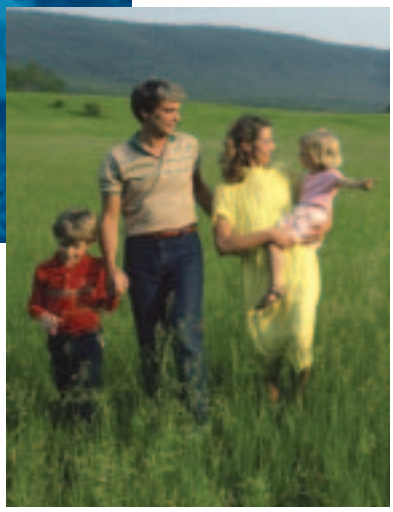
INTERNATIONAL SOCIETY ISMR OF MICROBIAL RESISTANCE

ISMR Update

VOLUME 1 | NUMBER 3 | AUGUST 2006

Community-Acquired Methicillin-Resistant *Staphylococcus aureus*: Right Here, Right Now

CME Opportunity
From the 2006 MRSA
Education Summit



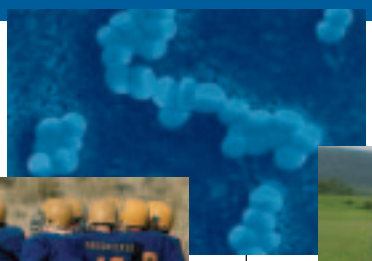
Risk factors for Community-Acquired MRSA infections

Review emerging *S aureus* genotypes

Prevention and treatment strategies

Supported by an unrestricted educational grant from Pfizer Inc.

Jointly sponsored by the University of Kentucky Colleges of Medicine and Pharmacy and the International Society of Microbial Resistance



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Community-Acquired MRSA: Right Here, Right Now

Release date: August 4, 2006
Expiration date: August 4, 2007

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Needs Statement

The epidemiology of bacterial infections can be highly dynamic. Evolution of antimicrobial resistance and disease patterns can occur so rapidly that it may be challenging to fully grasp a major new paradigm shift before another one appears. Among the most feared of the bacteria that cause infections are resistant forms of *Staphylococcus aureus*, a major cause of serious disease and mortality, both before and after the introduction of antibiotics.[1,2] Of particular concern are strains of *S aureus* that are resistant to the methicillin group of antibiotics (methicillin-resistant *S aureus*, or MRSA). Antimicrobial agents in this antibiotic group include oxacillin, cloxacillin, nafcillin, and dicloxacillin, among others. MRSA may also be resistant to antibiotics in the cephalosporin class. This monograph focuses on the changing patterns of infections due to MRSA, on the increasing seriousness of MRSA infections, and on new procedures and guidelines needed to treat and prevent infections caused by this problematic pathogen.

Accreditation Statements

Physician: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Kentucky College of Medicine and the International Society of Microbial Resistance. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

The University of Kentucky Colleges of Pharmacy and Medicine present this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected because of recognized expertise in their field.

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The University of Kentucky College of Pharmacy is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

This activity has been assigned ACPE #022-999-06-006-H04 and will award 1.0 contact hour (0.1 CEUs) of continuing pharmacy education credit in states that recognize ACPE providers. Statements of credit will indicate hours and CEUs based on successful completion of a posttest (score 70% or higher) The college complies with the Criteria for Quality for continuing education programming.

Learning Objectives

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

1) Identify the changing patterns of infections due to MRSA.
2) Discuss the increasing seriousness of MRSA infections.
3) Be aware of new procedures and guidelines needed to treat and prevent infections caused by this problematic pathogen.

Target Audience

This educational program is intended for physicians, pharmacists, and other healthcare professionals who manage the care of patients with MRSA infections, or who are at risk for MRSA infections.

Disclosure of Financial Interest

All faculty members participating in continuing medical education programs sponsored by the University of Kentucky Colleges of Pharmacy and Medicine Continuing Education Office are expected to disclose any real or perceived conflict of interest related to the content of their presentations. Faculty disclosures are listed above.

Estimated Time of Completion

This activity should take approximately 1.0 hour to complete.

