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Invited Editorial

Community-associated methicillin-resistant *Staphylococcus aureus*: It's time to pay attention

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Infectious disease physicians and infection control practitioners are aware of the multitude of diseases and clinical management issues associated with the “hospital” variety of methicillin-resistant *Staphylococcus aureus* (MRSA). Infections due to the hospital-associated MRSA (HA-MRSA) cause increased length of hospitalization, morbidity, mortality, and consequently increased economic burden on hospitals and patients. However, it is not certain if the same level of awareness exists for community-acquired or community-associated MRSA (CA-MRSA). CA-MRSA is phenotypically and genotypically different than HA-MRSA. Unlike HA-MRSA, CA-MRSA is generally susceptible to multiple classes of antibiotics, except for beta-lactams and occasionally erythromycin. It also produces Panton Valentine leukocidin (PVL), a tissue necrosis factor, which is considered one of its main virulence factors.

If the large number of reports on CA-MRSA outbreaks from all types of community settings are any guide, it is safe to conclude that it is indeed an emerging pathogen worldwide.

Primary care physicians are most likely to be the first to see patients with initial CA-MRSA-related infections, such as carbuncles, furuncles, impetigo, and other skin-related diseases. In order to manage these infections with greater clinical efficiency, it will be important to understand its microbiology, prevalence in the community, changing antibiotic resistance patterns, and evolving virulence makeup. Failure to do so may result in a delay in appropriate treatment and possibly unintended creation of resistant strains due to inappropriate use of antibiotics. An inadequate appreciation of new and common CA-MRSA-related syndromes and a failure to identify them in a timely fashion would only add to this serious public health problem in coming years.

The review article published in this special infectious disease issue of *Wisconsin Medical Journal* by Drews et al (p 52) gives a brief overview of CA-MRSA, which includes a discussion about its epidemiology, clinical manifestations and management, and prevention of transmission.¹ In a field where an enormous amount of scientific literature is published, the article by Drews et al succinctly addresses issues that can assist physicians when there is suspicion of CA-MRSA involvement in skin and tissue infections and provides an appropriate management scheme. The authors appropriately

recommend incision and drainage as the first step in treatment for mild cutaneous infections and suggest culturing of any purulent materials in cases of abscesses and furunculosis for precise use of antibiotics.

Why do we need to pay attention to CA-MRSA? It is because the epidemiology of MRSA is changing. It is no longer confined to nosocomial environments and now affects people in the community who do not have the traditional risk factors (diabetic condition and recent surgery, dialysis, antibiotic use, etc.) associated with acquiring MRSA. CA-MRSA is also important because of its emerging virulence, which is not limited to the tissue necrosis factor, PVL, but also to a plethora of virulence and toxin genes identified in them. Enhanced virulence is partly due to the acquisition of new virulence factors through phages that integrate into the CA-MRSA genome.² Plasmids that carry additional antibiotic-resistant genes contribute as well.

One of the relatively unexplored areas of the emerging virulence of CA-MRSA is the zoonotic sources of virulence traits. In one study, it was found that 58% (n=191) of *S aureus* strains recovered from a variety of animals such as cows, goats, sheep, rabbits, chickens, and cats harbored at least 1 of the 16 superantigen genes that were examined.³ Some virulence gene combinations were present

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in 23%-30% of the strains. Since similar gene clusters are observed in human strains, it's easy to see the potential role for zoonotic transmission of MRSA and/or their role as donor of virulence genes to human strains. This is an understudied aspect of emerging CA-MRSA virulence and needs to be explored further. If additional or newer virulence genes that continue to be identified in CA-MRSA strains are any indication, virulence of CA-MRSA is bound to take on dimensions of a more serious nature in the future.

