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Impact of community-acquired methicillin-resistant *Staphylococcus aureus* in the hospital setting

ABSTRACT

The epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) is undergoing a transformation as isolates of this historically health care–associated pathogen are reported with increasing frequency in otherwise healthy community-dwelling individuals. This article provides a brief review of the differences between health care–associated and community-acquired MRSA and discusses the potential impact of the changing epidemiology of MRSA on the hospital setting.

KEY POINTS

MRSA infections are no longer limited to health care settings and appear with increasing frequency in healthy, community-dwelling individuals.

The growing presence of a community reservoir for MRSA affects control of the pathogen in the hospital setting, and gradual expansion of this reservoir can lead to failure of traditional control measures.

Strains of community-acquired MRSA have already entered the health care setting, caused nosocomial infections, and, in some cases, displaced health care–associated strains.

Reconsideration of current control strategies for MRSA in hospitals is necessary in light of the emergence of community-acquired MRSA as a clinically significant pathogen.

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Methicillin-resistant strains of *Staphylococcus aureus* (MRSA) were first described in the early 1960s, shortly after the introduction of semisynthetic penicillins. The subsequent emergence of MRSA has historically been associated with the health care setting, and this pathogen is now a common cause of nosocomial infections generally resistant to multiple antimicrobial drugs. In fact, more than half of the infections caused by *S aureus* in intensive care units and more than 40% of *S aureus* infections outside of intensive care units in US hospitals are now attributable to MRSA,[1] which causes a variety of bloodstream, respiratory/urinary tract, and skin and soft-tissue infections.

Outside of the health care setting, MRSA infections are increasingly being reported in otherwise healthy, community-dwelling individuals without health care–associated risk factors for infection.[2–5] The incidence of so-called community-associated or community-acquired MRSA (CA-MRSA) infections was first reported in the early 1980s[6,7] and has since been on the rise. Outbreaks have been reported in specific geographic locations[4,8–12] and in several well-defined and characteristically "closed" populations, including Alaskan natives, American Indians, children, participants in team sports, military personnel, and correctional facility inmates.[13–19] CA-MRSA is now the predominant cause of community-associated skin infections.[20]

DEFINING 'COMMUNITY'

A survey of the available literature reveals a lack of a standard classification system to define CA-MRSA. Related terms are often used interchangeably, and different authors use varying degrees of specificity when describing "community." This variability in nomenclature and definition has been previously noted,[4] and the need for a clearer, better-delineated classification system for MRSA infections has recently been highlighted.[21,22] The currently used system for classification of MRSA infections **(Figure 1)** will likely under-

go future revision as we gain greater insight into the changing epidemiology of this disease.

Classification guided by time of isolation, risk factors

Two primary factors currently used in the categorization of MRSA infections are *time of infection isolation* and the presence or absence of *MRSA-related risk factors* **(Figure 1)**.[4,23]

Generally, MRSA strains isolated after 48 to 72 hours of admission to a health care facility, or those present at the time of admission in recently discharged patients or residents of long-term care facilities, are interchangeably referred to as *nosocomial*, *hospital-acquired*, *hospital-associated*, or *health care–associated* MRSA (HA-MRSA).

Terms used to describe cases of infection not involving a traditional health care setting (CA-MRSA) include *community-acquired*, *community-associated*, and *community-onset*. Of these, *community-onset* is generally used to refer to infections that begin outside of the health care setting (regardless of the presence of risk factors for MRSA), while infections occurring in a community setting in the absence of risk factors for MRSA are considered by some to represent cases of "true" CA-MRSA.[24]

Characteristics of community-acquired MRSA

Current criteria set forth by the Centers for Disease Control and Prevention[25] for distinguishing CA-MRSA from HA-MRSA state that patients with CA-MRSA infection tend to have all of the following characteristics:

- Diagnosis of MRSA made in the outpatient setting or on the basis of a positive culture for MRSA within 48 hours after hospital admission
- No medical history of MRSA infection or colonization
- No history in the preceding year of hospitalization, dialysis, surgery, or admission to a nursing home, skilled nursing facility, or hospice
- No permanent indwelling catheters or medical devices that pass through the skin into the body.

