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Community-Acquired Methicillin-Resistant *S. aureus* (CA-MRSA) Skin And Soft Tissue Infections

In this Issue...

Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) has emerged as an increasingly frequent cause of skin and soft tissue infections in adults and children. Over the past year, new data have become available to assist clinicians in how to better diagnose, manage, and prevent these infections.

In this issue, we review the epidemiology of skin and soft tissue CA-MRSA infections, the role of antibiotic therapy in the management of these infections, issues involved in selecting appropriate therapy, and approaches to the prevention of CA-MRSA skin infections.

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Expiration Date

December 5, 2009

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Guest Faculty Disclosure

Sara E. Cosgrove, MD, MS has disclosed that she has received an educational grant Merck. She has served on the Advisory Boards for Theravance/Astellas, Ortho McNeil and Cadence Pharmaceuticals.

Unlabeled/Unapproved Uses

The author has indicated that there will be references to unlabeled or unapproved uses of drugs or products in this presentation. Trimethoprim-sulfamethoxazole (TMP-SMX) is not FDA approved for treatment of any Staphylococcal infection.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe the evolving epidemiology of CA-MRSA
- Discuss key issues regarding antibiotic therapy of skin and soft tissue infections caused by CA-MRSA
- Explain the role of decolonization in management of CA-MRSA infections

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COMMENTARY

Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) were first observed decades ago, mostly in hospitalized patients with significant comorbidities. MRSA remained largely a hospital-associated pathogen until the early 2000s, when otherwise healthy people with no clear exposure to the healthcare system began to present with MRSA skin and soft tissue infections. Rates of infections with so-called community-acquired MRSA (CA-MRSA) have risen over the past 5 years, and while

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the skin and soft tissue infections still comprise the majority of CA-MRSA infections, two recent reports highlight the increased incidence of CA-MRSA as a cause of invasive MRSA infections, particularly bacteremia and pneumonia.^{1,2}

The results of a study by Moran and colleagues (reviewed herein) examining the etiology of purulent skin and soft tissue infections presenting to 11 university-affiliated emergency departments across the US are striking: 59% of all infections were caused by MRSA, with the majority of these infections caused by USA300, the predominant CA-MRSA strain in the US. Risk factors for CA-MRSA in this study included history of prior MRSA infection, reported spider bite, contact with another person with a similar infection, and use of any antibiotic in the past month.

Traditionally, antibiotics have not been recommended as adjunctive therapy to incision and drainage in skin abscesses; however, most studies were in the pre-CA-MRSA era.^{3,4} Four of the studies reviewed in this issue provide conflicting data on the role of antibiotics in skin and soft tissue infections caused by CA-MRSA. The Moran, Miller, and Rajendran studies noted that receipt of an antibiotic that was inactive against CA-MRSA did not affect patient outcomes, while Ruhe and colleagues found that receipt of inactive antibiotics was associated with treatment failure. Failure to undergo incision and drainage was the major predictor of treatment failure in the Miller study, but this variable could not be independently assessed in the Ruhe study because of the study design. Further confounding the picture is a 2005 report by Fridkin and colleagues; in their large study evaluating MRSA disease in three communities, they observed that receipt of inactive antibiotics did not appear to affect outcomes of patients with skin and soft tissue infection.⁵

While incision and drainage is clearly the mainstay of management of CA-MRSA skin infections and additional antibiotics are likely not needed in most patients with adequately drained abscesses, the Centers for Disease Control and Prevention have recommended that adjunctive antibiotic therapy be considered in patients with:

- severe or rapidly progressive infections
- the presence of extensive associated cellulitis
- signs and symptoms of systemic illness
- diabetes or other immune suppression
- advanced age
- location of the abscess in an area where complete drainage is difficult
- lack of response to incision and drainage alone.^{6,7}

In addition, therapy should be given before incision and drainage in patients with prosthetic heart valves or other conditions placing them at high risk for endocarditis.⁹

If antibiotics are used, then an agent that is known to have activity against CA-MRSA should be chosen rather than a β -lactam. Clindamycin, tetracyclines, and trimethoprim-sulfamethoxazole are the agents most commonly used for CA-MRSA infection. Unfortunately, the study by Han and colleagues (reviewed herein) demonstrated decreased rates of susceptibility to clindamycin and tetracycline in an outpatient clinic in Boston. This finding underscores the importance of examining local susceptibility data when making decisions about antibiotic choice, and also emphasizes the importance of judicious antibiotic use to prevent increasing rates of resistance when managing these infections.

