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Epidemiology, clinical manifestations, and treatment options for skin and soft tissue infection caused by community-acquired methicillin-resistant *Staphylococcus aureus*

Jason E. Farley, PhD, MPH, ARNP [Clinical Instructor; Adult Nurse Practitioner][1,2]

[1] *School of Nursing, Johns Hopkins University, Baltimore, Maryland* [2] *Division of Infectious Disease, School of Medicine, Johns Hopkins University, Baltimore, Maryland*

Abstract

Purpose: This article reviews the evolving epidemiology of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and the appropriate outpatient management of CA-MRSA skin and soft tissue infection. Further, the paper will provide the basis upon which an individualized patient educational plan may be developed.

Data Sources: To complete this review, a search of English language publications was conducted through Medline and CINAHL databases (1966–2006).

Conclusions: The epidemiology of CA-MRSA is becoming increasingly complex. Research that addresses the impact of this organism in high-risk populations and within families is urgently needed.

Implications for Practice: Nurse practitioners must remain informed of the epidemiology of common and emerging drug-resistant organisms in their patient populations.

Keywords

MRSA; community-acquired; *Staphylococcus aureus*

Introduction

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as an organism distinguishable from traditional healthcare-associated MRSA, primarily at the molecular level. Multiple investigations have reported the presence of the organism in diverse populations within the United States, including homeless persons (Charlebois et al., 2002), professional football players and college athletic teams (Centers for Disease Control and Prevention [CDC], 2003a; Romano, Lu, & Holtom, 2006), children (Adcock, Pastor, Medley, Patterson, & Murphy, 1998; Herold et al., 1998), ethnically closed communities (Baggett et al., 2003; Groom et al., 2001), nursing homes and long-term rehabilitation centers (Borer et al., 2002; Muder et al., 1991), households with greater than three inhabitants (Bratu et al.,

Correspondence Jason E. Farley, PhD, MPH, CRNP, Johns Hopkins University, School of Nursing, 600 North Wolfe Street, Carnegie 346, Baltimore, MD 21287. Tel: 410-614-5458 (office), 410-254-1964 (home); Fax: 410-614-0888; E-mail: E-mail: jfarley@son.jhmi.edu.

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2006), and among correctional populations (CDC, 2001, 2003b, 2003c; Pan et al., 2003). Case reports have demonstrated CA-MRSA infection as a fatal postinfluenza complication (Adam, McGeer, & Simor, 2007; Frazee, Salz, Lambert, & Perdreau-Remington, 2005). To complicate matters, CAMRSA has returned to the healthcare setting as a source of hospital-acquired infection among postpartum women (Saiman et al., 2003) and newborns (Bratu et al., 2005).

Infection with CA-MRSA is most commonly associated with skin and soft tissue infection (SSTI) (Eady & Cove, 2003); two case reports, however, have identified CAMRSA as a monomicrobial agent in necrotizing fasciitis; the first occurred in an adult patient (Miller et al., 2005) and more recently in a previously healthy neonate (Dehority et al., 2006). The organism has also been implicated in cases of necrotizing pneumonia (Francis et al., 2005; Obed et al., 2006) and severe sepsis syndrome (Mongkolrattanothai, Boyle, Kahana, & Daum, 2003) with evidence of invasive infections occurring throughout the country (Klevens et al., 2007), stressing the importance of clinical recognition and prompt, accurate treatment.

As this emerging infection continues to appear in new, previously unaffected populations, nurse practitioners (NPs) must be aware of the signs, symptoms, and risk factors of this potentially deadly infection. This article reviews the evolving epidemiology of CA-MRSA and the appropriate outpatient management of CA-MRSA– associated SSTI. To complete this review, a search of English language publications was conducted through Medline and CINAHL databases (1966–2006). Each search consisted of specific keywords or combinations of key words and included “MRSA,” “methicillin-resistant *Staphylococcus aureus*,” “community-acquired MRSA,” “community-associated MRSA,” and “panton–valentine leukocidin.”

Clinical microbiology

Staphylococcus aureus is a gram-positive organism that may exist as a resident or transient flora on the human host. The organism may infect or colonize the host with potential clinical and/or epidemiologic repercussions. SSTIs are among the most common clinical presentation and may manifest as cellulitis, boils, and furuncles (abscesses), which, if prolonged, may lead to osteomyelitis or the seemingly rare case of necrotizing fasciitis (Miller et al., 2005). *S. aureus* is also a possible causative organism in endocarditis, pneumonia, and bacteremia. In addition to the direct effects of the infecting organism, *S. aureus* produces a variety of toxins that result in indirect actions such as staphylococcal scalded skin syndrome or toxic shock syndrome (Lowy, 1998). Hospital-associated MRSA infection produces similar clinical conditions but requires more aggressive antimicrobial therapy and is associated with increased mortality among hospitalized patients (Klevens et al., 2006).

