The Way to the Wound Is through the Nose

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(See the article by Kuehnert et al., on pages 172–9.)

The US microbiologist Theobald Smith is credited with the view that “disease is an accident occurring in the development of the parasitic state” [1, p. 2]. This perspective can certainly be applied to the staphylococcus, an organism replete with strategies to establish harmony with its host in the form of nasal colonization. In this issue of the Journal of Infectious Diseases, Kuehnert et al. [2] provide the first large population-based assessment of nasal colonization with Staphylococcus aureus and, more importantly, with methicillin-resistant S. aureus (MRSA). As the frequency of community-associated MRSA infections continues to increase, investigation into the dynamics of nasal colonization will be valuable in the creation of plausible strategies for controlling this emerging pathogen.

It is well established that, at any given time, ∼30% of all persons are colonized with S. aureus, with the anterior nares serving as its critical niche [3]. Although colonization typically precedes infection, relatively few colonized individuals develop staphylococcal infections. There are, undoubtedly, a variety of host-organism interactions that play a role in this symbiosis; yet, much of what is known has been derived from the study of persons with clinical disease, not those in the asymptomatic carrier state.

Using the sample provided by the 2001–2002 National Health and Nutrition Examination Survey (NHANES), Kuehnert et al. assessed S. aureus nasal carriage in all participants ≥1 year old. Nearly 10,000 participants were enrolled; 2964 (32.4%) were colonized with S. aureus, of whom only 75 (0.8% of the total) harbored MRSA. These findings translate into weighted estimates of 89.4 and 2.3 million persons being colonized with S. aureus and MRSA, respectively, in the United States in 2001–2002. Thus, although the proportion of the US population colonized with MRSA was low, the absolute number of MRSA-colonized persons was already quite large in 2001–2002. Risk factors for MRSA colonization were age ≥60 years and being female; however, when the analysis was limited to community-associated MRSA (as determined by the presence of the staphylococcal cassette chromosome mec IV gene), younger children and non-Hispanic black persons were found to be at increased risk.

Kuehnert et al. also sought to understand the microbiological and molecular epidemiologic character of the colonization isolates from their study population. Their antibiotic-susceptibility data suggest what other investigators have reported for community-associated MRSA—namely, favorable resistance profiles for such agents as trimethoprim/sulfamethoxazole, rifampin, gentamicin, and vancomycin, as well as the variable presence of an inducible resistance phenotype for clindamycin. This information becomes increasingly germane to practitioners whose empirical choices of therapy for community-associated staphylococcal infections have moved away from the β-lactams. In addition, results of the analysis of the toxin repertoire were substantially different from what would be expected from simple extrapolation of data from invasive isolates; for example, although it appears that the genes for the cytolytic toxin Panton-Valentine leukocidin are found in the majority of clinical isolates of community-associated MRSA [4], its presence was less common (8.0% of MRSA) among the carriage strains in Kuehnert et al.’s population-based study, a finding that perhaps requires reevaluation.
The carriage estimates produced by Kuehnert et al. must be interpreted in their historical context. Their results from investigation of a large, national population are quite consistent with the results of local investigations completed at the same time. In 2001, colonization studies from geographically diverse institutions found a similar frequency of MRSA nasal carriage. Studies from Chicago, IL; Nashville, TN; Charlottesville, VA; and San Francisco, CA, suggested that a small but noteworthy reservoir of MRSA carriage existed in these areas, at prevalence rates ranging from 0.6% to 2.8% [7–12]. Because these data very closely match Kuehnert et al.’s results from the NHANES population, it would seem that they were not simply local phenomena; rather, it would seem that geographically specific colonization data are important harbingers that signal trends in staphylococcal epidemiologic patterns. All of these studies were conducted before the widespread emergence of community-associated MRSA infection, which, in some areas, now accounts for up to 75% of all community-associated staphylococcal infections in children [13]. In addition, the increased frequency of community-associated MRSA infection has been associated with reports of increased morbidity and mortality—specifically, a longer duration of fever, prolonged hospitalization, a higher incidence of pulmonary complications along with bone and joint infections, and the reemergence of a severe staphylococcal sepsis syndrome [14–16]. In 2004, to assess whether a change in the MRSA nasal colonization rate accompanied the increase in disease frequency, our group studied 500 healthy children [5]. Using the same methods that we had used in 2001, we found that 46 (9.2%) of the 500 children were colonized with MRSA. This percentage represented a >10-fold increase in the MRSA nasal colonization rate in the same community from 2001 to 2004 [5, 10]. Similarly, Pan et al. studied >300 homeless youths in the San Francisco area in 2004 and found that 6.2% of the enrolled subjects were colonized in the nares with MRSA [17]. Last, Alfaro et al. recently reported that ~22% of children admitted to Driscoll Children’s Hospital in Corpus Christi, TX, in 2005 were colonized with MRSA [18]. The times—along with MRSA colonization rates—are, indeed, changing.