Recurrent infection and infection among multiple household members are frequently seen in patients with CA-MRSA skin and soft tissue infections. The study by Wiese-Posselt and colleagues provides the first published evidence that an aggressive decolonization strategy, consisting of a combination of personal decolonization and cleaning of the environment and personal items, could control an outbreak of *S. aureus* skin infections in the community setting. All patients who present with CA-MRSA skin infections should be questioned about other household members with similar symptoms, and should be advised to undertake the household cleaning

protocols described in the Wiese-Posselt study. If patients experience recurrence, or if other household members develop symptoms despite these measures, then decolonization with mupirocin to the nares (if nasal swabs grow MRSA) and antiseptic skin and throat washes can be considered for the patient and all household members. However, as demonstrated in the study by Ellis and colleagues (reviewed herein), mupirocin therapy not performed in conjunction with these other approaches is unlikely to be helpful. Decolonization should occur after the patient's infection is controlled, and systemic antibiotics should not be used for decolonization alone.

CA-MRSA has emerged as a significant pathogen, and new research continues to advance our understanding of its epidemiology and approaches to prevention and treatment.

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EMERGENCE OF MRSA IN THE EMERGENCY DEPARTMENTS

Moran GJ, Krishnadasan A, Gorwitz RJ, et al. **Methicillin-resistant *S. aureus* infections among patients in the emergency department**. *N Engl J Med*. 2006;355:666-674.

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Moran et al studied patients aged 18 or older with acute, purulent skin and soft-tissue infections in 11 university-affiliated emergency departments in August 2004. Patients were eligible for enrollment if they had symptoms for less than 1 week. Demographics, risk factors, and information about clinical presentation were recorded, and multivariate analysis was performed to assess risk factors for MRSA infection. *S. aureus* isolates were sent to the Centers for Disease Control and Prevention (CDC) for evaluation of toxin production and Staphylococcal cassette chromosome *mec* (SCC*mec*) typing.

Four hundred twenty-two patients were enrolled with a mean age of 39 years. Infections consisted of abscesses (81%), infected wounds (11%), and cellulitis with a purulent exudate (8%). Three hundred twenty of 422 (76%) had wound cultures that grew *S. aureus*, and 249 (78%) of these isolates were methicillin resistant. Thus, 59% of all infections were caused by MRSA. Two hundred sixteen of the 218

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MRSA isolates that were tested at the CDC were CA-MRSA strains (212 were USA300, 2 were USA400, and 2 were USA1000). The vast majority were SCCmec type IV (98%) and produced the Panton-Valentine leukocidin toxin (98%). All MRSA isolates were susceptible to trimethoprim-sulfamethoxazole, 95% were susceptible to clindamycin, and 92% were susceptible to tetracyclines.

Independent risk factors for MRSA infection were black race, use of any antibiotic in the past month, reported spider bite, history of MRSA infection, and close contact with a person with a similar infection. The majority of patients were treated with incision and drainage and antibiotic therapy (66%); 19% received incision and drainage alone, 10% received antibiotics alone, and 5% received neither. In 100 of 175 (57%) MRSA infections, the antibiotic prescribed was not effective based on susceptibility testing; however, this did not seem to have an effect on cure.

This study indicates that CA-MRSA is now the most common cause of skin infections in patients who present to urban emergency departments. This diagnosis should be considered in patients who present with cellulitis associated with an abscess, isolated abscesses, or lesions that look like spider bites. In this study, as in some others, use of an antibiotic without activity against MRSA did not appear to affect outcomes, suggesting that incision and drainage is the most important part of therapy.

THE ROLE OF ANTIBIOTIC THERAPY

Ruhe JJ, Smith N, Bradsher RW, Menon A. **Community-onset methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: impact of antimicrobial therapy on outcome.** *Clin Infect Dis.* 2007;44:777-784.

