Community-acquired Methicillin Resistant *Staphylococcus aureus* and Endocarditis: An Emerging Pathogen?

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Endocarditis is a potentially life-threatening clinical disease with various manifestations such as fever of unknown origin, embolic phenomena, persistent bacteremia, or complications with cerebral vascular accidents (cerebral embolism). It is challenging to reach a definitive diagnosis of infective endocarditis (IE). Culture-negative endocarditis sometimes delays the proper diagnosis. Modified Duke's criteria are useful for clinical diagnosis, but a positive blood culture still provides the cornerstone for effective antimicrobial treatment.[1] The bacterial etiology of endocarditis consists of both Gram-positive cocci and negative bacilli. Among them, *Staphylococcus aureus* is one of the leading pathogens, especially among intravenous drug users.

S. aureus is a common pathogen in hospital-acquired infections, including respiratory tract infections, surgical wounds, and blood stream infections. Based on antimicrobial susceptibility profiles, *S. aureus* is traditionally classified into methicillin-resistant *S. aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA). The pathogen is further referred to as community-associated (CA) or health care-associated (HA) based on the possible origins of acquiring the microorganism. At the early stage of the antibiotics era, Alexander Fleming discovered penicillin, which was used to treat *S. aureus* infections. In approximately 1 year, penicillin-resistant *S. aureus* emerged. Methicillin was introduced to the market in 1959 for treating *S. aureus* infections, but MRSA was observed shortly after in the early 1960s. Although vancomycin has been approved for use since 1958, the drug is not generally used because of its side effects.[2,3] During the antibiotics era, MRSA emerged and prevailed, and HA-MRSA became the predominant strain in most hospitals, but community infections were still MSSA. In the 1990s, the first CA-MRSA was reported in the United States (US),[3] and the incidence of CA-MRSA has increased in recent years, not only within the US, but also all over the world.

CA-MRSA is distinct from HA-MRSA clinically, bacteriologically, epidemiologically, and genetically. CA-MRSA is primarily associated with healthy individual skin and soft tissue infections.[3,4] However, invasive diseases, including bacteremia, endocarditis, osteomyelitis, and hemorrhagic necrotizing pneumonia, have been reported.[4,5] It is uncommon to find CA-MRSA-related endocarditis among intravenous drug users. The antibiograms of CA-MRSA are easily distinguished from those of HA-MRSA, with bacteria sensitive to clindamycin, trimethoprim/sulfamethoxazole, and rifampin. To genetically differentiate CA-MRSA and HA-MRSA, pulse field gel electrophoresis (PFGE) was the typing method of choice in the late 1990s. Recently, multilocus sequence typing, staphylococcal chromosomal cassette *mec* (SCC*mec*) typing, and staphylococcus protein A (spa) typing have also been used to characterize *S. aureus* isolates.[4] Most of the CA-MRSAs belong to the type IV SCC*mec*, while HA-MRSAs belong to types I to III. Although the PFGE technique has been highly successful in identifying epidemiologically related isolates as well as simultaneously differentiating among unrelated isolates, there has been inconsistency among laboratories in the interpretation of the bending patterns and naming. The potent Panton-Valentine leukocidin (PVL) toxin gene is frequently associated with CA-MRSA and is detected in fewer than 5% of hospital strains. This toxin kills leukocytes by forming pores in the cell membrane and is associated with skin abscesses and rapidly progressive necrotizing pneumonia in both MRSA and MSSA.[3]

Before 2007, reports of cases of CA-MRSA IE were limited to industrialized and developed regions,

