Understanding the Success of Methicillin-Resistant Staphylococcus aureus Strains Causing Epidemic Disease in the Community

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(See the article by Zhang et al., on pages 195–204.)

Since it was first described in 1961, methicillin-resistant Staphylococcus aureus (MRSA) has been an increasingly important cause of health care–associated infections worldwide [1, 2]. For several decades, MRSA was almost exclusively a health care–associated pathogen and was not considered a significant threat to healthy persons in the general community. During the 1990s, new strains of MRSA emerged and caused community-associated infections on multiple continents [3]. The genetic backgrounds of these strains vary geographically but are distinct from those of MRSA strains that were established as health-care pathogens in the corresponding regions. This situation suggests that the new strains arose independently in different geographic areas via acquisition of methicillin resistance by strains of S. aureus circulating in the community [4]. Despite their disparate genetic backgrounds, MRSA strains that emerged in community settings worldwide share some common characteristics. For example, they tend to be susceptible to most classes of antimicrobial agents other than β-lactams, unlike previously described MRSA strains [3]. This finding can be explained in part by differences in the mobile genetic element termed “staphylococcal cassette chromosome mec” (SCCmec), which contains the methicillin-resistance (mecA) gene. Strains of MRSA that appear to have originated in the community typically carry SCCmec type IV or V, both of which are smaller and carry fewer additional resistance genes than do the SCCmec types most commonly found in MRSA strains classically linked to health-care transmission [5, 6]. Nonetheless, strains of MRSA with SCCmec type IV or V may possess or acquire additional chromosomal or plasmid-associated antimicrobial-resistance elements [7, 8].

Perhaps most important, the newer strains of MRSA are clearly capable of causing infection in previously healthy persons, and they have spread rapidly in the community [9]. Typical of community-associated S. aureus infections, most of these infections are skin and soft-tissue infections (SSTIs) that are not life threatening [10]. However, some of these SSTIs can be locally severe or can progress to invasive infections [11]. Severe and sometimes rapidly fatal infections have also occurred in previously healthy persons without any preceding SSTIs [12]. Community-origin strains have now entered and are being transmitted in health-care settings, with the potential for increased morbidity and mortality from MRSA infections in these settings [13].

One potential explanation for the increased virulence of these strains is the presence of bacteriophage-associated genes for Panton-Valentine leukocidin (PVL). PVL genes are commonly found in MRSA strains linked to community transmission in most parts of the world but are rarely found in strains classically associated with health-care–associated transmission [3]. Because the PVL bacteriophage and SCCmec integrate into distinct sites on the S. aureus chromosome, it is not likely that PVL genes have been transmitted incidentally in association with SCCmec IV or V [14]. This lack of physical proximity on the chromosome makes it even more intriguing that these genetic elements are closely associated in diverse strains of MRSA that emerged in community settings worldwide at approximately the same time.

PVL is an exotoxin belonging to the pore-forming toxin family and has been shown to induce lysis of human leukocytes [15]; however, the relative importance of PVL versus other factors in the...
pathogenicity and epidemicity of *S. aureus* has been debated. The presence of PVL genes in *S. aureus* has been associated with the clinical syndromes of necrotic skin lesions (furuncles) and severe necrotizing pneumonia [16, 17]. PVL genes have also been associated with more severe local disease, greater systemic inflammatory response, and an increased complication rate in children with *S. aureus*-related osteomyelitis [18, 19], as well as with decreased survival in patients with community-acquired *S. aureus*-related pneumonia [16]. The role that PVL plays in MRSA pathogenicity has been addressed in 2 recent studies using animal models [20, 21]. Comparing PVL-positive wild-type strains of MRSA associated with community transmission in the United States versus isogenic PVL-negative strains, Voyich et al. [21] found no difference in lethality in a mouse model of sepsis and no difference in abscess volume or amount of skin necrosis when these strains were injected subcutaneously in mice. Furthermore, both lysis of human neutrophils and pathogen survival after phagocytosis were similar in wild-type and PVL-negative mutant strains. Labandeira-Rey et al. [20] observed minimal lung-tissue damage when a PVL-negative strain of *S. aureus* was used to infect mice in a pneumonia model. However, significant inflammation and tissue necrosis were observed when the same strain, either lysogenized with a PVL-carrying phage or complemented with a plasmid containing the PVL operon under the control of its own promoter, was used. They also found that purified PVL resulted in concentration-dependent lung-tissue damage. Although the results of these 2 studies are seemingly contradictory, it is possible that PVL is primarily important as a virulence factor in certain clinical syndromes, such as pneumonia. Moreover, although both of these studies advance our understanding of the contribution that PVL makes to pathogenicity, the animal models used in these studies may not replicate human infection.