CA-MRSA was first implicated as a virulent pathogen after it was identified as the causative organism in the death of four previously healthy children in Minnesota and North Dakota in 1999 (CDC, 1999). The CA-MRSA virulence factor initially believed to facilitate the increase in morbidity and mortality is the Panton–Valentine Leukocidine (PVL) toxin. This toxin's genetic and biological activities have been well characterized (Prevost et al., 1995). In brief, the toxin produces destruction of leuko-cytes and leads to tissue necrosis (Lina et al., 1999). This is proposed as the main pathophysiologic mechanism associated with the excessive exudates seen in CA-MRSA positive SSTIs. A recent analysis by Voyich et al. (2006) calls into question the link between PVL and virulence noting similar pathogenic effects in mouse models infected with MRSA with and without the PVL gene, suggesting that PVL is not a major virulence factor in CA-MRSA (Voyich et al.). Further study is clearly needed to uncover the underlying pathophysiology.

The evolution of antibiotic resistance in MRSA

With the widespread introduction of penicillin (PCN) into the worldwide population during and shortly after World War II, penicillinase, also known as β-lactamase, producing strains of *S. aureus* began to emerge within hospitalized patients (Barber, 1948). β-lactamase is an enzyme produced by the *bla* gene and confers the ability to block the binding of PCN to cell wall precursors, thereby preventing the interruption of bacterial cell wall synthesis by PCN. This phenomenon necessitated the development of β-lactamase-resistant antibiotics, including methicillin, nafcillin, and the cephalosporins in the late 1950s (Wright, 1999). By 1961, the first isolates of MRSA were described (Barrett, McGehee, & Finland, 1968) and MRSA quickly developed into a healthcare-associated organism throughout the world.

In the United States, the upward trend of hospital-acquired MRSA increased dramatically through the 1980s and 1990s with estimates as high as 50% among hospitalized patients by 2000 (Chambers, 2001; Crossley, Landesman, & Zaske, 1979; Peacock, Marsik, & Wenzel, 1980). The evolution of MRSA into a community-associated organism in persons with healthcare-associated (i.e., nosocomial) risk factors was initially described in the early 1980s among a population of injection drug users (Saravolatz, Markowitz, Arking, Pohlod, & Fisher, 1982a; Saravolatz, Pohlod, & Arking, 1982b). Healthcare-associated MRSA moved freely between the community and the hospital, often necessitating enhanced infection control screening of newly admitted patients.

To date, no further recommendations or changes have been made to clarify admission surveillance activities in persons without healthcare-associated risk factors; therefore, the onus is on the individual healthcare provider or institution to understand the clinical microbiology of the organisms as well as risk for colonization or infection. Additionally, the Infectious Disease Society of America (IDSA) has published guidelines detailing possible microbial causes and general management of SSTI (IDSA, 2005); however, the current guideline does not address the evolving epidemiology of CA-MRSA.

Mechanisms of antibiotic resistance in CA-MRSA

The mechanisms of antibiotic resistance in healthcare-associated MRSA and CA-MRSA are identical. Resistance is either acquired from other organisms or is a result of internal chromosomal mutation in response to antimicrobial pressures. Acquired resistance in MRSA isolates occurs through the acquisition of a gene called *mec*. The *mec* gene facilitates production of “penicillin-binding protein 2a” (PBP2a) and is carried on a mobile genetic element, staphylococcal cassette chromosome (SCC*mec*). PBP2a strengthens the cell wall and increases resistance to β-lactam antibiotics by blocking the β-lactam binding site (Ito et al., 2001). At present, five SCC*mec* types, delineated I–V, have been assigned by DNA sequencing. The most common hospital-acquired MRSA organisms contain SCC*mec* I, II, and III, genetic elements that encode resistance to several antibiotics in addition to β-lactams. SCC*mec* type IV and V are smaller (15 kb), lack high-level resistance to multiple antibiotics, and are considered more easily transferred to other *S. aureus* (Daum et al., 2002). Type IV is currently found in CA-MRSA and predominates in individuals without hospital-associated risk factors. To complicate matters, there are recent reports of CA-MRSA infection causing outbreaks within hospital settings. Table 1 compares the molecular characteristics of nosocomial MRSA to CA-MRSA (Baba et al., 2002; Daum et al., 2002; Naimi et al., 2001).