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with most originating in the US, and a few case reports in developing countries thereafter.[5,6] A comprehensive literature survey by Millar et al identified 23 cases of CA-MRSA IE, and the authors stressed the characteristics of a documented history of some form of skin lesion, including intravenous drug abuse and native valve involvement with predominately the tricuspid valve.[5] In the December 2009 issue of the *Journal of the Chinese Medical Association*, Chao et al[7] reported 37 episodes of community-acquired endocarditis. They retrospectively reviewed the patients' clinical manifestations and bacteriological characteristics. The most common clinical symptoms were fever and embolic phenomena, with predominately MSSA (76%) infections. Aside from the common bacterial species, the authors reported 4 cases of CA-MRSA IE among intravenous drug users. They had previously reported the first HIV positive patient with CA-MRSA IE in Taiwan.[8] Further molecular analyses, including PFGE and polymerase chain reaction for marker and virulent genes (such as PVL, *Hlg* and *mec*) confirmed the heterogeneous origin. Interestingly, the prototypic CA-MRSA, USA300, which contains the type IV SCC*mec* that enhances its antimicrobial resistance, was not found in this study. Instead, there was a predominance of type III SCC*mec*, which principally resides in the HA-MRSA, indicating a mixing between CA-MRSA and HA-MRSA or outward spreading of the HA-MRSA to the community. It would be more convincing for the authors to combine the multilocus sequence typing and SCC*mec* techniques to confirm the origins of the study isolates. Another toxic gene, PVL, which is associated with abscess formation, was detected in half (2/4) of the CA-MRSA cases. It is interesting that the authors reported combined SCC*mec* type III and PVL positive isolates among IE patients, again indicating a possible mixing of hospital and community origins. Previous reports have indicated that CA-MRSA is invading the hospitals. It is very likely that the vice versa will occur.[3]

The prototypic CA-MRSA type, USA300, was first reported in 2003 by McDougal et al as 1 of the 8 initial MRSA "USA" strain types.[9] The "USA300" strain type carries the genes encoding PVL and SCC*mec* type IV. *S. aureus* isolates of this linage show closely related PFGE banding patterns, indicating a family of isolates with related PFGE patterns. Previous findings of CA-MRSA reported in Taiwan show a predominant SCC*mec* type IV and a novel V_T type.[10]

Treating bacterial endocarditis requires a comprehensive evaluation of the patient's clinical condition and the choice of the best modality, including effective and prolonged antibiotics administration, surgical intervention, or both.[5] Oxacillin-based treatment for MSSA endocarditis has been reported to be superior to vancomycin-based treatment in terms of cure rates and preventing relapse.[11,12] For the treatment of endocarditis caused by MRSA, few choices are left. Traditionally, glycopeptides such as vancomycin are the drugs of choice.[5] However, treatment with vancomycin is significantly associated with relapse.[12] Recently introduced antimicrobial agents for drug resistant *S. aureus* infections such as linezolid, daptomycin, or tigecycline, might play a role.[12] Linezolid is a synthetic bacteriostatic agent and its long-term use is prohibited due to serious adverse drug effects such as bone marrow suppression, optic neuropathy and lactic acidosis. Daptomycin is another new class of semi-synthetic cyclic lipopeptide, which exerts its bactericidal effects through calcium-dependent insertion of the drug into bacterial cell membranes and causing potassium leakage. Several double-blind controlled studies have demonstrated the superiority of daptomycin over vancomycin on right-side MRSA endocarditis.[11] Although there were insufficient data for left-side endocarditis treatment, preliminary results were promising. However, daptomycin is not indicated for the treatment of pulmonary infections due to the inhibitory effect of surfactant. It would be problematic to treat endocarditis complicated with pulmonary septic emboli with daptomycin alone. Surgical intervention with valvular replacement is another arm of treatment, especially when the patient presents with persistent bacteremia, embolic lesions over vital organs, or valvular damage.

In conclusion, the emergence of CA-MRSA IE among intravenous drug users is a cause for concern. Considering the limited effective antimicrobial agents against CA-MRSA IE, it is imperative to cautiously and properly use antibiotics. At the same time, combining close surveillance of the CA-MRSA epidemiological trend and appropriate infectious control tactics, it might be possible to halt the spread of CA-MRSA.

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