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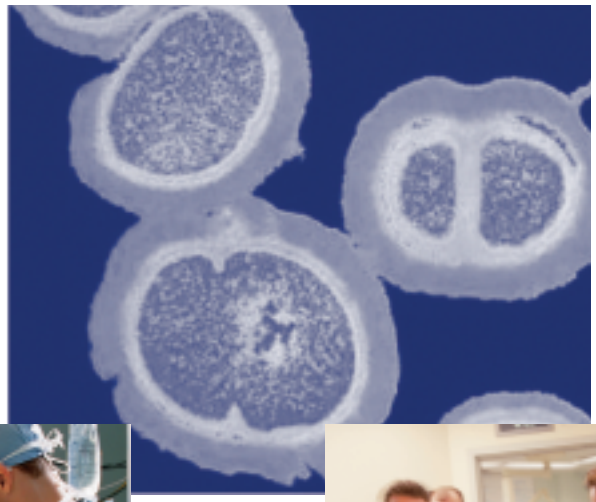
MRSA INFECTION IN THE EMERGENCY DEPARTMENT

A Review of the Evidence



Prevalence of MRSA Infections in the ED

Diagnostic Considerations of MRSA Infections

Current Treatment Options

Community-associated Methicillin-resistant *Staphylococcus aureus*:
Emergency Department Perspective

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Dear Reader:

In late 2005 the International Society of Microbial Resistance (ISMR) began planning a series of live CME meetings and associated monographs, designed to update health care providers about the prevalence and presentation of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in community and hospital settings. The ISMR effort has culminated in the 2006 MRSA Summit program, which blends educational opportunities through interactive live meetings and monographs that will draw attention to the challenges of diagnosing and managing MRSA infections in the community and in special patient populations.

There is no better place to start the monograph series than to review the types of MRSA infections seen in the Emergency Department (ED); a busy intersection between the community and the hospital. With the growing prevalence of serious community MRSA infections and changes in patterns of health care delivery, the ED has become an important default treatment center for a growing number of patients. In this review, Doctors Abrahamian and Talan offer a critical overview of the current literature, describing the types and attributes of MRSA infections seen in the ED, and review treatment options with special attention to the growing problem of antibiotic resistance in community pathogens.

Subsequent monographs will draw attention to the growing problem of MRSA prevalence in community settings, pharmacokinetic and pharmacodynamic considerations when selecting antibiotic therapy, and resource utilization associated with management of MRSA infections. Together, these monographs will direct health care providers to the growing literature on MRSA, and offer broad resources for individual health care providers to become regional champions of cutting-edge MRSA management.

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Community-associated Methicillin-resistant *Staphylococcus aureus*: **Emergency Department Perspective**

ABSTRACT:
Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections have become an emerging global health problem. Compared to health care-associated strains, CA-MRSA strains more frequently produce toxins and appear to be more virulent. They also demonstrate variable susceptibility patterns to various classes of antibiotics. Recent emergency department-based studies have demonstrated that CA-MRSA is now the most commonly identifiable cause of skin and soft-tissue infections. Empiric antibiotic therapy for patients with skin and soft-tissue infections, and those presenting with severe, life-threatening infections should include an agent that is active against MRSA.

KEY WORDS:
Methicillin-resistant, *Staphylococcus aureus,* emergency medicine, community-associated, sepsis, pneumonia

Multitudes of clinical syndromes, ranging from mild to life-threatening infections, have been associated with common infections associated with *S aureus* include skin and soft-tissue infections, osteomyelitis, septic arthritis, endocarditis, severe pneumonia, toxic shock syndrome, severe sepsis, and septic shock.