SCC*mec* type IV has greater sensitivity to non-β-lactam antimicrobial agents (Baba et al., 2002) but are considered highly virulent because of the high prevalence of PVL-producing strains. PVL has, to date, been found predominantly in SCC*mec* type IV and V CA-MRSA and, as previously noted, is clinically responsible for the excessive amount of leukocyte destruction leading to large amounts of pus. In settings where CA-MRSA is suspected, an

understanding of the molecular epidemiology is required to further assist the clinician to uncover virulence factors and identify the source of outbreaks within healthcare, correctional, or long-term care facilities. This knowledge will assist the clinician in prevention planning.

Risk factors for hospital-acquired and CA-MRSA

Risk factors for nosocomial MRSA infection have been well established and include recent hospitalization or surgery, residence in a long-term care facility, dialysis, prolonged antimicrobials, and indwelling percutaneous medical devices or catheters (Brumfitt & Hamilton-Miller, 1989; Thompson, Cabezudo, & Wenzel, 1982). In comparison, a recent meta-analysis on CA-MRSA found that individuals without recent healthcare contact were 90% less likely to have MRSA than individuals who had recent healthcare contact (i.e., no hospitalization of self or family and no outpatient appointments) (relative risk [RR], 0.10; 95% confidence interval [CI], 0.05–0.21) (Salgado, Farr, & Calfee, 2003).

The epidemiology of CA-MRSA has not been fully elucidated; however, several important risk factors for the development of CA-MRSA have been described in the literature. Demographically, younger, non-White adults have a higher prevalence of CA-MRSA as compared to older White adults, who have a higher prevalence of nosocomial MRSA (Naimi et al., 2001; Salgado et al., 2003; Thompson et al., 1982). The rationale for this apparent discrepancy is not known. Additional risk factors for healthcare-associated MRSA include a history of hospitalization within the past 12–24 months (Warshawsky et al., 2000), previous antimicrobial utilization (Graffunder & Venezia, 2002; Monnet et al., 2004), and intravenous drug use (Charlebois et al., 2002). According to a recent abstract presented at the 16th International AIDS Conference, HIV-positive individuals are 18 times more likely to become infected with CA-MRSA than the general population (Crum-Cianfione, 7 A.D.). Additional CA-MRSA risk factors are summarized in Table 2 (Bratu et al., 2006; Cook, Furuya, Larson, Vasquez, & Lowy, 2007; Johnston et al., 2006; Miller et al., 2007; Stemper et al., 2006).

Studies on the prevalence of MRSA infection among closed or semiclosed communities are limited; however, one study among a rural American Indian population noted an increase in MRSA from 4% in 1989 to 57% in 1997 among clinical isolates (Groom et al., 2001). This study examined medical records to determine location of onset but was unable to determine risk factors for individuals with CA-MRSA because of the retrospective cohort study design. A study among naval military personnel suggested that close-quarter environments increase exposure and contributes to the transmission of CA-MRSA (LaMar, Carr, Zinderman, & McDonald, 2003).

MRSA colonization

Colonization is the presence of an organism on the body without clinical signs and symptoms of infection (i.e., fevers, redness, swelling, and exudate). Large population-based samples have shown that the rate of MRSA colonization in the community ranges from 0.26% to 9.2%, depending upon population characteristics of the sample (Creech, Kernodle, Alsentzer, Wilson, & Edwards, 2005; Graham, Lin, & Larson, 2006; LaMar et al., 2003; Shopsin et al., 2000). In a recent publication, investigators examined data from the National Health and Nutrition Examination Survey for 2001–2002 and noted a methicillin-sensitive *S. aureus* prevalence of 31.6%, with MRSA colonization noted in 0.84% of participants (Graham et al.). These studies did not distinguish healthcare-associated MRSA from CA-MRSA.

After colonization, studies have shown that MRSA may persist on the body for months and even years (Sanford, Widmer, Bale, Jones, & Wenzel, 1994; Scanvic et al., 2001). Risk factors for prolonged colonization include breaks in skin, presence at greater than or equal to two body sites, and previous history of fluoroquinolone use (Sanford et al.; Scanvic et al., 2001). Calfee

et al. (2003) demonstrated persons living in a household with individuals who have MRSA colonization or infection were 7.5 times more likely to be colonized with MRSA than persons without household contact (Calfee et al.).

