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Community-Associated Methicillin-Resistant *Staphylococcus aureus*: It's Not Just in Communities Anymore

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections continue to spread worldwide. From an epidemiologic perspective, the risk factors for infections caused by health care-associated strains of methicillin-resistant *S. aureus* (HA-MRSA) include hospitalization within the last year; having had surgery, received dialysis, or resided in a long-term care facility in the previous year; having a permanent indwelling catheter or percutaneous medical device; or having previously had an MRSA infection. Strains causing infections in patients without risk factors for MRSA are called community-associated MRSA (CA-MRSA). The laboratory definition of CA-MRSA is more of a moving target. While CA-MRSA strands typically are resistant only to oxacillin and macrolides, carry SCCmec type IV, and harbor the genes encoding the Panton-Valentine leukocidin toxin, there are at least four distinct lineages defined by pulsed-field gel electrophoresis that fit this definition. CA-MRSA strains are already moving into a variety of health care institutions and causing infections. Thus, the line between HA- and CA-MRSA is blurring.

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) isolates are a major cause of infections in health care settings worldwide (1,2). Such strains are typically resistant to multiple antimicrobial agents and often become endemic in hospitals, causing line-associated bacteremia, surgical-site infections, and nosocomial pneumonia (3). Recently, MRSA isolates have been recognized as a cause of infections in community settings (4-6). At first, community infections were attributed to strains that had "escaped" from hospitals and found a niche in community reservoirs (7,8). However, more recent studies have shown that community-associated strains of MRSA, or CA-MRSA,

usually have different pulsed-field gel electrophoresis (PFGE) types and toxin profiles from those that cause health care-associated infections (9-13), and they tend to be more susceptible to antimicrobial agents (12-14). If CA-MRSA strains were present only in community settings and were all a single strain type, the label CA-MRSA would make sense. Unfortunately, CA-MRSA strains come from multiple lineages and have already been noted to cause nosocomial infections (15-18). Here, I will explore the many facets of the problem of CA-MRSA.

From an epidemiologic perspective, MRSA isolates fall into one of three categories. First are the isolates that cause infections in patients in health care centers that arise >48 hours after the patient has been admitted to the hospital (the classic National Nosocomial Infections Surveillance [NNIS] definition of a nosocomial infection) (19). These isolates were known formerly as nosocomial MRSA and more recently as health care-associated MRSA (HA-MRSA). The second group of

MRSA isolates constitutes those that do not meet the definition of HA-MRSA (isolated from patients within 48 h of admission to a health care center or in a community setting) yet can be linked to health care institutions, i.e., the patients had risk factors for MRSA infection. The risk factors include hospitalization within the last year; having had surgery, received dialysis, or resided in a long-term care facility in the previous year; having a permanent indwelling catheter

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or percutaneous medical device; or having previously had an MRSA infection (20). At times, simply because these infections did not meet the criteria of a nosocomial infection, they have been classified erroneously as “community-acquired MRSA.” The MRSA isolates in this group often have PFGE patterns that are consistent with classic HA-MRSA isolates. When the HA-MRSA that met the nosocomial definitions and those from patients who have defined risk factors for MRSA are excluded, the third group of MRSA isolates is left. These strains typically cause skin or skin structure infections or necrotizing pneumonia and appear to have a reservoir outside of the hospital. From an epidemiologic point of view, this third group constitutes the true CA-MRSA.

The microbiologic or laboratory definition of CA-MRSA is more of a moving target. Multiple articles in the medical literature have enumerated the characteristics of those MRSA that were defined epidemiologically as CA-MRSA. First, such isolates typically carry staphylococcal cassette chromosome *mec* (SCC*mec*) type IV (21). This is the smallest of the five defined SCC*mec* cassettes and does not contain other resistance determinants. In fact, CA-MRSA isolates are often resistant only to beta-lactam agents and macrolides (3,12,13). CA-MRSA isolates also typically contain the two genes encoding the Panton-Valentine leucocidin toxin (PVL), known as *lukF-PV* and *lukS-PV* (22-24). Thus, the microbiologic definition of CA-MRSA that has emerged in the literature is for isolates of MRSA that carry SCC*mec* type IV, harbor the genes for PVL, and are not multidrug resistant. The problem is that even when limited to MRSA from the United States, there are four very distinct lineages, defined by both PFGE and multilocus sequence typing (MLST) that fit this definition (USA