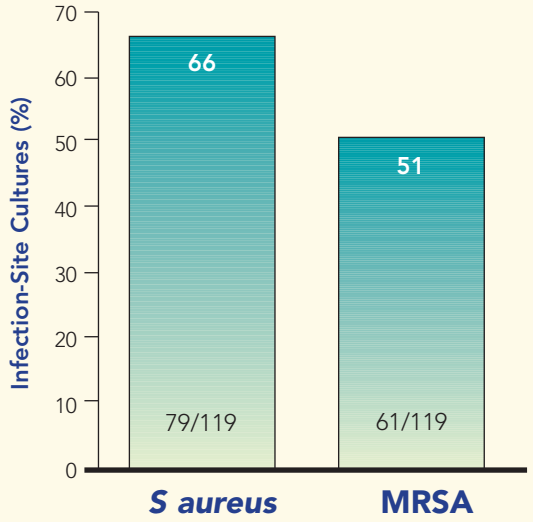
Humans are a natural reservoir for this organism and colonization commonly occurs on the skin, nasopharynx (especially anterior nares), or perineum.[1] In the general population, the mean rate of *S aureus* nasal carriage is 37.2% (range, 19.0%-55.1%). In healthy subjects, over time, about 20% of people are persistent carriers, 60% are intermittent carriers, and 20% rarely carry *S aureus*. Patients with insulin-dependent diabetes mellitus, those undergoing hemodialysis, and intravenous drug users have increased carriage rates of 56.4%, 51.5%, and 55.2%, respectively.[2] Nasal carriage of *S aureus* has been associated with an increased risk of *S aureus* bacteremia, the development of staphylococcal infection in patients who are post-surgical, undergoing hemodialysis or receiving continuous ambulatory peritoneal dialysis, and infected with the human immunodeficiency virus.[2-8]

S aureus has a remarkable ability to adapt to new environments and develop resistance to antibiotics. Reports of staphylococcal resistance to penicillin and methicillin arose soon after the introduction of these agents. Initially, most reports of antimicrobial resistance were among the hospital isolates, but over the years, resistance among community isolates has developed and continues to evolve to this day. Currently, regardless of the clinical setting (ie, hospital vs. community), more than 90% of staphylococcal isolates produce penicillinase.[9] The latest report by the National Nosocomial Infections Surveillance (NNIS) System revealed that methicillin-resistant *S aureus* (MRSA) accounted for 48.1% of infections among intensive care unit (ICU) patients, 44.9% in non-ICU inpatient wards, and 24.6% in outpatient areas. During the period of January 2003 through December 2003, there was an 11% increase in the nosocomial MRSA infections in ICU patients when compared with the mean MRSA infection rate over the previous 5 years.[10] Historically, established risk factors for acquiring MRSA infections have included recent hospitalization or surgery, residence in a long-term care facility, undergoing dialysis, and the use of indwelling percutaneous medical devices and catheters.[11-14] However, more recently MRSA has been documented in individuals without such known risk factors in a variety of community settings, populations, and geographic areas.[15-21] Such infections, due to the absence of identifiable risk factors, are termed community-associated MRSA (CA-MRSA) infections. Most CA-MRSA infections involve skin and soft-tissue infections (SSTIs).[22-25] Invasive infections such as bacteremia, meningitis, necrotizing pneumonia, osteomyelitis, and necrotizing fasciitis resulting in death have been reported with CA-MRSA.[16,26-28] The current prevalence of asymptomatic CA-MRSA colonization in the general population is unknown.

Hospital and CA-MRSA differ in their epidemiological, molecular, microbiological, and clinical characteristics.[24,29] In a study of more than 1000 MRSA infections (12%, community-associated; 85%, health care-associated; 3%, unclassified) those with CA-MRSA were younger (median age, 30 years vs. 70 years; P<.001) and more often non-white (odds ratio [OR], 3.13; 95% confidence intervals [CI], 2.16-4.32; P<.001) than those with health care-associated MRSA. Community-associated infections were more likely to involve the skin and soft-tissue (OR, 4.25; 95% CI, 2.97-5.90; P<.001), and were less likely to involve the respiratory (OR, 0.22; 95% CI, 0.09-0.49; P<.001) or urinary tract (OR, 0.04; 95% CI, 0-0.24; P<.001) systems. CA-MRSA strains were also more likely than health care-associated MRSA (HA-MRSA) strains to be susceptible to ciprofloxacin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole (TMP/SMX) (OR, 5.88; 95% CI, 4.86-6.64).[24] This is in contrast to the characteristic multidrug resistant pattern usually encountered in HA-MRSA strains.[1,30] Indeed, susceptibility to all of the above four antibiotics was an independent predictor of having a community-associated case by definition (adjusted OR, 2.44; 95% CI, 1.35-3.86).[24]

Compared to health care-associated strains, CA-MRSA strains more frequently produce toxins and

Figure 1. Prevalence of *Staphylococcus aureus* and methicillin-resistant *S aureus* (MRSA) in purulent skin and soft-tissue infection-site cultures.[23]



appear to be more virulent. The Panton-Valentine leukocidin (PVL) genes, which produce cytotoxins that cause tissue necrosis, damage host cell membranes, and leukocyte destruction, are commonly seen with CA-MRSA and rarely with HA-MRSA strains. Strains of CA-MRSA that possess these genes are commonly associated with SSTIs and necrotizing pneumonia, and have been reported from various geographic areas globally.[24,28,31-40]

