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Evolution of community- and healthcare-associated methicillin-resistant *Staphylococcus aureus* ☆

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ABSTRACT

Staphylococcus aureus is a prominent cause of human infections globally. The high prevalence of infections is compounded by antibiotic resistance—a significant problem for treatment. Methicillin-resistant *S. aureus* (MRSA) is endemic in hospitals and healthcare facilities worldwide, and is an increasingly common cause of community-associated bacterial infections in industrialized countries. Although much focus is placed on the role of *S. aureus* as a human pathogen, it is in fact a human commensal organism that has had a relatively long coexistence with the human host. Many *S. aureus* infections can be explained by host susceptibility or other predisposing risk factors. On the other hand, the emergence/re-emergence of successful *S. aureus* clones (referred to as epidemic waves) suggests a rapid bacterial adaption and evolution, which includes the emergence of antibiotic resistance and increased virulence and/or transmissibility. It is within this context that we review our understanding of selected *S. aureus* epidemic waves, and highlight the use of genome sequencing as a means to better understand the evolution of each lineage.

1. Introduction

Staphylococcus aureus is a remarkably successful pathogen. Despite the availability of effective antimicrobial agents to treat *S. aureus* infections, it continues to be a major cause of morbidity and mortality worldwide (Lowy, 1998). Epidemics due to the spread of successful clones continue to be reported from virtually every geographic region (Chambers and DeLeo, 2009). As a result, *S. aureus* has proven to be among the most persistent of pathogens in the healthcare and community setting. In both venues the emergence of antimicrobial resistant strains, especially those that are resistant to methicillin, has been a constant feature. Many factors appear to contribute to the success of *S. aureus* as a pathogen, however its capacity to persist as a commensal, its frequent resistance to multiple antimicrobial agents and its armamentarium of virulence determinants, often with redundant functions, are among the most important (Fluit et al., 2001; Foster, 2005; Otto, 2010).

Methicillin-resistant *S. aureus* (MRSA) are well established in both the healthcare setting and in the community. They are among the most common causes of such nosocomial infections as intravenous catheter associated infections, ventilator associated pneumonias and surgical wound infections in some industrialized countries such as the United States (Klevens et al., 2006; Rosenthal et al., 2012). More recently nosocomial infective endocarditis due to MRSA has become a major concern (Benito et al., 2009). In the community, MRSA are the most common cause of skin and soft tissue infections in the United States (US). Five to ten percent of community-based infections are invasive and potentially life threatening (Fridkin et al., 2005; Klevens et al., 2007; Moran et al., 2006). The emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) as an important pathogen has occurred over the past 15–20 years (Chambers, 2001; David and Daum, 2010; DeLeo et al., 2010). In the United States, a single epidemic clone—USA300, emerged as the predominant isolate accounting for the vast majority of cutaneous infections. These community-based strains appear to have enhanced virulence as well as an enhanced capacity to colonize multiple body sites and to survive on environmental surfaces (DeLeo et al., 2010; Otto, 2010; Uhlemann et al., 2011). As a result they are also more easily spread from person to person.

CA-MRSA infections were initially defined by a set of criteria established by the CDC (Buck et al., 2005). These definitions excluded infections arising from traditional healthcare-associated risks such as residence in a long-term care facility, recent hospitalization or the need for hemodialysis. The infection was further defined as starting in the community and, for hospitalized patients,

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isolation of the clinical isolate within 48 h of admission. Alternatively investigators identified the strains associated with community-based outbreaks and infections based on the molecular characteristics of the isolates. These included the pulsed field gel electrophoresis (PFGE) profile, multilocus sequence type (MLST or ST) or staphylococcal protein A (*spa*) type as well as the staphylococcal chromosomal cassette *mec* (SCC*mec*) type (see below for more details). The SCC*mec* type defines the mobile element that carries the gene responsible for methicillin resistance. A final distinction between the community and healthcare-associated (HA) staphylococci was their antibiotic susceptibility with the healthcare-associated isolates having a broad range of resistance to different antibiotic families while the CA-MRSA isolates, while resistant to methicillin, were susceptible to many other antibiotics (David and Daum, 2010; Miller et al., 2007).

Many of the discriminating features that distinguished the community from the HA strains are no longer valid (David et al., 2008; Miller et al., 2007). Increasingly, the highly successful community-based clones have invaded the healthcare setting and are now successful nosocomial pathogens. In many medical centers they have become a common cause of healthcare-associated bacteremias (Jenkins et al., 2009; Seybold et al., 2006). Along the way they have also become increasingly antibiotic resistant. As a result, PFGE types such as USA300 are now commonly found in both settings.