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Miller LG, Quan C, Shay A, et al. **A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and -susceptible *Staphylococcus aureus* skin infection.** *Clin Infect Dis.* 2007;44:483-492.

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Rajendran PM, Young D, Maurer T, et al. **Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection.** *Antimicrob Agents Chemother.* 2007;51:4044-4048.

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Ruhe and colleagues performed a retrospective cohort study of 492 adult patients with 531 episodes of community-onset MRSA skin and skin structure infections (abscesses, furuncles or carbuncles, and cellulitis) at two tertiary care center clinics to determine the impact of appropriate antibiotic therapy on patient outcomes. The day of the first incision and drainage procedure (if performed), or the day of the first positive wound culture result, was defined as zero time. Treatment failure, the primary outcome, was defined as a documented worsening of signs of infection at least 2 days after zero time, accompanied by one of more of the following: performance of an additional incision and drainage, hospital admission, occurrence of a new MRSA skin or soft tissue infection while on therapy, or persistence of cultures growing MRSA after completion of antibiotic therapy. Demographics, comorbidities, and information about clinical presentation were recorded, and multivariate analysis was performed to assess risk factors for treatment failure.

The investigators reported that 361 infections were abscesses, 116 were cellulitis,



and 54 were furuncles and carbuncles. All cases of cellulitis were associated with another skin lesion such as folliculitis, a skin ulcer, or an abscess. Appropriate antimicrobial therapy was given in 312 (59%) cases. Forty-five (8.5%) patients had treatment failure; reasons for failure (patients could have more than one reason) included the need for additional incision and drainage (n= 38), subsequent hospitalization (n=20), new lesion (n=2), and microbiological failure (n=1). Twenty-nine of these 45 patients received inappropriate therapy, the majority of which was with a β -lactam agent. Failure to start appropriate therapy within 48 hours of zero time was the only independent predictor of treatment failure (adjusted OR = 2.8, 95% CI 1.26-6.22). This finding was also seen in the subgroup of 427 episodes in which incision and drainage was performed at zero time. Size of the lesion was not associated with treatment failure.

Miller and colleagues performed a prospective study of 117 patients who were hospitalized for CA-MRSA or CA-MSSA (community-acquired methicillin-susceptible *S. aureus*) skin infections between February and October of 2004. At the time of enrollment, patients underwent a survey regarding exposures, and data on risk factors and comorbidities were collected. After hospital discharge, patients were contacted by telephone at 30 days, and again at 120 days, after enrollment and asked about clinical outcomes, new infections in themselves or family members, and antibiotic use. The primary outcome was non-response at 30 days, defined as: 1) infection relapse at the original site, 2) new *S. aureus* skin infection, or 3) need for a new course of antibiotic treatment. Secondary outcomes included the need for additional surgery, rehospitalization, and new skin infection in a family member.

Of these patients, 84% were adults and 16% were children. Seventy patients had CA-MRSA infections and 47 had CA-MSSA infections. Patients with CA-MRSA were younger (median age 37 vs 46 years), less likely to have diabetes (20% vs 49%), and more likely to have a history of snorting drugs (30% vs 10%). Thirty-six (31%) patients experienced non-response at 30 days; there was no difference in rates of response among patients with CA-MRSA infection (33%) and CA-MSSA infection (28%). Failure to undergo incision and drainage was more common in non-responders - 20% did not undergo incision and drainage compared to only 1% of responders. Receipt of inappropriate antibiotic therapy was not associated with a higher failure rate.

Rajendran and colleagues performed a randomized, double-blind trial of 166 adult outpatients comparing cephalexin (500 mg orally 4 times a day for 7 days) to placebo after surgical incision and drainage of uncomplicated skin abscesses by an attending surgeon from November 2004 to March 2005. Patients were excluded if they were severely ill with evidence of sepsis, if they had evidence of infection involving bone, joints, or prosthetic material, or if they were penicillin allergic. The primary outcome measure was clinical cure, defined by resolution of purulent drainage, erythema, fluctuance, warmth, pain, and edema.