The study by Zhang et al. in this issue of the *Journal* [22] describes the prevalence of PVL and other virulence genes in MRSA USA400 isolates from the Calgary Health Region in Canada and compares the clinical and demographic features of patients colonized or infected with PVL-positive versus PVL-negative isolates. USA400 is a pulsed-field gel-electrophoresis type (PFT) that has been a predominant cause of epidemic community-associated MRSA (CA-MRSA) infections in Western Australia [23], Canada [24, 25], and some areas of the United States [26–28]. It has been associated with both SSTIs and severe invasive infections in previously healthy persons. However, it appears to have been largely replaced by MRSA PFT USA300, as a cause of CA-MRSA infections in most areas of the United States [9, 29], and a similar trend has been described in Canada [30]. Although MRSA USA400 isolates in the United States and Canada have been primarily described as PVL positive [3, 24, 25], PVL-negative USA400 isolates have been a primary cause of CA-MRSA infections in Western Australia [31, 32]. PVL-positive strains of MRSA USA400 have been detected only recently in eastern Australia, in communities where other PVL-positive PFTs are endemic, suggesting horizontal spread of PVL determinants [31].

In contrast to most previous reports from the United States and Canada, in which PVL genes were commonly identified in USA400 isolates [3, 24, 25], Zhang et al. identified PVL genes in only 22.3% of MRSA USA400 isolates from the Calgary Health Region during the period from 2000 through 2005. Although the total number of newly diagnosed cases of MRSA infection or colonization that were identified by Zhang et al. increased each year, the proportion of MRSA isolates that were USA400 peaked at 19.2% in 2001 and remained close to 5% during the remaining years. This finding indicates that other strains contributed to the increasing MRSA rates in this area. Zhang et al. reviewed medical records of 42 inpatients in whom MRSA USA400 was identified in association with a hospital admission. The majority of these isolates were PVL negative, regardless of whether the patient had colonization, mild infection, or severe infection with MRSA; however, there was a trend toward increasing prevalence of PVL genes with increasing severity of disease. The proportion of MRSA USA400 isolates that were PVL positive was similar for cultures of nares, skin lesions, and sterile sites. Zhang et al.’s study, along with previous evidence, such as the results from Western Australia, indicates that PVL is not necessary for epidemic spread of MRSA in the community. It also suggests that PVL is not a primary virulence factor for all forms of infection with MRSA USA400 and demonstrates that PVL-negative strains are capable of causing severe infection. However, because the data were not reported in terms of clinical syndrome, it is not possible to assess the association between PVL-positive strains and certain clinical syndromes, such as pneumonia.

Other investigators have scrutinized the genetic composition of strains of MRSA USA300 and USA400 to identify key virulence and transmissibility factors [7, 30, 33]. Diep et al.’s sequencing of an epidemic strain of USA300 has revealed the presence of arginine catabolic mobile element (ACME) [7]. Those investigators hypothesized that the products of this gene cluster, also found commonly in *S. epidermidis*, enhance the capacity of USA300 strains to survive at low pH on human skin and within phagocytic cells. Unlike the PVL bacteriophage, ACME integrates into the attachment site for SCCmec, suggesting that SCCmec and ACME could be transferred together [7]. Subsequent analysis of a diverse collection of *S. aureus* isolates has indicated that ACME is primarily associated with a subset of USA300 strains that contain SCCmec IVa but that it is also present in some USA100 isolates [34]. In that subsequent analysis, positive isolates included the strain USA300-0114, which is widely disseminated in the United States and has been identified as the cause of multiple outbreaks [9, 35]. ACME was not identified
in USA400 or other PFTs associated with community transmission, which may explain in part why USA300 has become predominant across the United States. However, strains of MRSA that do not contain ACME have also been implicated as causes of community transmission of SSTIs and invasive infections, indicating that other factors contribute to the success of these strains.

It is important to identify the primary factors that contribute to increased virulence and transmissibility of epidemic MRSA strains. This knowledge could lead to improved prevention and treatment strategies, such as vaccines or immunoglobulin products that target key toxins. In addition, host genetic factors that may predispose certain persons to colonization or infection with these strains should be explored, because this could allow targeted delivery of prevention measures. Nonetheless, there is currently no compelling evidence to suggest that, to select therapy for individual patients, MRSA isolates should be tested routinely for the presence of PVL or other toxin genes. Clinical-management decisions regarding patients with suspected or confirmed MRSA infections should be based on clinical syndrome, severity of illness, and patient factors such as comorbidities that could predispose to a poor outcome.

References