SSTIs, mainly cutaneous abscesses, are common presenting conditions to emergency departments (EDs). Recent ED-based studies have demonstrated that CA-MRSA is now the most commonly identifiable cause of SSTIs in many departments.[23,25] A recent prospective study from a single urban ED found that of 119 purulent SSTIs, 79 (66.4%) grew *S aureus*. MRSA was isolated from 61 (51.3%; 95% CI, 42.3-60.2) infection-site culture specimens (Figure 1).[23] Approximately 82% of the MRSA infections were skin abscesses (50.8% deep abscess; 31.2% superficial abscess which was classified as furuncle). Results of multivariate logistic regression analysis revealed that superficial skin abscess was a strong independent predictor of MRSA infection (OR, 28.6; 95% CI, 3.6-225.4) and nasal colonization (OR, 5.0; 95% CI, 1.6-15.4). Ninety-four percent of MRSA isolates possessed the PVL exotoxin genes. Antibiotic susceptibilities among the MRSA isolates were as follows: vancomycin and TMP/SMX 100%, clindamycin 94.3%, tetracycline (a surrogate for doxycycline) 85.7%, levofloxacin 56.8% (28.4% with intermediate susceptibility), and erythromycin 3.6%. All of the strains were resistant to oxacillin (a substitute for methicillin). Oxacillin resistance equates resistance to all ß-lactam antibiotics, including cephalosporins. Two (2.4%) patients exhibited inducible clindamycin resistance (Table 1). Of the patients with MRSA infection who were treated with antibiotics, 78.7% were initially prescribed a ß-lactam, an agent which is universally inactive against MRSA strains.[23]

In another single urban ED study of SSTIs, MRSA was isolated from 46% of 96 patients.[25] Most patients had skin abscesses and no clinical or epidemiological features were reliably predictive of a MRSA etiology. Similar to other studies, the common presenting complaint was a spontaneous abscess as a result of "spider bite."[23,25,41] Antibiotic susceptibilities among the MRSA isolates were as follows: TMP/SMX 100%, clindamycin and rifampin 98%, tetracycline 82%, levofloxacin 16% (64% with intermediate susceptibility), and erythromycin 2%. None of the patients exhibited inducible clindamycin resistance (Table 1).[25]

In light of these findings, physicians should anticipate that CA-MRSA may be a frequent cause of SSTIs and should culture more of these lesions in order to understand the prevalence and susceptibility patterns of CA-MRSA in their community. Wound cultures are also appropriate for those patients who will be started on antimicrobial therapy. If local MRSA prevalence is already known to be high, culturing a first-time, simple, uncomplicated abscess is not necessary since the majority of these infections will heal with incision and drainage (I&D) alone.

Simple cutaneous abscesses (ie, without cellulitis) are most often monobacterial, infected with *S aureus*, and will most likely be cured with I&D alone without adjunctive antibiotic therapy. In a study of 69 immunocompetent children with culture-proven CA-MRSA cutaneous abscesses who had I&D, no significant differences were found in response rates between those with organisms susceptible or resistant to prescribed antibiotics.[42] Since CA-MRSA strains appear to be more virulent and with a propensity to recur, it is unknown at this time if the addition of antibiotics to such wounds would diminish the chance of recurrence. Antibiotics, in addition to abscess I&D, would be appropriate for patients who are immunocompromised, have evidence of systemic toxicity, a significant area of associated cellulitis, or those with large, multiple, or recurring abscesses.

Oral antibiotics that have adequate in vitro susceptibility against CA-MRSA isolates include TMP/SMX, rifampin, clindamycin, and linezolid. Due to the rapid emergence of strains resistant to rifampin, this drug should not be used alone. It is often used for synergy and in combination regimens with other drugs, most commonly with TMP/SMX or doxycycline. Rifampin also has the potential of eradicating nasal MRSA colonization and possibly reducing the likelihood of recurrent infections.[2,43-46]

Clindamycin has adequate coverage for both MRSA and *Streptococcus pyogenes* with additional coverage for anaerobes. Potentially, it also has the capability of inhibiting toxin production.[47-49] Some strains of MRSA exhibit inducible clindamycin resistance with a prevalence that can vary by region, age group, and methicillin susceptibility. Pretherapy, these strains demonstrate in vitro erythromycin-resistant and clindamycin-sensitive susceptibilities. However, when exposed to clindamycin, they develop in vitro resistance to clindamycin. Inducible resistance can be detected by the double-disk diffusion

Table 1. Antibiotic susceptibilities among the methicillin-resistant *Staphylococcus aureus* (MRSA) isolates recovered from purulent skin and soft-tissue infection-site cultures.