A unique feature of the repeated worldwide MRSA epidemics has been the discrete number of staphylococcal clones associated with these events (Chambers and DeLeo, 2009). Rather than a diversity of strains causing disease as is seen with methicillin-susceptible *S. aureus*, the MRSA outbreaks have been limited to a relatively small number of staphylococcal lineages. This is true for both the strains classically associated with healthcare, as well as community-based infections. These different staphylococcal lineages have evolved over time, accumulating mutations that alter gene expression and function, and perhaps most importantly, acquiring new genetic elements via horizontal gene exchange (Malachowa and DeLeo, 2010). These new elements have been critical in altering animal species specificity, the nature of invasive infections, and the type antimicrobial resistance associated with the strains. The capacity to acquire novel elements is essential to the success of these clones.

The recent emergence of whole genome sequencing as a technique that can be efficiently and inexpensively performed on a large scale has provided a powerful new tool to explore the evolution of these highly successful clones. Insights have included a better understanding of the contribution of selected genes to virulence, the epidemiology of outbreaks and strain transmission and an understanding of the molecular changes that facilitate the spread of these strains from one animal species to another (DeLeo et al., 2011; Harris et al., 2010; Uhlemann et al., 2012b). In this paper, we review the evolution of three highly successful community and healthcare-associated lineages, clonal complex 30 (CC30), ST239, and ST8 (USA300) (Table 1). These unique clones demonstrate remarkable plasticity in their ability to adapt to environmental changes. The contribution of the new sequencing methods to our understanding of the evolution of these clones is also discussed.

2. Evolution of healthcare-associated MRSA: the CC30 lineage

As a first step toward understanding the evolution of healthcare-associated *S. aureus*, it is important to provide a cursory description of methods used to categorize or type *S. aureus*. Phage-typing was among the first successful methods used to understand *S. aureus* epidemiology and outbreaks (Williams et al., 1953). The method utilizes the differential susceptibility of *S. aureus* clones and isolates to cytolysis by different bacteriophages. Although phage typing was an important advance for early epidemiological studies of *S. aureus*, it has since given way to more precise molecular typing methods. MLST (or ST) is a widely used typing method that indexes variation accumulating slowly over time, and can thus be used to measure evolution over an extended period (Enright et al., 2000; Enright and Spratt, 1999). By comparison, PFGE indexes variation that accumulates rapidly and is highly discriminatory; typing by this method is appropriate for studies of outbreaks or short-term epidemiological studies (Enright and Spratt, 1999). The US Centers for Disease Control and Prevention (CDC) established a national database of PFGE types to monitor the prevalence of MRSA (McDougal et al., 2003). A third widely used typing method, known as *spa* typing, is suitable for analysis of local or widespread *S. aureus* outbreaks (Shopsin et al., 1999). Based on MLST, PFGE, and *spa* typing, there are multiple healthcare-associated MRSA (HA-MRSA) lineages and clones worldwide (Chambers and DeLeo, 2009; Grundmann et al., 2010).

Table 1
Characteristics of selected epidemic *S. aureus* clones

Strain (clonal complex)	SCC*mec* type	Time period	Geographic locations	Characteristics
Phage-type 80/81 (CC30)	NA	1950s–1960s	Australia, New Zealand, North America (United States, Canada), Europe (United Kingdom, Denmark)	HA and CA infections. Notorious for causing fatal infections in neonates.
EMRSA-16 (CC30/ST36)	II	1992–present	Europe (especially the United Kingdom), North America (United States), South America (Brazil)	HA-MRSA. Leading cause of MRSA infections in the United Kingdom in the 1990s and early 2000s. This clone contains inactivating mutations in genes encoding alpha-hemolysin and accessory gene regulator subunit C.
Southwest Pacific Clone (CC30/USA)	IV		Australia, New Zealand, Samoa, Europe (primarily the United Kingdom), Asia, North America, South America	CA-MRSA.
ST239, Brazilian or Hungarian clone, EMRSA-1 (CC8)	III	1980s–present	Asia (includes Saudi Arabia, Russia, China, Korea), Australia, Europe (includes Portugal, Spain, United Kingdom, Germany), North America (United States), South America (Brazil), Southeast Asia (e.g., Malaysia, Thailand, Singapore)	Pandemic clone. A recombinant strain comprised of genomic DNA from CC8 and CC30 lineages.
USA300 (CC8/ST8)	IV	Early 2000s–present	Primarily North America & South America; but also present in Europe	Epidemic CA-MRSA strain. Most prominent cause of community bacterial infections in the United States. Now also a cause of HA-MRSA infection.

NA, not applicable; HA, hospital-associated; CA, community-associated; SSTI, skin and soft tissue infections.

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