The authors report that 82 patients received cephalexin and 84 received placebo. There were no significant differences in baseline characteristics in the two groups. Approximately two-thirds of the lesions involved only subcutaneous tissue and one-third involved the fascia or muscle. Twenty-eight patients had abscesses greater than 5 cm in length, 34 patients had abscesses greater than 5 cm in width, and 24 patients had abscesses greater than 5 cm in depth. *S. aureus* was isolated as the only pathogen in 69% of cepalexin-treated patients and 67% of placebo-treated patients; 87 of 99 (88%) of the isolates tested for susceptibility were MRSA, and 93% of the MRSA isolated produced PVL. Sixty-nine of 82 (84.1%) patients who received cephalexin and 76 of 84 (90.5%) of patients who received placebo had clinical cure.

These studies provide conflicting data on the impact of appropriate antibiotic therapy on the outcomes of patients with skin infections caused by CA-MRSA. In the Ruhe study, receipt of inappropriate antibiotics for CA-MRSA skin and soft tissue was associated with treatment failure. The relative effect of incision and drainage on outcome, which would be expected to be significant, could not be assessed in this study because zero time was defined as the time of incision and drainage if performed. In addition, it appears that incomplete incision and drainage was the major factor leading to failure, given that 38 of 45 (84%) failures required additional incision and drainage; antibiotics would not be expected to modify the

course in this situation. While the participants in this study attended clinics at a tertiary care medical center and a VA hospital, and may have had more comorbidities than average (e.g., 17% had diabetes), none of the comorbidities measured in the study were associated with treatment failure. Although the authors had a standardized definition for failure, the retrospective nature of the study may have led to bias in assessing outcomes.

In the Miller study, receipt of inappropriate antibiotics was not associated with treatment failure. In contrast to Ruhe, this study assessed both CA-MSSA and CA-MRSA skin infections in patients who were ill enough to be hospitalized. Because patients were followed prospectively, outcomes may be more reliable; however, the numbers of patients who failed and received inappropriate antibiotic therapy were quite small. Incision and drainage was the only predictor of treatment failure, emphasizing the importance of this procedure in the management of skin infections caused by *S. aureus*.

The Rajendran study offers another perspective on the role of antibiotics in the management of uncomplicated skin abscesses. Despite the fact that the majority of patients had CA-MRSA that would not be expected to be treatable with either cephalexin or placebo, true clinical failures with worsening abscess or inadequate healing occurred in only 8% of patients. The results of this study suggest that antibiotics are not beneficial in the majority of patients with CA-MRSA skin abscesses - provided that a complete incision and drainage is performed. A useful follow-up study would compare an agent expected to be active against CA-MRSA vs placebo in the same population.

INCREASING RESISTANCE TO FIRST-LINE ORAL AGENTS

Han LL, McDougal LK, Gorwitz RJ, et al. **High frequencies of clindamycin and tetracycline resistance in methicillin-resistant *Staphylococcus aureus* pulsed-field type USA300 isolated collected at a Boston ambulatory health center.** *J Clin Microbiol.* 2007;45:1350-1352.

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Han et al studied 123 CA-MRSA isolates from patients presenting to a community health center in Boston between May 2004 and November 2005 to assess resistance to the antibiotics commonly used for management of CA-MRSA (clindamycin, tetracycline, levofloxacin, and mupirocin). One hundred fifteen isolates had a known source - 90% were from skin and soft tissue sites, and 10% were from the nares or nasopharynx. Eighty-three percent of total isolates were MRSA strain type USA300, the predominant CA-MRSA strain in the US; 59% were USA300-0114, and 24% were USA300-0247. Both strains had significant rates of resistance to several commonly used antibiotics, as detailed in the table below:

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Prevalence of Resistance to Antibiotics

Antibiotic	Number of Resistant Isolates (% resistant)	
	USA300-0114 (N=73)	USA300-247 (N=29)
Levofloxacin	58 (79%)	29 (100%)
Clindamycin	36 (49%)	22 (76%)
Tetracycline	10 (14%)	21 (72%)
Trimethoprim-sulfamethoxazole	0 (0%)	0 (0%)
Resistance to erythromycin, levofloxacin, clindamycin, and tetracycline	2 (3%)	16 (55%)

In addition, 12 isolates with resistance to erythromycin, levofloxacin, clindamycin, and tetracycline were sent to the CDC; these isolates were susceptible to minocycline and doxycycline. All 12 were found to be resistant to mupirocin.