	MRSA Isolate Susceptibility (%)	
Antibiotic	Frazee et al[23]	Moran et al[25]
TMP/SMX*	100	100
Rifampin	Not performed	98
Clindamycin	94.3 (2.4†)	98 (0†)
Tetracycline	85.7	82
Levofloxacin	56.8 (28.4‡)	16 (64‡)
Erythromycin	3.6	2

*TMP/SMX: Trimethoprim-Sulfamethoxazole †Inducible resistance ‡Intermediate susceptibility

assay (D test) which is unfortunately not a routine test in many centers.[50-52] The clinical relevance of inducible resistance is not so clear. Both clinical cure and treatment failures/recurrences have been reported with patients inflicted with such strains.[50,52-56] Inducible resistance should not entirely preclude the use of clindamycin, but physicians should be aware of this phenomenon as a potential cause of treatment failures. Since there are limited numbers of antimicrobials that can combat MRSA infections, and there is the potential for increasing resistance, it is best to keep clindamycin as a second-line oral agent (eg, for patients who cannot take TMP/SMX). Clindamycin is a suitable first-line intravenous agent for patients with mild-to-moderate suspected MRSA infections. Clinical trials investigating the efficacy of clindamycin as a single agent in severe infections caused by MRSA are sparse.[57] For severe infections, clindamycin is best used in combination with another agent (eg, vancomycin).

Patients who present with cellulitis may be infected or co-infected with *S pyogenes* (group A streptococcus).[58,59] Studies of patients with pure cellulitis are limited because of the absence of culture material, and no recent studies exist to assess the role of CA-MRSA and other pathogens in these infections. Although some have tried to associate the etiology of cellulitis with nasal culture results, no conclusive determination can be made from such extrapolation.[23] Presumably, these infections are also polymicrobial in origin and MRSA coverage should be instituted for moderate-to-severe infections. Outpatient treatment of mild cellulitis could be with a first-generation cephalosporin or penicillinase-resistant penicillin either alone, or in areas with a high MRSA prevalence, with TMP/SMX. Alternatively, clindamycin can be used alone. TMP/SMX does not have adequate activity against *S pyogenes* and should not be used as monotherapy for patients presenting with cellulitis.[60,61]

Other intravenous antimicrobials that can be used for CA-MRSA infections include vancomycin, linezolid (Zyvox®), quinupristin-dalfopristin (Synercid®), and daptomycin (Cubicin®). Vancomycin is considered the mainstay antibiotic against multidrug resistant MRSA infections. However, with the fear of increased prevalence of vancomycin-resistant enterococci, and the emergence of vancomycin-intermediate/resistant *S aureus*, linezolid, quinupristin-dalfopristin, and daptomycin provide alternative therapies to vancomycin for the treatment of MRSA infections.

The in vitro susceptibility of MRSA to quinupristin-dalfopristin is excellent with reported resistance rates of <1%.[62] However, in clinical trials its efficacy in the management of infections specifically caused by MRSA is hindered by small sample sizes. Main side effects include high rates of adverse events (eg, thrombophlebitis), myalgias, and arthralgias.[63-65]

Similar to quinupristin-dalfopristin, daptomycin also has excellent in vitro activity against MRSA. In comparison, its in vitro bactericidal activity is superior to that of vancomycin and comparable to linezolid.[66-68] To date, there has been only one report of clinical failure from daptomycin-resistant MRSA.[69] Daptomycin has been approved for the use in complicated skin and soft-tissue infections caused by MRSA. However, in clinical trials with patients admitted for severe community-acquired pneumonia,

daptomycin failed to achieve equal clinical efficacy against ceftriaxone (clinical efficacy: daptomycin 79% vs. ceftriaxone 87%). A potential explanation, through animal experimentation, is inhibition of daptomycin activity by pulmonary surfactant.[70] An adverse reaction to daptomycin can include myositis with elevated creatine phosphokinase.