Table 1. Characteristics of community associated-methicillin-resistant *Staphylococcus aureus* strains

USA type ^a	Multi-locus sequence	Type (agr type) ^b	Other name	Usual toxin profile ^c
USA300	8	I	—	PVL
USA400	1	III	MW2	PVL, SEA, SEB
USA1000	59	IV	Alaska clone	PVL, SEB
USA1100	30	III	Western Pacific Clone/ Samoan Clone	PVL

^aSee reference 24.

^bagr, accessory gene regulator.

^cPVL, Panton-Valentine leukocidin; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B.

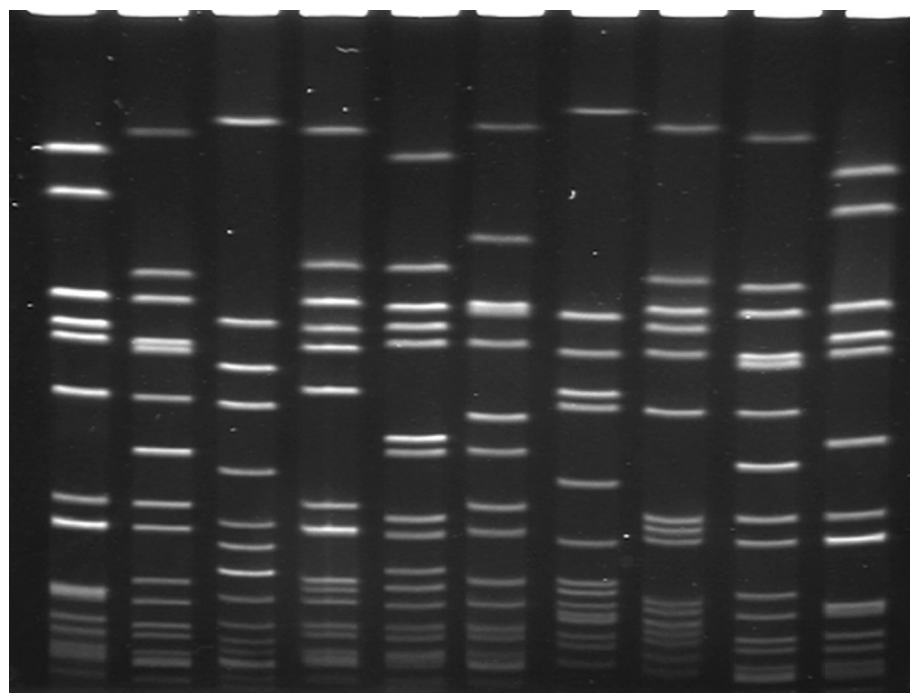


Figure 1. *S. aureus* isolates typed by pulsed-field gel electrophoresis using the restriction endonuclease *Sma*I. USA typed as defined by McDougal et al. (9).

300, MLST sequence type 8 [ST 8]; USA 400, ST 1; USA 1000, ST 59; and USA 1100, ST 30) (9) (see Table 1 and Fig. 1). Which are real CA-MRSA? They all are.

Historical Perspective

CA-MRSA has been a problem in

Australia since the early 1960s (25) and continue to cause problems in both community and health care settings throughout that continent (26). CA-MRSA first appeared in the U.S. in Detroit in the early 1980s among intravenous drug users (27). Those infected did not have risk factors for HA-MRSA. The strain

types of those isolates, however, are unknown. Fast forward to 1999, when four children from Minnesota and North Dakota died of MRSA infections even though they were treated, seemingly appropriately, with first-generation cephalosporins for staphylococcal infections (4). Those infections met the epidemiologic definition of CA-MRSA infection. The isolates were ST 1 and PFGE type USA 400. Within the next few years, CA-MRSA isolates of PFGE type USA 400 were reported to cause infections in Native Americans in several states (28) and among children in daycare centers (5). The genomic DNA sequence of the prototype CA-MRSA isolate from Minnesota, designated MW2, was published by Baba et al. (29). It harbored SCC mec type IV and the PVL genes and featured several pathogenicity islands and bacteriophage-encoded proteins that seemed to make it an ideal candidate for causing infections in community settings. It produced several adherence factors, grew more rapidly in vitro than HA-MRSA isolates, and was resistant to the antimicrobial agents commonly used to treat community *S. aureus* infections, i.e., beta-lactams and macrolides. It was what most investigators considered the prototype CA-MRSA strain.