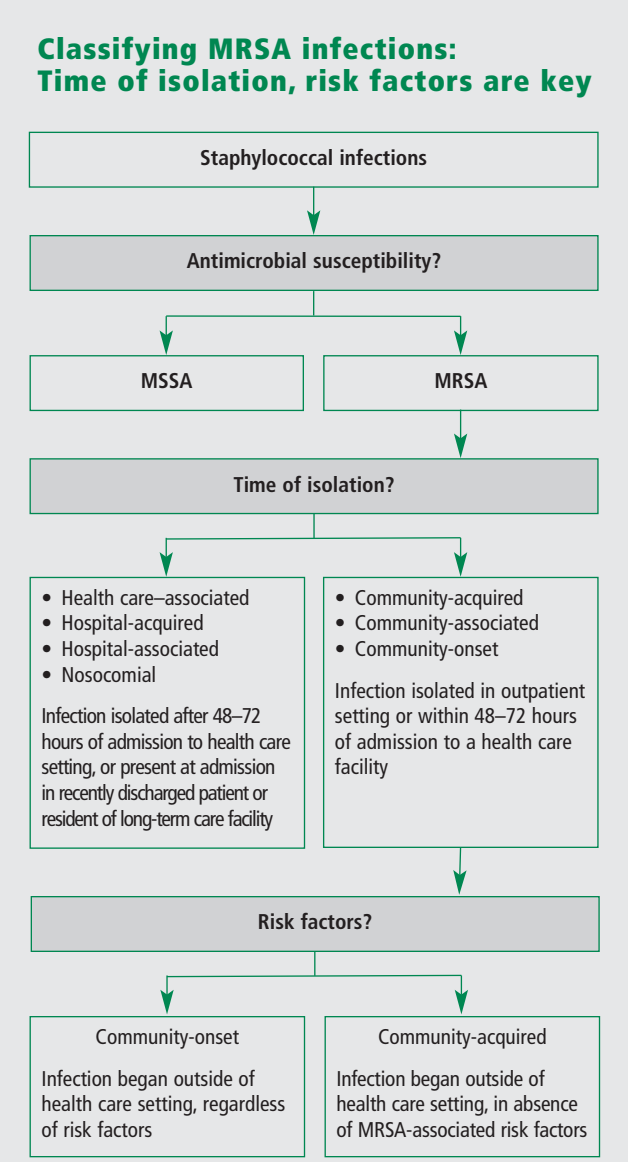

FIGURE 1. Generalized classification of infections caused by methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) strains of *Staphylococcus aureus*. Based on data in references 4 and 23.

HOW COMMUNITY-ACQUIRED MRSA DIFFERS FROM HEALTH CARE–ASSOCIATED STRAINS

Community-acquired strains of MRSA are distinct from HA-MRSA strains from genotypic, phenotypic, and epidemiologic perspectives.[26–29]

At a genetic level, CA-MRSA is more similar to methicillin-susceptible *S aureus* (MSSA) than to traditional MRSA,[28] and its emergence appears to be due to the acquisition, by an MSSA strain, of the staphylococcal cassette chromosome (SCC) carrying *mec*A, the gene encoding the methicillin-resistant penicillin-binding protein.[30] Strains of CA-MRSA are more frequently susceptible to a variety of non–beta-lactam antibiotics. Although a small percentage contain SCC*mec* type V, these strains predominantly carry SCC*mec* type IV, which is smaller in size than the gene cassette found in most strains of HA-MRSA (types I, II, and III). This observed differential in SCC size may allow for more efficient transfer of resistance among different bacteria,[13] a factor that may be relevant in the alarmingly rapid emergence of CA-MRSA.