Linezolid also has an excellent in vitro activity against MRSA similar to that of vancomycin.[71-73] The oral formulation is almost 100% bioavailable and as a result, allows for easy intravenous-to-oral continuation therapy.[74] It has good tissue penetration, and due to its unique structure and mechanism of action, no cross-resistance with other classes of antimicrobial agents has been observed.[71,75,76] Linezolid has been evaluated for the treatment of MRSA infections in various clinical settings (eg, complicated SSTI, pneumonia, urinary tract infection, bacteremia) and has been shown to have favorable efficacy and safety profiles.[77-80] In a study of complicated SSTIs, linezolid outcomes were superior to vancomycin outcomes at the test-of-cure visit for patients with MRSA infections ($P<.001$), suggesting that linezolid may be the empiric drug of choice in areas in which MRSA is a frequent cause of these infections. The differences between linezolid and vancomycin results were most dramatic in patients with abscesses and surgical-site infections caused by MRSA.[79] When compared to vancomycin, multiple studies have also shown that the use of linezolid for the treatment of MRSA infections has resulted in significantly shorter hospital stays, likely related to the availability of an oral formulation with 100% bioavailability.[81-84] Myelosuppression (eg, thrombocytopenia and anemia) has been reported after prolonged administration (>14 days) but is reversible after discontinuation of the drug.[80,85]

Given the rising prevalence of MRSA, we recommend empirical coverage of this organism for patients presenting with other severe, life-threatening infections that may be due to *S aureus* (eg, severe sepsis, septic shock, severe pneumonia, endocarditis, necrotizing skin infections, and bone and joint infections).[27,61,86,87]

Regarding infection control, discharged patients should be advised to cover purulent wounds with appropriate dressings. Since transmission occurs through person-to-person contact, such patients should not share towels and should be reminded to keep good hand and personal hygiene. For those with confirmed or recurrent MRSA infections, nasal swabs should be obtained looking for MRSA colonization. Patients with positive cultures should be treated for 5 days with mupirocin 2% nasal ointment, which has been shown to be an effective agent for the elimination of *S aureus* carriage.[2,88] Other methods, that may also be of benefit can include washing the body with chlorhexidine-containing soap (eg, chlorhexidine gluconate 4% soap), local application of silver sulfadiazine 1% cream, or tea tree oil regimens (eg, tea tree 10% cream or tea tree 5% body wash).[17,89] In comparison to mupirocin, these interventions are less effective regimens for MRSA eradication.[89] Hand disinfectants containing both alcohol and chlorhexidine (Hibisol®) are more effective against MRSA than scrubs based only on chlorhexidine (eg, Hibiscrub®).[90]

For those patients who are going to be admitted to the hospital and are suspected of having MRSA infection, the current practice is to admit them to isolation and adhere to contact isolation precautions. Similar to HA-MRSA, the goal is to prevent the spread of CA-MRSA and protect vulnerable hospital patients from nosocomial transmission. However, considering the increasing prevalence of CA-MRSA, busy EDs, limited number of beds (especially isolation beds), and long waits for admission, this strategy might not be a practical one, and MRSA infection control strategies may need to be revised.

Conclusion

CA-MRSA is now the most commonly identifiable cause of SSTIs presenting to EDs in many cities in the United States. A known common presenting sign is a spontaneous abscess with a complaint of "spider bite." CA-MRSA demonstrates high susceptibility rates to vancomycin, TMP/SMX, rifampin, and clindamycin. Most CA-MRSA strains are resistant to macrolides and quinolones. Linezolid, quinupristin-dalfopristin, and daptomycin are newer, alternative intravenous therapies to vancomycin.

Given the rising prevalence of MRSA, patients presenting with complicated SSTIs, other than simple abscesses, should empirically be treated for MRSA. In addition, we recommend empirical coverage of this organism for patients presenting with other severe, life-threatening infections that may be due to *S aureus* (eg, severe sepsis, septic shock, severe pneumonia, endocarditis, and bone and joint infections).

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Community-associated Methicillin-resistant *Staphylococcus aureus*: **Emergency Department Perspective**

Abstract:

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections have become an emerging global health problem. Compared to health care-associated strains, CA-MRSA strains more frequently produce toxins and appear to be more virulent. They also demonstrate variable susceptibility patterns to various classes of antibiotics. Recent emergency department-based studies have demonstrated that CA-MRSA is now the most commonly identifiable cause of skin and soft-tissue infections. Empiric antibiotic therapy for patients with skin and soft-tissue infection, and those presenting with severe, life-threatening infections should include an agent that is active against MRSA.

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