MRSA: Deadly Super Bug or Just Another Staph?

David A. Talan, MD

From the Department of Emergency Medicine, Division of Infectious Diseases, David Geffen School of Medicine at UCLA, Olive View–UCLA Medical Center, Sylmar, CA.

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Commenting on an article by Klevens et al1 in the Journal of the American Medical Association that described the incidence of invasive methicillin-resistant Staphylococcus aureus (MRSA) infections, an editorialist estimated that more patients died with invasive MRSA than died because of HIV/AIDS in the United States in 2005.2 Simultaneous reports of MRSA outbreaks among high school athletes and deaths in previously healthy children set off a media frenzy calling MRSA a deadly “super bug.”3 Certainly the emergency department (ED) would seem to be a good place to study the epidemiology of this new disease whose impact has been confused and sensationalized. In this issue of Annals, Pallin et al4 attempt to answer the question of whether MRSA infection is associated with more patients being treated in EDs with skin and soft tissue infections than in the past.

We already know that the ecology of skin and soft tissue infections has changed dramatically. Our ED-based emerging infections surveillance network, EMERGEncy ID NET, reported that MRSA caused 59% of skin and soft tissue infections among 422 adults treated at 11 geographically diverse US EDs in August 2004.5 Almost all isolates were the newly recognized community-associated MRSA USA 300, which contained genes for Panton-Valentine leukocidin toxin and carried staphylococcal cassette chromosome (SCCmec) type IV. Before this millennium, MRSA was rarely found in community-presenting infections. For example, we found no MRSA, either community-associated MRSA or the older health care–associated strain, in a bacteriologic study of 160 cutaneous abscesses among patients presenting to the ED from 1992 to 1994; methicillin-susceptible Staphylococcus aureus was the most common pathogen, found in 50%.6

Although community-associated MRSA now is recognized to cause more of patients’ skin and soft tissue infections, does it cause more people to have skin and soft tissue infections? In other words, has the emergence of community-associated MRSA resulted in an increased burden of disease, not just a change in the strain-specific cause? This is the question that Pallin et al4 attempted to answer.

Epidemiology is about counting, and counting is affected by what, where, and how one counts. With increased awareness of MRSA and recognition that standard antimicrobials used to treat methicillin-susceptible Staphylococcus aureus, such as cephalaxin, lack in vitro activity against this new strain, it is likely that health care providers more frequently obtain cultures for skin and soft tissue infections than in the past. Increased pathogen identification would be expected to lead to more cases attributable to MRSA (ie, evaluation bias). What Pallin et al4 counted was the types of skin and soft tissue infections that one would think would be commonly caused by Staphylococcus aureus (eg, abscesses). Because they did not count just skin and soft tissue infections for which Staphylococcus aureus grew from culture, the results were independent of evaluation bias.

The authors used data from the National Hospital Ambulatory Medical Care Survey (NHAMCS), collected from 1993 to 2005, and report that the population-adjusted number and proportion of visits coded for skin and soft tissue infections increased more than 200%, and there was a significant increase in use of agents typically active against community-associated MRSA.4 To put this in further perspective, during this same period the number of ED visits increased approximately 20%.7

There are a number of potential confounding factors that might suggest that these data do not represent a true increase of the incidence of disease. The analysis did not address the influence of where these cases were counted; is there more disease or just more people coming to EDs and fewer to other settings with this disease? It is possible that as public concern has increased, patients who otherwise might have successfully treated their abscess at home with warm compresses or waited to see their physician now more often rush to the ED for evaluation. Also, some of the factors associated with ED use may also predispose to developing skin and soft tissue infections (eg, lack of insurance and homelessness). A previous NHAMCS study of skin and soft tissue infections found that total ambulatory care visits and those to physician offices did not change between 1992 to 1994 and 2001 to 2003, and visits to hospital outpatient and EDs increased by only 59% and 31%, respectively.8 However, the increase in skin and soft tissue infection cases observed by Pallin et al4 was not gradual, as would be expected if tied to the growing numbers of uninsured, but rather had an inflection point coincident with the emergence of community-associated MRSA around 2000 and extended 2 more years to 2005, during which time the prevalence of community-associated MRSA skin and soft tissue...
infections was also observed to increase, suggesting that their data represent a true increase in disease incidence. In 2005, cellulitis and abscess codes ranked seventh among the top 20 primary diagnosis groups (just ahead of sprains and strains, excluding of the ankle and back), whereas in 2001 this diagnosis group was not even on the list.

A patient history of a “spider bite” is now a well-recognized teleologic explanation for what appears to be a spontaneously developing painful, red, and swollen skin lesion. One of the earliest community-associated MRSA outbreaks was first thought to be spider infestation of a jail, a theory that was investigated and later rejected. With the advent of MRSA mania, how health care providers diagnose skin conditions may have changed. They may be more likely than before to diagnose noninfectious conditions (such as actual insect bites) as skin and soft tissue infections. The authors investigated this possibility and found no concomitant decrease in noninfectious skin-related diagnoses.

NHAMCS data come from medical record reviews by staff who assign International Classification of Diseases, Ninth Revision, Clinical Modification codes according to their interpretation of the physician’s diagnosis. Although NHAMCS has a quality control sample and reports low error rates, the authors did not do their own validation, and data derived by these methods not infrequently challenge face validity. For example, in this report, 48% of skin and soft tissue infection patients had fever, a figure that seems very high. Although the high proportion of patients with fever would suggest that the sample was incomplete and biased toward more severely ill patients, the hospital admission rate was low, 14%, and similar to that found in our investigation.