TABLE 1
Microbial profiles of health care–associated and community-acquired strains of MRSA

Strain	SCC*mec* gene	Antibiotic resistance	PFGE type	Toxins	PVL genes	Infection spectrum
HA-MRSA	Types I, II, and III	Multidrug-resistant	USA 100	Fewer	Rare	Bloodstream, respiratory tract, urinary tract infections
CA-MRSA	Types IV and V	Resistance typically limited to beta-lactams and erythromycin, although multidrug resistance can occur	USA 300	More	Common	*Commonly:* skin and soft-tissue infections *Occasionally:* necrotizing fasciitis, necrotizing pneumonia

HA-MRSA = health care–associated methicillin-resistant *Staphylococcus aureus*
CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*
SCC*mec* = staphylococcal cassette chromosome *mec*
PFGE = pulsed-field gel electrophoresis
PVL = Panton-Valentine leukocidin

The potential of CA-MRSA strains to cause serious illness is further underscored by their production of a relatively greater number of recognized staphylococcal virulence factors compared with HA-MRSA. Most notably, CA-MRSA strains frequently carry the Panton-Valentine leukocidin genes that produce cytotoxins associated with tissue necrosis and leukocyte destruction, although controversy remains concerning the definitive role of these genes in CA-MRSA.[31] Based on pulsed-field gel electrophoresis, almost all CA-MRSA strains are from a single clone (USA 300).[20,34]

These and other characteristics of both types of MRSA are contrasted in **Table 1**.

EMERGENCE OF COMMUNITY-ACQUIRED MRSA: EVIDENCE AND IMPLICATIONS

Reports of CA-MRSA prevalence vary widely among different studies.[4] This is due, in part, to the lack of a standard definition for CA-MRSA and differences among studies in patient setting and associated risk factors.[23,24] The overall prevalence CA-MRSA appears to be increasing.[21,24,32] In some recent studies, the percentage of community-associated *S aureus* that was resistant to methicillin has exceeded 50%.[33,34]

In one study conducted from October 2003 through February 2004 in Oakland, California, 137 emergency department patients with skin and soft-tissue infections were evaluated for CA-MRSA.[33] Of 119 infection-site cultures obtained, 79 (66.4%) grew *S aureus*, of which 61 (77.2%) were methicillin-resistant. Seventy-six percent of these cases met the clinical definition of CA-MRSA, with 99% of the MRSA strains positive for the SCC*mec* IV allele and 94% positive for Panton-Valentine leukocidin genes.

A more recent study found that MRSA was the cause of 59% of skin abscesses among adults presenting to 11 emergency departments across the United States.[20] The USA 300 strain accounted for 97% of the MRSA isolates that were typed.[20]

Community-acquired strains enter the hospital setting

Strains associated with the community setting have been introduced into hospitals in recent years, resulting in nosocomial infections and, in some cases, displacement of health care–associated strains.[5,35–39] In a 2003 meta-analysis of 27 retrospective and 5 prospective studies, CA-MRSA was found to account for 30.2% and 37.3%, respectively, of MRSA isolates from hospitalized patients.[4] While a large majority (85%) of these patients had one or more health care–associated risk factors for MRSA,[4] the remainder represent cases of "true" CA-MRSA. In this same analysis, the pooled colonization rate for MRSA among community-dwelling individuals was found to be 1.3%, with an even lower rate (0.2%) among those without *any* health care contacts. While these findings show a comparatively higher prevalence of CA-MRSA strains in the health care setting, molecular evidence shows the emergence of MRSA strains in the community to be independent of a hospital reservoir.[5,35–39]

In a more recent study that included 319 patients with CA-MRSA infection who presented to one of several rural hospitals in Idaho or Utah, 75% of these patients did not have any identified risk factor for MRSA.[40] Another study from a single medical center in Atlanta evaluated 384 persons with microbiologi-

cally confirmed community-onset *S aureus* skin infections, of which 72% were due to MRSA.[34] Among all *S aureus* isolates, 63% were considered to be community-acquired and 99% were the USA 300 clone. This rate of CA-MRSA represents a much higher percentage than reported in the meta-analysis and suggests that the actual incidence of CA-MRSA is increasing.