Data are emerging suggesting that nasal colonization may be less important in cases of CA-MRSA skin infection than originally hypothesized. A recent study by Zafar and colleagues (2007) noted significant variations in CAMRSA within households. In their study only 50% of household contacts with noted MRSA colonization shared the same strain as the household member with CA-MRSA infection. This identifies the need for the clinician to consider the potential for exposure within the home environments as well as external sources. Risk reduction education must be tailored to the individual based on such evaluations.

Laboratory diagnosis of SSTI secondary to CA-MRSA

As previously noted, the IDSA has published evidence-based guidelines for the management of SSTI. These guidelines encourage the clinician to consider local trends and the individual's epidemiologic profile but fall short of providing recommendations for appropriate antimicrobial therapy and wound care for SSTI caused by CA-MRSA.

Laboratory diagnosis for *S. aureus* begins with culture and Gram stain. Traditionally, laboratories perform disk diffusion, an oxacillin screening agar plate or broth micro-dilution (in many cases using an automated instrument) for susceptibility testing. An oxacillin minimum inhibitory concentration (MIC) greater than or equal to 4 μg/mL is diagnostic of MRSA; however, it may require 2–4 days to completely confirm an organism as oxacillin resistant. Polymerase chain reaction (PCR) testing is quickly replacing this tedious process by assessing the *S. aureus* genome for the *mecA* gene. The result is often available in as little as 1–2 h (Jonas, Speck, Daschner, & Grundmann, 2002).

A culture of the wound may be obtained prior to incision and drainage by withdrawing pustular material through a large-bore needle, or after the procedure by culturing the wound margins. It is important to note that once the wound is opened, the exudative materials should be cleaned away and not sent for culture.

Outpatient management of SSTI secondary to CA-MRSA

Several recent reports have evaluated the effectiveness of oral antimicrobial agents against CA-MRSA. To determine whether an antibiotic is appropriate for a given infection, the NP must consider the agent's pharmacodynamic and pharmacokinetic properties, the patient's allergy profile, as well as the patient's concomitant illnesses. After this, the clinician must decide whether to empirically treat an SSTI with an agent active against *S. aureus* alone or to use a broader spectrum agent that includes activity against CA-MRSA. Once a risk factor evaluation is completed and the clinician has considered the local epidemiology of SSTI infection in his/her community, an antimicrobial agent may be chosen.

While a standardized treatment approach has yet to be adopted by any particular group, data are emerging to support clinician choice of antimicrobial therapy. Kaka et al. (2006) determined that trimethoprim–sulfamethoxazole was rapidly bactericidal against CA-MRSA with a greater than 2 log bacterial reduction within 8 h of dosing. The sample size in this analysis was relatively small at 44 adult patients (Kaka et al., 2006); however, proof of concept was achieved. Fridkin et al. (2005) reviewed the antibiotic susceptibilities of clinical CA-MRSA isolates in three large metropolitan areas and found that 98% were sensitive to trimethoprim–sulfamethoxazole with 87% sensitivity in Baltimore, Maryland.

Scant data are available on the long-acting tetracyclines (i.e., doxycycline and minocycline) for treatment of CAMRSA; however, Ruhe, Monson, Bradsher, and Menon (2005) performed a small retrospective review (n = 24) of patients treated with doxycycline or minocycline and noted the drugs were well tolerated with an 83% clinical cure rate (Ruhe et al.). Rifampin continues to be a common treating agent but has been shown to rapidly develop resistance (Munckhof, Kleinschmidt, & Turnidge, 2004) and data are limited as to its efficacy in CA-MRSA (Le & Lieberman, 2006).

A slightly older analysis among children with CA-MRSA in Texas revealed a significant increase in clindamycin resistance throughout the 3-year study period (2001–2004) (Kaplan et al., 2005). To complicate macrolide use, inducible resistance has been identified among isolates characterized as clindamycin susceptible but erythromycin resistant. An antibiogram (*in vitro* sensitivity testing) that indicates this pattern requires further investigation, and the clinician must request a D-zone analysis to uncover the presence of inducible clindamycin resistance from the microbiology lab. The management of more severe infection requiring inpatient treatment is beyond the scope of this article; however, further data are available in the literature for clinicians seeking this information.