Many staphylococcal enterotoxins function like superantigens by generating excessive immunostimulatory response in hosts. These superantigens act by crosslinking major histocompatibility complex (MHC) II molecules with T cell receptors. The crosslinking triggers a massive release of cytokines such as interleukin (IL)-2, interferon (IFN)- γ , tumor necrosis factor (TNF)- β from T cells and IL-1 β and TNF- α from macrophages that manifest a toxic shocklike-syndrome.⁴

Fortunately, not all commonly identified *S aureus* exotoxin or enterotoxin genes are present in all CA-MRSA strains. The precise role of some of the newly identified toxin genes in disease-specific scenarios is also not yet clear. The severity and invasiveness of CA-MRSA-associated infection is probably dependent on a number of toxins acting synergistically with PVL to mount a more severe attack. It is believed that the syndromes not commonly associated with *S aureus* (eg, necrotizing fasciitis, Waterhouse-Friderichsen syndrome, necrotizing pneumonia, purpura fulminans, and other deep and invasive infections) are due to an increasing virulence arsenal in CA-MRSA.^{2,5-8} Certainly, synergistic effects of the myriad virulence factors and their true pathogenic potential need to be investigated further in both in vitro and animal model studies.

It is important to understand that some clones of community-associated methicillin-susceptible *S aureus* (CA-MSSA) could be as virulent as their corresponding CA-MRSA clones.^{6,8,9} Recent reports of fatal cases of purpura fulminans in Minnesota were due to both toxin-producing CA-MRSA and CA-MSSA strains.⁸ Similarly, fatal cases of sepsis and Waterhouse-Friderichsen syndrome in children in the Chicago area were due to clonally related strains of virulent MSSA and MRSA.⁶ Indeed, the primary virulence of CA-MRSA (or CA-MSSA) manifests from its ability to colonize and invade deeply due to its suite of virulence factors and not from its methicillin resistance gene, *mecA*.

Statewide Surveillance Needed

No state or federally-funded population-based surveillance of MRSA is ongoing in Wisconsin. Some hospitals and outpatient clinics do keep track of MRSA numbers as part of good infection control practices, but this will not be enough to understand the breadth and depth of the CA-MRSA burden in our communities. Therefore, it would appropriate to propose the establishment of a statewide surveillance of MRSA-related infections that would include a minimum of collection and archiving of the isolates, strain typing, and antibiotic susceptibility testing, including the emerging problem of erythromycin inducible resistance to clindamycin. Data from such a project would go a long way in helping us understand the population structure and transmission dynamics of CA-MRSA clones in the state. Study of virulence genes in a temporal collection of isolates will also enable us to study the evolving pathogenicity of CA-MRSA.

A prospective surveillance of MRSA in Wisconsin will only com-

plement the data available from a retrospective molecular epidemiologic study done by Stemper et al of over 600 MRSA strains collected from 77 well-spread health care facilities in central and northern Wisconsin during 1989-1997.^{10,11} That study was possible because of the availability of archived MRSA isolates. One finding of the Stemper et al work was that the hypervirulent midwestern CA-MRSA strain, MW2, which caused 4 pediatric deaths in North Dakota and Minnesota in 1997-1998, had been circulating in the Native American communities in Wisconsin since 1992-1993.^{10,12}

What could we do now? The first step is to have a genuine suspicion of CA-MRSA involvement in skin and soft tissue related infections in low MRSA-risk patients. As Drews et al suggest, quite often incision and drainage of CA-MRSA-associated wounds is all that is needed to take care of the mild cases.¹ For advanced cases, culturing and identification of the pathogen is recommended. A general understanding of the rate of prevalence of CA-MRSA in the community and an antibiogram would be useful for empirical antimicrobial therapy. Availability of prevalence and antibiogram data would only be possible if physicians request culturing, identification, and susceptibility testing of the isolate. Certainly, any empirical antibiotic-based therapy to treat suspected MRSA infections should be guided by the antibiogram of the isolate, as it will help reduce the unwanted development of the antibiotic-resistant strains. Knowledge of the emerging virulent clones in the local community would be useful in deciding about case isolation and its management. This will also help in instituting an appropriate clinical, environmental, and infection control-based management of MRSA. Finally, health care professionals should empha-

size to patients that there is no substitute for good personal and interpersonal hygiene practices at both work and home environments to limit the spread of CA-MRSA. Fortunately, this is very achievable.

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