Community-associated MRSA appears to be relatively efficient at causing infection among individuals who are colonized. A study of military recruits found 28% colonized in their nares initially with methicillin-susceptible S. aureus and 3% with MRSA. At the end of a 10-week training period, skin and soft tissue infections developed in 3% of methicillin-susceptible S. aureus-colonized recruits compared with 38% of MRSA-colonized recruits. Patients with community-associated MRSA skin and soft tissue infections are frequently colonized with this strain.

Fortunately, MRSA colonization rates in the general population at the present time are low. However, it is not surprising to see outbreaks after exposure to an index case among groups with close skin-to-skin contact, such as athletes and family members. These observations support the Pallin et al findings and the idea that skin and soft tissue infections are more common because of the emergence of community-associated MRSA; however, whether or not this pathogen is more invasive and lethal than methicillin-susceptible S. aureus, which it displaced, is another question.

There have been increasing reports of severe infectious syndromes caused by community-associated MRSA. Among the first observations were fatal cases of community-associated MRSA sepsis in children. Community-associated MRSA necrotizing pneumonia, toxic shock syndrome, necrotizing fasciitis, pyomyositis, and osteomyelitis have also been recognized. It has been postulated that Panton-Valentine leukocidin toxin is responsible for increased virulence of community-associated MRSA because genes coding for Panton-Valentine leukocidin are nearly universally present in disease-causing community-associated MRSA strains. Panton-Valentine leukocidin toxin genes are less common in methicillin-susceptible S. aureus (approximately 40% of skin and soft tissue infections strains and more often with invasive infections) and rare in health care–associated MRSA isolates, although recently, novel cytolytic peptides have been implicated. However, all these syndromes have been described before with methicillin-susceptible S. aureus. Certain features, such as the increased proportion and monomicrobial nature of MRSA necrotizing fasciitis and increased reporting of pneumonia deaths in previously healthy children and young adults, suggest that these more severe infections, although rare, may be more common, not just more commonly reported.

Pallin et al observed no increase in the proportion of patients admitted to the hospital during the study period, suggesting that skin and soft tissue infections in the era of community-associated MRSA are no more serious than previously encountered skin and soft tissue infections. Other investigations of hospitalized adults and neonates found no additional cost or mortality associated with community-associated MRSA infections compared with methicillin-susceptible S. aureus infections. Some pediatric hospitals have recently reported significant increases in skin and soft tissue infection admissions. However, these findings may be greatly influenced by changes in awareness, admission practices, and referral patterns. Thus, it is not clear whether community-associated MRSA has a greater tendency to cause more severe infections than methicillin-susceptible S. aureus, and despite increased reporting, the best evidence indicates that community-associated MRSA deaths remain rare. Klevens et al found the population-based mortality of invasive community-associated MRSA infection in 2005 to be 0.5 per 100,000, of which most deaths occurred in the elderly. This is approximately equal to the risk of dying from forces of nature (e.g., lightning, earthquakes, storms, and extremes of temperature).

According to the Pallin et al investigation, compared with rates in 1993, which were observed to be relatively stable until 2000 when corrected for the 2005 census, there are approximately 2 million additional ED visits annually for skin and soft tissue infections in the United States. Although these findings require validation and association is not proof of causality, if community-associated MRSA does result in more people getting skin and soft tissue infections, even if the skin and soft tissue infections they acquire are no more serious than observed in the past because of methicillin-susceptible S. aureus, then this would still result in a tremendously increased burden of disease, with an additional 200,000 to 300,000 patients.
hospitalized each year, even though almost all will be successfully treated. This estimate is consistent with a recent report noting an increase in MRSA-related hospitalizations.\textsuperscript{26}

MRSA is not the next HIV/AIDS. The report by Klevens et al\textsuperscript{1} described the population-based incidence of all types of invasive MRSA infections in 2005. However, health care-associated MRSA and community-associated MRSA need to be distinguished. In that study, health care-associated MRSA accounted for the majority of MRSA cases and an even greater proportion of deaths. The incidence of health care-associated MRSA is related to the use of vascular catheters in chronically ill and hospitalized patients with significant comorbidities who have a relatively limited life expectancy. Patients died with MRSA but not necessarily from MRSA. Health care-associated MRSA-associated mortality cannot be projected on to community-associated MRSA with the implication that community-associated MRSA (or “locker room staph”) infections have greater consequences than HIV/AIDS.

Community-associated MRSA is not a deadly super bug. It is more like an aggressive type of standard honeybee than the Africanized variety; more apt to sting, usually causing a mild and sometimes uncomfortable lesion that is infrequently more serious, but only rarely fatal. Although community-associated MRSA appears to be more efficient at causing infection in healthy individuals than methicillin-susceptible \textit{S. aureus}, particularly among groups with frequent skin-to-skin contact, most infections are uncomplicated skin and soft tissue infections. Patients with community-associated MRSA skin and soft tissue infections should be reassured that they have a good prognosis and many antibiotic treatment options, including several inexpensive oral drugs. Continued surveillance for invasive community-associated MRSA will help determine whether the low rate of more serious community-associated MRSA infections is increasing. Despite limitations, the Pallin et al\textsuperscript{4} findings are compelling and suggest that community-associated MRSA has resulted in a significantly increased burden of disease and that additional attention and resources should be directed to monitor, prevent, and control this emerging problem.

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\textbf{Address for correspondence:} David A. Talan, MD, Department of Emergency Medicine, Olive View–UCLA Medical Center, 14445 Olive View Drive, North Annex, Sylmar, CA 91342; 818-364-3107, fax 818-364-3268; E-mail idntucla.edu.

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