

Community-associated MRSA: a dangerous epidemic



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Although a relatively unspectacular, nonmotile coccus, *Staphylococcus aureus* is a dangerous pathogen and a major public health concern. In addition to being a common food-poisoning agent, it can cause serious skin and soft tissue infections and life-threatening diseases. Furthermore, resistance to multiple antibiotics, most notably to penicillin and methicillin, is common in *S. aureus* and makes treatment especially difficult. However, the biggest current threat from this human pathogen is the pandemic spread of community-associated methicillin-resistant *S. aureus* (CA-MRSA), a crisis affecting many aspects of our social life and second only to HIV/AIDS in scope and importance.

Infections with MRSA have traditionally been limited to healthcare settings and individuals with risk factors for infection. Therefore, it came as quite a shock when MRSA infections unrelated to hospitals were reported in healthy individuals beginning in the late 1990s: first in children, later in professional football players and other sports teams, prisoners and men who have sex with men (MSM). The strains that cause these infections are remarkable because they combine antibiotic resistance with exceptional virulence and transmissibility, a phenomenon unprecedented with *S. aureus*. Moreover, while most *S. aureus* infections were previously thought to originate from nasal colonization, transmission of CA-MRSA includes body-to-body and sexual contacts. Within a very short period of time, CA-MRSA have become not only the most frequent causes of soft- and skin-tissue infections in the community, but are also replacing traditional MRSA strains in hospitals on a large scale.

Where did CA-MRSA come from so suddenly? It is generally agreed that CA-MRSA have evolved from highly pathogenic methicillin-susceptible *S. aureus* (MSSA) strains in the community by the

acquisition of methicillin-resistance elements. Interestingly, all CA-MRSA strains have the same type of resistance element that was probably acquired from *Staphylococcus epidermidis*, indicating an important role for this less virulent skin commensal as a reservoir for the horizontal transmission of genetic factors to *S. aureus*.

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In contrast to this relatively clear theory about the establishment of methicillin resistance, we are far from understanding what causes the exceptional virulence of CA-MRSA. Epidemiological comparisons cannot help much, because all CA-MRSA strains belong to a very limited number of clonally related backgrounds. Nevertheless, Panton-Valentine leukocidin (PVL) was initially declared as the one factor responsible for the extraordinary CA-MRSA virulence. However, it should be noted that PVL is only one of many genes that are associated with CA-MRSA strains. Unfortunately, a preconceived notion that PVL is responsible for the prominence of CA-MRSA rapidly developed, although solid molecular evidence to support a function of PVL in CA-MRSA pathogenesis has never been produced. Contributing to the overall confusion, a recent study – the design of which addressed the toxicity of PVL – was erroneously interpreted as proof for a role of PVL in CA-MRSA pathogenesis [1]. Additionally, an alleged gene-regulatory role of PVL, suggested in the study as an explanation for how PVL confers enhanced virulence, turned out to be incorrect [2]. In contrast, all studies that have used isogenic CA-MRSA *lukS/F-PV* (encoding PVL)-deletion strains, including studies using a series of animal-infection models, have failed to find a role for PVL in virulence, or any influence of the leukotoxin on gene expression [3]. In addition, experiments with human neutrophils, a primary

target of PVL and a key cell type for defense against *S. aureus*, have led to the same conclusion. Thus, all sound scientific data available to date indicate that PVL does not play a significant role in CA-MRSA disease.

It would have been convenient to be able to pinpoint the virulence of the most dangerous *S. aureus* strains to just one factor – which, by the way, would have been in remarkable contrast with everything that we have learned over the years on the multi-facetted causes of *S. aureus* virulence. Unfortunately, we have to accept that the initial PVL euphoria was unfounded, which sets us back to the start. If not PVL, what then? Although unlikely, there is still the chance that a gene with an unknown function, specific to the CA-MRSA genomes, may emerge as the sole cause for this big difference in pathogen success. Furthermore, while the current facts do not suggest a significant role of host factors for skin and soft-tissue infections, the possibility that some individuals may be more susceptible to CA-MRSA infection than others, especially to severe and/or recurrent infections, should not be excluded. For epidemic CA-MRSA, it is much more likely that the key to pathogenesis will be bacterially determined, and more complicated. In that regard, some very interesting recent progress has been made in identifying factors that influence CA-MRSA virulence. Importantly, these recent studies also suggest that we have to think much more in terms of gene and protein expression, and not only gene presence, when trying to elucidate the molecular basis of CA-MRSA pathogenesis.

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Novel cytolytic peptides of *S. aureus* with a pronounced capacity to lyse human neutrophils have recently been identified. These peptides, the *S. aureus* α -type phenol-soluble modulins (PSMs), are expressed at high levels in CA-MRSA, whereas expression is low in standard hospital-associated MRSA [4]. Murine models of bacteremia, skin- and soft-tissue infection and peritonitis established an exceptional role of α -type PSMs in CA-MRSA virulence. Thus, one novel characteristic of CA-MRSA strains might be the strong expression of virulence determinants that interact with host defenses. In addition, CA-MRSA may have acquired genes to improve the establishment of an infection. The most frequently found CA-MRSA strains of

pulsed-field gel electrophoresis type-USA300 harbor a mobile genetic element named arginine catabolic mobile element (ACME) that adds an additional arginine deaminase locus to the *S. aureus* genome [5]. This element might contribute to enhanced colonization due to the role of ammonia production in pH homeostasis on epithelia. In fact, recent results demonstrate a significant difference in the survival of isogenic USA300 ACME-positive and -negative strains in a rabbit infection model, suggesting that the presence of ACME influences pathogen success [6].

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Of note, similar to the CA-MRSA-specific methicillin-resistance element, the ACME element was likely transferred to CA-MRSA from *S. epidermidis*, which is a specialist in skin colonization. Interestingly, the factors that now emerge as potentially crucial for CA-MRSA virulence, specifically acute virulence factors such as lytic toxins and colonization/adhesion factors, traditionally underlie contrasting regulation in *S. aureus* and are thus not commonly expressed concurrently. CA-MRSA strains might have evolved to combine the high-level expression of colonization factors and toxins without adverse effects on growth.

Fortunately, and in contrast with many hospital-associated MRSA strains, CA-MRSA are susceptible to antibiotics other than methicillin and β -lactam antibiotics, leaving antibiotic treatment as an efficient therapy method for CA-MRSA infection up to now. However, the current epidemic also raises the question about therapeutic possibilities. Not only do CA-MRSA strains appear to cause severe and/or fatal infections to an extent not previously seen with *S. aureus*, such as necrotizing fasciitis and the Waterhouse–Friderichsen syndrome, they may also acquire resistance to additional antibiotics in the future. This would lead to a public-health catastrophe as we are running out of effective antibiotics for *S. aureus* and a working vaccine for *S. aureus* infections is not in sight. Owing to the revised notion about the role of PVL, a vaccine against staphylococcal infections will not likely be improved by simply adding PVL to the formula, as some have suggested. Rather, the lesson from the CA-MRSA

epidemic is that of an increased urge to put more resources into drug and vaccine development. As the molecular basis of CA-MRSA virulence turns out to be multifactorial and likely due to the new combination and stronger expression of virulence factors, finding efficient drugs against CA-MRSA will not be substantially different from previous efforts to find anti-*S. aureus* drugs. The CA-MRSA epidemic just shows us that we have to be fast.

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