The question remains: To what extent does colonization with S. aureus (and with MRSA, in particular) confer increased risk to the host? If we are to understand the implications of Theobald Smith’s assertion that disease is accidental, then we must understand just how “accident prone” the circulating strains of community-associated MRSA are. A recent study of US soldiers by Ellis et al. helps to clarify this issue [6]. Of 812 soldiers who were enrolled at the start of basic training, 24 (3%) were colonized with community-associated MRSA. Nine (38%) of the 24 soldiers developed soft-tissue infections during the 2-month study period. This rate was significantly higher than that (i.e., 28%) observed among the 229 participants colonized with methicillin-susceptible S. aureus, of whom only 8 (3%) developed clinical staphylococcal infections (relative risk, 10.7 [95% confidence interval, 4.6–25.2]). In a similar vein, Pan et al. [17] have suggested that, among community-associated MRSA, there are distinct populations that are successful colonizers, successful pathogens, or both. What factors govern these distinctions remain largely unknown.

These studies highlight the changing epidemiologic profile of MRSA in the community and suggest that community-associated MRSA may have acquired 2 properties that are of particular concern: first, it has the ability to colonize effectively, even in the absence of antimicrobial pressure—and potentially via mechanisms that allow them to outcompete other staphylococcal strains in the nares; second, it possesses a variety of virulence factors necessary to cause an array of disease, from simple, uncomplicated furunculosis to deep abscesses, osteomyelitis, necrotizing pneumonia, and sepsis [13–16, 19]. This combination of factors demonstrates the profound adaptability of the staphylococcus.

In light of the increasing frequency of community-associated MRSA infection, new antimicrobials are needed, particularly given the emergence of glycopeptide-resistant strains. Yet, new antimicrobials will remain fingers in the proverbial dike until a more-definitive solution can be found. Can staphylococcal colonization be prevented? If not, can we develop a strategy to prevent invasion and establishment of infection? For the better part of a century, scientists have considered the composition and application of a staphylococcal vaccine, refined over time via an improved understanding of the virulence factors specific to staphylococci. Now, stimulated by the successes that Haemophilus influenzae type b (Hib) vaccine and pneumococcus conjugate vaccine have had in both eliminating the carriage state (a particular success for the conjugate Hib vaccine) and preventing infection, several major pharmaceutical manufacturers have turned their attention to the creation of a staphylococcal vaccine. The appropriate components of such a vaccine (such as capsular polysaccharides, surface-exposed proteins, and/or extracellular toxins) remain an area of active research, but early successes confirm that the vaccine-based approach is a viable undertaking. For example, the persistent reduction of S. aureus bacteremia 40 weeks after vaccination of patients with end-stage renal disease who are undergoing dialysis highlights the potential of a vaccine-based approach to the prevention of staphylococcal disease [20]. Whether such a vaccine should be used universally—or whether it should be targeted to those with risk factors for disease or administered in persons undergoing certain medical procedures that
confer a high risk of staphylococcal wound infections—remains to be determined.

Studies of the ecological patterns of S. aureus colonization in the US population, such as the study conducted by Kuehnert et al., will continue to be important as we attempt to understand the evolution of antimicrobial resistance, the risk factors that predict the carriage state, and the molecular characteristics of circulating strains. Ultimately, it is hoped that such studies will provide a measure of the impact that staphylococcal vaccination has on colonization in the population.

References