believe, lies in the finding that, submerged within the group of isolates identified as possibly healthcare associated by the risk factor criterion, there are a number of isolates with laboratory characteristics that suggest CA-MRSA. These isolates were recovered from people who had incidental healthcare exposure but probably were acquired in the community setting, further underscoring the increasing overall importance of CA-MRSA strains.

As clinicians working in the emergency department or outpatient setting, we would be comfortable using clindamycin or doxycycline to treat uncomplicated SSTI in patients who lacked healthcare-associated risk factors, even in a geographic area with a known high prevalence of MRSA among outpatients with SSTI. On the other hand, in the David et al. study [3], clindamycin susceptibility was only 40% among strains recovered from patients with healthcare-associated risk factors, an unacceptably low figure if the infection is a serious or aggressive (complicated) SSTI or is located somewhere other than skin or soft tissue. These patients are generally admitted to the hospital anyway, until the infection has been controlled, or they are treated as outpatients and started on parenteral (vancomycin or daptomycin) or oral antimicrobial therapy using agents that are active against hospital-associated MRSA (e.g., linezolid) until the infecting organism’s antibiotic susceptibilities are known. So, from a clinical standpoint, the CDC criterion remain useful for identifying 2 groups of patients: those with apparent staphylococcal disease who should respond to clindamycin as outpatients and patients for whom initial therapy would need to target HA-MRSA, which is more likely to be MDR. As S. aureus continues to evolve, as its epidemiology is better understood, as host-microbe interactions continue to be better defined, and as we apply antimicrobial therapy more wisely, we can hope that the result is an ever-improving balance between host and microbe—in our favor.

References