A threat to resistance control measures

The emergence of CA-MRSA and the growing presence of a community reservoir for methicillin-resistant strains threatens future control of antimicrobial resistance in the health care setting. Since CA-MRSA may now significantly contribute to nosocomial dissemination of MRSA within hospitals, the distinction between CA-MRSA and HA-MRSA within the hospital setting has become blurred. The migration of resistant strains from the community reservoir into hospitals is a potentially troubling development, and gradual increases in this community reservoir can be expected to lead to failure of traditional control measures. Recognition and isolation of symptomatic individuals, along with contact-tracing and quarantining, are two basic measures of control[41] that cannot be used effectively in a community setting. Isolation of infected individuals and carriers is much less manageable in a community setting compared with the relatively closed and controlled environment of the hospital. For this reason, the presence of a community reservoir from which resistant strains can recurrently be transmitted into the health care setting is a significant and growing challenge for the control of MRSA.

Differing spectrums of disease

It is important that clinicians be aware of the spectrum of disease caused by CA-MRSA, which differs from that of HA-MRSA in distribution and pattern of infection. Patients infected with CA-MRSA tend to be significantly younger than those infected with traditional strains of MRSA.[32] Unlike traditional MRSA strains, which often are isolated from the bloodstream and the respiratory and urinary tracts, CA-MRSA strains are typically found on skin and in soft tissue and occur in settings that involve crowding, contact, and compromised hygiene.[4] Interestingly, because skin infections due to CA-MRSA often have a necrotic center, many have been mistaken for spider bites.

Among 1,647 patients with CA-MRSA in a population-based surveillance study in Maryland, Georgia, and Minnesota, 77% had skin or soft-tissue infections, 10% had wound infections, 5% had respiratory tract infections (3% sinusitis, 2% pneumonia), and 4% had urinary tract infections.[42] A separate study that compared HA-MRSA and CA-MRSA infections in Minnesota found that they broke down by infection type as follows[43]:

HA-MRSA	CA-MRSA
Skin and soft tissue, 36%	Skin and soft tissue, 74%
Respiratory tract, 22%	Otitis media, 7%
Urinary tract, 20%	Respiratory tract, 6%
Bloodstream, 9%	Bloodstream, 4%
Others, 13%	Others, 9%

Stevenson et al reported similar distributions by site of infection in their study of HA-MRSA and CA-MRSA in rural communities in Idaho and Utah.[40]

Differing resistance patterns

Another difference between the two strains is that HA-MRSA is usually resistant to multiple classes of antimicrobials, whereas the usual pattern for CA-MRSA is resistance to the beta-lactams and erythromycin but susceptibility to other drugs tested. However, as CA-MRSA strains may disseminate within the hospital, it is possible that they may develop additional antimicrobial resistance. CA-MRSA strains are often susceptible to clindamycin, but the emergence of resistance during therapy has been reported, especially among erythromycin-resistant strains. Thus, an erythromycin-induction test (D-test) should be performed on such isolates to determine the presence of in vitro inducible resistance. Although these infections are generally mild in nature, more serious infections leading to hospitalization or death have occasionally been described, including bacteremia, necrotizing fasciitis, and necrotizing pneumonia.[2,10,44–48]

FUTURE NEEDS: VIGILANCE, MORE STUDIES, REVISED CONTROL MEASURES

The continuing emergence of CA-MRSA as a nosocomial pathogen is a serious public health problem that warrants increased vigilance to ensure correct diagnosis and proper management of suspected staphylococcal infections. Overall, infection with resistant strains of *S aureus* has been shown to carry a worse prognosis than infection with methicillin-sensitive strains of the pathogen, and hospitalized patients with MRSA face longer hospital stays, higher inpatient costs, and a higher mortality risk than do patients with MSSA.[49–52] This burden can only be expected to increase in the presence of a community reservoir for methicillin-resistant strains. The possibility for accumulation of added resistance patterns among CA-MRSA strains will further increase this

burden and have a significant negative impact on the hospital setting.

Our current understanding of the epidemiology of CA-MRSA is incomplete, and further studies are needed to better define optimal control measures.[53] Overall, the changing epidemiology of MRSA will require implementation of a revised set of control measures in both the hospital and community settings.

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