Ultimately, the choice of antimicrobial agent(s) should be based on a thorough clinical evaluation, sound knowledge of community and hospital epidemiology, as well as individual patient factors, including severity of infection. Table 3 summarizes the steps in the outpatient evaluation and treatment of CA-MRSA.

Recurrent CA-MRSA SSTI

Recurrence of various types of SSTI is common and often troubling for the patient. Studies addressing decolonization have often evaluated the efficacy of a single agent or method. A recent evaluation documenting success of MRSA decolonization recommends a multimethod approach. Simor et al. (2007) investigated the success of a decolonization protocol that randomized patients (3:1) to chlorhexidine gluconate washes with 2% mupirocin ointment intranasally and oral rifampin and doxycycline for 7 days versus placebo. The study noted significant differences in culture positive results at 3 months between the treated and the nontreated groups (74% vs. 32%, $p < 0.0001$). After 8 months, 54% of patients treated had maintained negative surveillance cultures (Simor et al., 2007). This appears to be the first published report combining three different modalities simultaneously.

NP research

From this literature review, there appears to be a paucity of published research articles or evidence-based literature reviews within the NP literature regarding CA-MRSA. In one report, an emergency department (ED) patient recently released from a correctional setting with a CA-MRSA SSTI led a group of NPs to perform a retrospective chart review to identify a point-prevalence of CA-MRSA within their ED and outpatient clinics. These practitioners noted a 10-week CA-MRSA prevalence of 16.3% among tissue or wound cultures (Fleming, Brown, & Tice, 2006).

Conclusions

As front-line clinicians evaluating and following patients with CA-MRSA infections, NPs are uniquely equipped to facilitate patient-centered, evidence-based care that prevents recurrence of SSTI as well as spread within households through risk-reduction education. This requires a thorough knowledge of the patient's individual risk profile and education about specific behaviors or circumstances that increase the patients' or their family's risk. The CDC “Infection

Control in Healthcare Settings" Web site provides an efficient way to stay informed about prevention efforts and is available at http://www.cdc.gov/ncidod/dhqp/index.html.

The clinical and public health implications of CA-MRSA are clear. Antibiotic resistance is an ongoing concern which, for the foreseeable future, is rapidly growing. NPs must remain cognizant of the epidemiology of common and emerging drug-resistant organisms in their patient populations and respond quickly and effectively once a problem organism has been identified. Research that addresses the impact of this organism in high-risk populations and within families is urgently needed.

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Table 1

Molecular comparison of HA-MRSA and CA-MRSA

	HA-MRSA	CA-MRSA
SCC*mec* type	I, II, and III	IV and V
PFGE type	USA 100	USA 300 and 400
PVL gene	Rare	Common
Antimicrobial susceptibilities	Highly resistant	Less resistant to non-β-lactam antimicrobials
Toxins	Traditional MRSA toxins	18 additional toxins
Clinical picture	Traditional clinical presentation	SSTI (very common); necrotizing fasciitis (rare)
Transmissibility	Direct contact with person or environment	Direct contact with person or environment

Note. HA-MRSA, hospital-acquired MRSA; PFGE, pulsed field gel electrophroresis; references noted in text.

Table 2

Risk factors for CA-MRSA

Recent arrest or incarceration
Recent antibiotics
Intravenous and intranasal drug use
Household with greater than three members
Lower socioeconomic status
Child in day care
Athletic or sports participation
Street or prison tattoo
Closed populations
Long-term care facility
Healthcare workers
Homelessness
Sexual contact
Military personnel
HIV infection

Note. References provided in text.

Table 3

Basic steps in evaluation and treatment of CA-MRSA

1	Perform thorough history of present illness, systemic review of symptoms, and risk factor evaluation (see Table 2)
2	Consider differential diagnosis including cellulitis, abscess (boil), impetigo, and rule out potentially life threatening necrotizing fasciitis, if symptoms warrant
3	For fluctuant abscesses, obtain aspirated pus/exudate from wound prior to performing incision and drainage (I/D) or obtain a culture of the wound margins after I/D—send for Gram stain and anaerobic/aerobic culture and sensitivity results
4	Consider individual patient risk profile as well as community and hospital epidemiology of skin and soft tissue infections todetermine appropriate empiric antimicrobial therapy
5	Consider if the patient would benefit from a single parenteral dose before discharge; if no clinical indication, provide oral antimicrobial on an outpatient basis for 7–10 days
6	Schedule patient for follow-up evaluation in 24–48 h with appropriate provider
7	Review antimicrobial sensitivities and follow-up with changes to therapy as appropriate