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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 a 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 infections, the association between antibiotic use and CA-MRSA, 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.

THIS ISSUE

Course Directors

John G. Bartlett, MD
Professor of Medicine
Department of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, MD

Paul G. Auwaerter, MD
Associate Professor of Medicine
Clinical Director
Division of Infectious Diseases
The Johns Hopkins University
School of Medicine
Baltimore, MD

Sara E. Cosgrove, MD, MS
Assistant Professor of Medicine
Division of Infectious Diseases
Director
Antibiotic Management Program
Associate Hospital Epidemiologist
The Johns Hopkins University
School of Medicine
Baltimore, MD

GUEST AUTHOR OF THE MONTH

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Commentary & Reviews:

Sara E. Cosgrove, MD, MS
Assistant Professor of Medicine,
Division of Infectious Diseases
The Johns Hopkins University School of Medicine

Guest Faculty Disclosures

Sara E. Cosgrove, MD, MS, has disclosed that she is a research investigator for Merck. She is on the Advisory Boards of Ortho McNeil and Cadence Pharmaceuticals.

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The author has indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in this presentation.

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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

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 to the point where most clinicians have had at least some experience treating patients with CA-MRSA infections.[1] Nevertheless, the results of a study by Moran and colleagues 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.

Prior use of antibiotics as a risk factor for CA-MRSA was also demonstrated in a large study using a database of ~3.2 million patients in general practices in the United Kingdom by Schneider-Linder and colleagues. Exposure to any antimicrobial drug within the year was an independent predictor of MRSA, and this association was most marked for patients who received fluoroquinolones or macrolides. Interestingly, the use of fluoroquinolones has previously been implicated as increasing the incidence of MRSA colonization, perhaps by increasing fibronectin-binding protein and allowing for increased adherence of MRSA in the nasal mucosa.[2] The association between antibiotic use and subsequent CA-MRSA colonization and infection provides an additional reason to limit antibiotic use in the outpatient setting as much as possible.

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] Three of the studies reviewed here provide conflicting data on the role of antibiotics in skin and soft tissue infections caused by CA-MRSA. Both the Moran and Miller 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; this variable could not be independently assessed in the Ruhe study because of the study design. Fridkin and colleagues also observed that receipt of inactive antibiotics did not appear to affect outcomes of patients with skin and

soft tissue infection in a large study evaluating MRSA disease in 3 communities.[4]

While incision and drainage is clearly the mainstay of management of CA-MRSA skin infections, the Centers for Disease Control and Prevention have recommended that adjunctive antibiotic therapy be considered in patients with:

1. severe or rapidly progressive infections
2. the presence of extensive associated cellulitis
3. signs and symptoms of systemic illness
4. diabetes or other immune suppression
5. advanced age
6. location of the abscess in an area where complete drainage is difficult, and
7. lack of response to incision and drainage alone[5]

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.[6]

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 demonstrates 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 when managing these infections to prevent increasing rates of resistance.

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. 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 DEPARTMENT

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 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 SCC*mec* 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 ASSOCIATION BETWEEN ANTIBIOTICS AND CA-MRSA IN OUTPATIENTS

Schneider-Lindner V, Delaney JA, Dial S, Dascal A, Suissa S. **Antimicrobial drugs and community-acquired methicillin-resistant Staphylococcus aureus, United Kingdom.** *Emerg Infect Dis.* 2007;13:994-1000.

Abstract: No link available View full article

Schneider-Lindner et al performed a case-control study to determine the impact of receipt of antibiotics and subsequent development of CA-MRSA among a group of adult patients with no previous diagnosis of MRSA who had not been hospitalized in the past 2 years. All data came from the records of ~3.2 million patients from >400 general practices in the United Kingdom. Case patients had a clinical diagnosis of MRSA between 2000 and 2004 based on diagnosis codes; however, the most common code did not differentiate between MRSA colonization and infection. Ten control patients per case patient were matched on practice and age. With adjustment for variables such as age, BMI, and underlying medical conditions, the association between antibiotics and MRSA diagnosis was determined using multivariate analysis.

One thousand nine hundred eighty-one patients with an MRSA diagnosis were eligible for the study and were matched to 19,779 control patients. After adjustment for demographics and comorbid conditions, exposure to any antimicrobial drug in the preceding 30 to 365 days remained an independent predictor of MRSA, conferring a 3-fold increased risk of this diagnosis. The association was stronger for patients who received more prescriptions (adjusted odds ratio [OR] = 6.24 for ≥4 prescriptions) and for patients who received macrolides (adjusted OR = 2.5) and fluoroquinolones (adjusted OR = 3.37). Nearly 40% of case patients had received no antibiotics in the year before diagnosis of MRSA.

This study suggests that there is an association between prior antibiotic exposure and the development of colonization or infection with CA-MRSA, although one third of patients who developed CA-MRSA had no prior antibiotic exposure. The strongest correlation was with 2 antibiotic classes commonly prescribed in the outpatient setting, macrolides and fluoroquinolones. This lends further evidence to the notion that limiting antibiotic prescriptions to essential use in the outpatient setting benefits individual and public health. The data source used in the study, records from a national primary care database in the United Kingdom, did not contain information as to whether patients were infected or just colonized with MRSA; however, most outpatients are not routinely screened for MRSA colonization, suggesting that most were likely infected. In addition, specific data regarding the place of residence of study subjects, such as long-term care facilities or group homes where hospital-acquired strains may be present, was not reported. Finally, due to the retrospective nature of the study, no strain typing was performed to confirm that the isolates were actually community-acquired strains of MRSA.

THE ROLE OF ANTIBIOTIC THERAPY

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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 methicin-resistant and –susceptible Staphylococcus aureus skin infection.** *Clin Infect Dis.* 2007:44:483-492.

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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 2 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.

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 comorbidites 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.

In the Ruhe study, 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, defined as the need for additional incision and drainage in 38 patients, subsequent hospitalization in 20, new lesion in 2, and microbiological failure in 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.

In the Miller study, 84% of patients 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.

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. However, in the subgroup of patients who underwent incision and drainage, appropriate choice of antibiotics also improved outcomes. 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 (eg, 17% had diabetes), but 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*.

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:

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. This finding 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

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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Wiese-Posselt and colleagues 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.

From 1998 to 2005, 42 primary cases and 59 relapses of furuncles or abscesses occurred in 27

people. Fifteen (36%) patients required hospitalization. One hundred forty-one of 144 (98%) villagers participated in the study. Independent risk factors for development of furuncles and abcesses 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.

This study demonstrates that an aggressive 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 (eg, bathtubs and showers) and items that contact skin (eg, sheets, towels, clothing); when used alone, these individual approaches are less likely to be as effective as when combined. Patients with infections in this study had similar risk factors for infection that have been identified for CA-MRSA infections, including contact with another infected patient, sharing objects, and having underlying skin disease.

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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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- **Paul G. Auwaerter, MD** has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme. He is on the Speakers' Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson & Johnson.
- **Sara E. Cosgrove, MD, MS** has disclosed that as a co-investigator, she has received grants or research support from Merck and served on the Advisory Boards for Ortho-McNeil and Cadence Pharmaceuticals.

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