This study demonstrates that there are areas in the US where there is increasing resistance to agents that are commonly used to treat CA-MRSA skin and soft tissue infections, in particular clindamycin and tetracycline, and emphasizes the importance of examining local resistance data when determining empiric antibiotic choices for these infections. The high prevalence of fluoroquinolone resistance is not surprising, as resistance to fluoroquinolones arises quickly and commonly in *S. aureus* strains; consequently, fluoroquinolone use is discouraged in the management of skin and soft tissue infections caused by *S. aureus*. Of great concern is this study's finding of concomitant mupirocin resistance in the highly resistant strains, given that mupirocin is the only commercially available agent for *S. aureus* decolonization of the nares. One encouraging finding, though, is that all isolates retained susceptibility to trimethoprim-sulfamethoxazole, an effective agent in the management of MRSA skin and soft tissue infections. It is important to remember that trimethoprim-sulfamethoxazole has poor activity against Group A streptococci; thus, its use as monotherapy for routine cellulitis in which Group A streptococci are suspected as a pathogen is discouraged.

THE ROLE OF DECOLONIZATION

Ellis MW, Griffith ME, Dooley DP, et al. **Targeted intranasal mupirocin to prevent colonization and infection by community-associated methicillin-resistant *Staphylococcus aureus* in soldiers: a cluster randomized controlled trial.** *Antimicrob Agents Chemother.* 2007;51:3591-3598.

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Wiese-Posselt M, Heuck D, Draeger A, et al. **Successful termination of a furunculosis outbreak due to lukS-lukF-positive, methicillin-susceptible *Staphylococcus aureus* in a German village by stringent decolonization, 2002-2005.** *Clin Infect Dis.* 2007;44(11):e88-95. Epub 2007 Apr 25.

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Ellis and colleagues performed a cluster randomized, double-blind, placebo-controlled trial of mupirocin compared with placebo for decolonization of MRSA-colonized soldiers to determine if mupirocin could decrease CA-MRSA infection in

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the treated individual as well as other individuals in their training groups. Training groups were enrolled between January 2005 and December 2005. Soldiers underwent nasal cultures for CA-MSRA on the first day of training, and those with cultures positive for CA-MRSA were treated with either mupirocin or placebo. Eight to 10 weeks later, a second nasal culture was obtained. All participants were followed prospectively for development of skin and soft tissue infections for 16 weeks.

Seven training groups (1,669 soldiers) were randomized to the placebo arm and seven training groups (1,778 soldiers) were randomized to the mupirocin arm. Results are shown as below:

	Placebo	Mupirocin
Baseline CA-MRSA colonization	4%	3.8%
Percent of possible study drug doses given	99.5%	99.2%
CA-MRSA infections in 16 week follow-up period in treated soldiers	7.7%	10.6%
CA-MRSA infections in all soldiers	4.3%	3.5%
Elimination of CA-MRSA colonization at 8 – 12 weeks	64.6%	87.9%

The Wiese-Posselt et al paper is a report on the investigation and termination of an outbreak of *S. aureus* that began in 1998 in a German village of 144 residents in 58 households. The MSSA strain causing the outbreak contained the lukS-lukF gene, which encodes for Panton-Valentine leukocidin (the toxin that has been implicated in causing aggressive skin infections in CA-MRSA strains). A retrospective cohort study was performed to assess risk factors for infection. All village residents who consented to participate completed a standardized questionnaire about demographics, risk factors, comorbidities, and occurrence of furuncles since 1998. A "case" was defined as a person with a skin abscess >0.5 cm or an abscess in another organ occurring from 1998-2004; a "case contact" was a household member, a friend, or relative with whom time was spent or personal objects were shared, or a person with whom skin contact occurred.

