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REVIEW

The emergence of infections with community-associated methicillin resistant *Staphylococcus aureus*

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Summary Recently there have been reports indicating an increased incidence of MRSA infections, afflicting individuals with no apparent risk factors for hospital acquisition. Patients with community-associated (CA) MRSA are significantly younger and had different distributions of clinical infections compared with HA-MRSA patients. CA-MRSA infections have mostly been associated with staphylococcal strains bearing the SCC*mec* type IV element and PVL genes. These strains are more frequently susceptible to a variety of non-beta-lactam antibiotics. Clinicians must be aware of the wide and, in some cases, unique spectrum of disease caused by CA-MRSA. Continued emergence of MRSA in the community is a public-health problem that warrants increased vigilance in the diagnosis and management of suspected and confirmed staphylococcal infections.

Introduction

As long as we are able to identify the causative micro-organism for infections, *Staphylococcus aureus* has been the most important cause of nosocomial infections.[1,2] In the community, *S. aureus* is currently the most common cause of skin and soft-tissue infections.[1,2] The consequences of infections are severe, especially when there is no effective anti-microbial treatment available. In 1941, the mortality rate of *S. aureus* bacteremia at the Boston City hospital was reported to be 82%.[3] Treatment of serious *S. aureus* infections remains challenging today, and the associated mortality rate of bacteremia is 20–25% despite the availability of highly active anti-microbial agents.[2] At the introduction of benzylpenicillin into chemotherapy in the early 1940s *S. aureus* isolates were fully susceptible and several of the first successes of penicillin therapy were related to the cure of formerly untreatable staphylococcal diseases. But by the mid 1950s the number of *S. aureus* clinical

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isolates showing high-level resistance to penicillin (due to the production of the acquisition of a plasmid-borne penicillinase) increased rapidly, to such an extent that penicillin ceased to be a useful therapeutic agent against staphylococcal infections. Methicillin, originally called celbenine, was the first mechanism-based anti-microbial agent: it is a semisynthetic derivative of penicillin chemically modified to withstand the degradative action of penicillinase. The drug was introduced into therapy in Europe in 1959–1960. However, only 1 year later, the first methicillin-resistant *S aureus* (MRSA) strains were detected,[4] and the first clinical failure by an MRSA strain was described,[5] followed by a report on the first MRSA outbreak in 1963.[6] Since then, MRSA has become the most prevalent pathogen causing hospital infection throughout the world, and MRSA incidence is still increasing in many countries.[7]

Although MRSA has become a worldwide problem, the prevalence of MRSA varies widely between countries. The prevalence is consistently higher in the United States, Japan, and Southern Europe than in other countries; in these countries more than 40% of *S. aureus* infections are caused by MRSA, compared with less than 2% in Scandinavia, The Netherlands, and Switzerland.[8,9] According to recent estimates, the rate of methicillin resistance among *S. aureus* strains causing nosocomial infections in intensive care unit patients has already approached 50% in US healthcare facilities.[10] MRSA infections are associated with increased morbidity, mortality and length of hospital stay, and represents a major burden on healthcare services.[11,12] The antibiotic of choice for treating MRSA infections is the glycopeptide vancomycin, but reports of vancomycin intermediately susceptible *S. aureus* (VISA), first isolated in Japan in 1997, and vancomycin resistant *S. aureus* (VRSA) caused widespread alarm among physicians fearful of an era of untreatable MRSA infections.[13,14]

Since, the first reports the paradigm for MRSA acquisition was that it occured exclusively in the healthcare setting; MRSA was considered a multidrug-resistant pathogen that was strongly associated with infections in individuals with established risk factors associated with healthcare facilities. Despite the growing prevalence of MRSA in hospitals, these healthcare-associated MRSA strains (HA-MRSA) were uncommon in the community. When a case of MRSA infection was identified in the community, a thorough investigation usually revealed a history of recent hospitalization, or the presence of other risk factors. More recently, however, cases of MRSA have been documented among healthy community-dwelling persons without these established risk factors for MRSA acquisition.[15,16] Because these infections are apparently acquired in the community, they are referred to as community-acquired or community-associated MRSA infections (CA-MRSA). Some authors state that the term community-onset MRSA (CO-MRSA), which simply describes the patient's location at the time of identification of MRSA, would be more technically correct, implying that the site of MRSA acquisition is not exactly known.[17] Despite their designation as community-onset MRSA strains, these strains are not restricted to that setting, since CA-MRSA strains have now been found in association with nosocomial infections as well.[18,19]

In 1980, the first community outbreak of MRSA was reported among intravenous drug addicts.[20] One of the earliest and best documented outbreaks is the emergence of CA-MRSA infections in the remote aboriginal communities of the Kimberley in Western Australia.[21–23] CA-MRSA infections were shown to be significantly more common in aboriginals compared to non-aboriginals, and showed a strong association with skin and soft tissue infection. Later, patients in the northern Great Plains of the United States were reported acquiring MRSA in the community.[24] Many more reports have been published since than and today, CA-MRSA has been reported from all around the world.

In this review, we summarize the available information regarding CA-MRSA, emphasizing on the (molecular) epidemiology, clinical presentation, treatment and prevention of carriage and infection with CA-MRSA.

Mechanism of resistance to methicillin

Resistance to penicillin is now widespread in *S. aureus* and may be conferred by the production of a beta-lactamase coded by the *blaZ* gene. Resistance to methicillin confers resistance to all penicillins and cephalosporins and requires the presence of the *mec* A gene, and encodes for the production of PBP 2a.[25] The origin of the *mec* element is not known. The assembly of the several *mec* element structures that have been found may have evolved from multiple hosts, possibly among coagulase-negative staphylococci.[26] The few staphylococci expressing borderline methicillin resistance related to the over-expression of penicillinase are not clinically relevant.[27] PBP 2a is a transpeptidase that catalyzes the formation of cross-bridges in bacterial cell wall peptidoglycan, and has a low affinity for all beta-lactam antibiotics. It takes over