The CA-MRSA story takes an interesting twist in the year 2000 when the CDC investigated outbreaks of staphylococcal infections among prisoners in correctional facilities in Mississippi, Georgia, and Texas (30,31). Remarkably, among the MRSA isolates recovered from all three correctional facilities, isolates with a common PFGE pattern were apparent, and they were not USA 400 but USA 300, a different lineage belonging to ST 8 (9). ST 8 belongs to clonal complex 8, a lineage of MRSA isolates that includes many of the major HA-MRSA strains from Europe and South America, including the Iberian clone, the Archaic clone, and the Brazilian clone (1,32,33). Those three clones, however, were all multidrug resistant. Like USA 400, USA 300 carries SCC mec type IV and the PVL toxin genes and is typically resistant only to beta-lactams and macrolides, thus fitting the “standard microbiologic definition” of CA-MRSA. Strains of USA 300 were also isolated from children in Tennessee and Texas (34-36), sports participants

(37,38), military recruits (39), and men who have sex with men (40). Did this represent a shift in lineages in CA-MRSA isolates in the U.S.? To answer this, we need to consider additional information from the west coast of the U.S.

Investigators in San Francisco had been following a cohort of homeless people who received care in the city’s clinics but were also frequently admitted to San Francisco General Hospital (41). In San Francisco, even in the early 2000s, the line between HA-MRSA and CA-MRSA was already blurred. Approximately 40% of MRSA strains isolated from hospitalized patients, including those that met the CDC definition of HA-MRSA, carried SCC mec type IV. The PFGE types were myriad but included USA 300 (ST 8), USA 400 (ST 1), and USA 1000 (ST 59). Epidemiologists began to ask the question, “What do you call an MRSA isolate that meets the CDC definitions of a health care-associated infection when it has a classic CA-MRSA strain type?” On the eastern coast of the U.S., an analogous problem arose — dissemination of USA 400 isolates (MW2 type) on a maternity unit of a New York hospital (16). The USA 400/MW2 strain was apparently introduced into the hospital by a patient who developed mastitis as an outpatient. To many, this provided additional data showing that classifying MRSA as either CA-MRSA or HA-MRSA had limited utility.

Current Perspectives

CA-MRSA isolates are clearly gaining the attention of emergency room physicians, as such strains are fast becoming the most common cause of furunculosis observed among patients seeking care at emergency rooms (42,43). CA-MRSA isolates are also causing a significant proportion of skin disease in the urban poor (44). Data indicate that incision and drainage are critical factors in the care of such lesions, perhaps more important than the choice of antimicrobial therapy, if drainage is performed rigorously (42,43). Using the term CA-MRSA would seem to have some merit in alerting physicians to this emerging problem, in part because the term MRSA has connotations of multidrug resistant, hospital-associated organisms

that require treatment with vancomycin, and vancomycin is not the drug of choice for community-associated skin infections.

Nonetheless, the term CA-MRSA still has value in describing this new phenomenon of highly virulent staphylococci that do not respond to beta-lactam agents and that present in patients who have had no recent contact with the health care system. We must be aware, however, that the utility of this term will be short-lived. All four lineages of CA-MRSA, and likely more to come, will soon be appearing as HA-MRSA outside of the San Francisco and New York environs. As they move into the antimicrobial agent-filled health care system, they will, no doubt, expand their antimicrobial-resistance profiles. The difference will be their heightened virulence, bolstered by PVL and perhaps other pathogenicity factors (10, 29). At that point, the terms CA-MRSA and HA-MRSA will lose utility as we struggle to control a new wave of MRSA infections both inside and outside of health care systems.

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