The intervention to control transmission of MSSA was an aggressive decolonization protocol for the affected patient and all household members initiated in July 2004. The protocol consisted of 5 days of the following: 1) mupirocin ointment to the nares 3 times daily, 2) daily treatment of skin and hair with an octenidin-based wash, 3) gargling with 0.1% chlorhexidine solution 3 times daily, 4) daily disinfection of personal items such as combs, razors, glasses, and jewelry, 5) daily disinfection of the bathtub or shower floor, 6) daily changing and hot water washing of towels, sheets, and clothing, 7) enhanced hand hygiene with alcohol-based hand gel, and 8) minimized contact with other villagers during the 5-day period. Nasal swab specimens were obtained at 3 days, 7 weeks, and 20 weeks after the decolonization protocol, and physicians were asked to report any new cases of furunculosis.

One hundred forty-one of 144 (98%) villagers participated in the study. The investigators report that 42 primary cases and 59 relapses of furuncles or abscesses occurred in 27 people from 1998 to 2005. Fifteen (36%) patients required hospitalization. Independent risk factors for development of furuncles and abscesses were nasal colonization with lukS-lukF-positive *S. aureus* (adjusted OR 9.2, 95% CI 1.2-73.1), contact with case patients (adjusted OR 4.7, 95% CI 1.3-17.3), being a member of the local fire brigade (adjusted OR 5.5, 95% CI 1.6-19.0), sharing objects with neighbors (adjusted OR 3.6, 95% CI 1.1-12.2), and having a chronic skin disease (adjusted OR 12.3, 95% CI 1.5-100.2).

Fifty-three patients underwent the decolonization protocol. All nasal cultures were negative at 3 days. At 7 weeks, 4 (8%) patients were found to be colonized with lukS-lukF-positive *S. aureus* and received 10 days of trimethoprim-

sulfamethoxazole and rifampicin. At 20 weeks no patients were colonized with lukS-lukF-positive *S. aureus*. Clinical follow-up of patients revealed 1 new case of furunculosis and 3 relapses; these patients and their household contacts underwent the decolonization protocol again. In the year following decolonization, no new or recurrent cases were identified.

These two studies provide information about the effectiveness of decolonization strategies in the management of CA-MRSA infections. Ellis and colleagues found no benefit of intranasal mupirocin in preventing infections with CA-MRSA in subjects colonized with CA-MRSA or their contacts, despite the fact that mupirocin did result in decolonization of the nares in most patients. The authors note that the infection rate of 7.7% in the placebo group was significantly lower than that observed in a previous study by the same group in which 38% of soldiers colonizing with CA-MRSA went on to develop infection¹; they hypothesize that there may have been heightened awareness of the importance of good hygiene among all study participants in the later study. Nevertheless, these findings suggest that mupirocin therapy alone is unlikely to be beneficial in preventing CA-MRSA infections in patients colonized with CA-MRSA.

The study by Wiese-Posselt and colleagues demonstrates that an aggressive multi-faceted decolonization strategy can lead to control of *S. aureus* infections in the community. Although the patients in the study had infections caused by MSSA, the predominant strain contained the same virulence factor (Panton-Valentine leukocidin) as do many CA-MRSA strains. It is important to note that the decolonization protocol involves the use of nasal decolonization with mupirocin and skin decolonization in combination with cleaning of the environment (e.g., bathtubs and showers) and items that contact skin (e.g., sheets, towels, clothing); when used alone, these individual approaches are less likely to be as effective as when combined (as demonstrated by the Ellis study).

References

1. Ellis MW, Hospenthal DR, Dooley DP, Gray PJ, Murray CK. [Natural history of community-acquired methicillin-resistant *Staphylococcus aureus* colonization and infection in soldiers.](#) *Clin Infect Dis.* 2004;39:971-979.

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Post-Test — [back to top](#)

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Statement of Responsibility — [back to top](#)

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Target Audience — [back to top](#)

This activity has been developed for the Dermatologist, PharmD, Nurses, Dermasurgeon, Dermatopathologist, Pediatric Dermatologist, Immunodermatologist, and Wound Care Specialist.

Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Describe the evolving epidemiology of CA-MRSA
- Discuss key issues regarding antibiotic therapy of skin and soft tissue infections caused by CA-MRSA
- Explain the role of decolonization in management of CA-MRSA infections

Internet CME/CNE/CPE Policy — [back to top](#)

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- **Susan Matra Rabizadeh, MD, MBA** has disclosed no relationships with commercial supporters.

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