Method of Participation

There are no fees for participating in and receiving credit for this activity. The participant should: read the objectives and monograph; answer the multiple-choice posttest; and complete the answer sheet with registration and evaluation and mail to:
Attn: Distance Education, Continuing Education Office, Colleges of Pharmacy and Medicine, University of Kentucky, One Quality St, 6th Floor, Lexington, KY 40507-1428.
Certificates will be mailed to participants in approximately 4 weeks after receipt of the mailed or faxed submissions. This credit is valid through August 4, 2007.

Support Statement

This activity is supported by an unrestricted educational grant from Pfizer Inc.

Joint Sponsorship Statement

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Community-Acquired MRSA: Right Here, Right Now

The epidemiology of bacterial infections can be highly dynamic. Evolution of antimicrobial resistance and disease patterns can occur so rapidly that it may be challenging to fully grasp a major new paradigm shift before another one appears. Among the most feared of the bacteria that cause infections are resistant forms of *Staphylococcus aureus,* a major cause of serious disease and mortality both before and after the introduction of antibiotics.[1,2] Of particular concern are strains of *S aureus* that are resistant to the methicillin group of antibiotics (methicillin-resistant *S aureus*, or MRSA). Antimicrobial agents in this antibiotic group include oxacillin, cloxacillin, nafcillin, and dicloxacillin. MRSA may also be resistant to antibiotics in the cephalosporin class. This monograph focuses on the changing patterns of infections due to MRSA, on the increasing seriousness of MRSA infections, and on new procedures and guidelines needed to treat and prevent infections caused by this problematic pathogen.

S aureus, particularly MRSA, is becoming an increasingly important, major pathogen.[3-7] Treatment of *S aureus* infection is associated with clinical failure and, often, hospitalization, even when disease is caused by strains susceptible to the methicillin group of antibiotics (methicillin-susceptible *S aureus*, or MSSA).[2,7,8-10] While staphylococcal infections have always presented challenges for the medical community, particularly in hospitals and other healthcare settings such as nursing homes, recent changes in the strains of pathogenic MRSA have resulted in severe infections in people in the general community formerly not suspected of being at risk for MRSA, such as young people and immunocompetent healthy persons.[4,5,11,12] Of grave concern are particular strains of MRSA that recently have arisen in the community, or community–acquired (CA-MRSA) infections. One of the primary CA-MRSA strains in the United States—identified by pulsed-field gel electrophoresis typing as USA300—has genetic differences from the typical strain that has been circulating in the recent past.[13] The differences require reevaluation in the approach to diagnosis and treatment in both community and healthcare settings. Given the seriousness of many of these infections, it is crucial for healthcare professionals to familiarize themselves with new guidelines so that appropriate patient care can be implemented in a timely manner. Furthermore, changes in public health approaches must address the recent epidemiologic changes in MRSA infection and transmission.

Changing Epidemiology of MRSA Infections

The first penicillin-resistant strains of *S aureus* appeared in the 1940s shortly after penicillin was introduced.[14] By the 1970s, penicillin-resistant isolates constituted the majority of *S aureus* strains recovered from infections found in hospitals and the community; including rural, urban, and suburban settings across the United States and elsewhere in the world.[14] With the introduction of methicillin in 1961 came methicillin resistance. By the mid-1980s, 5% to 10% of hospital-associated (HA) *S aureus* isolates were MRSA.[14,15] By 1998, 50% of *S aureus* isolates found in intensive care units were methicillin-resistant[14] (see Figure 1).

Traditionally those at greatest risk for colonization or infection with *S aureus* (MRSA or MSSA) have been intravenous drug users, hemodialysis or surgical patients, and patients with diabetes mellitus or AIDS,[16,17] while individuals most likely to contract a MRSA infection were those in hospitals, particularly in intensive care units, patents in long-term care facilities, or those with prior antibiotic exposure or exposure to MRSA-colonized patients.[14] Until recently, patients with community infections typically had contact with MRSA strains from healthcare settings, contact with healthcare workers, or had a history of antibiotic use.[14,15]

However, by the mid-1990s CA-MRSA infections were being described in populations that did not have these traditional risk factors, and the newly observed strains associated with these infections were genetically distinct from those that were found in healthcare settings, an unanticipated development.[15,18] Moreover, the rates of CA-MRSA appeared to be rising dramatically within the community as a whole, with most CA-MRSA infections involving skin and soft tissue; there also were some indications that skin and soft-tissue infections (SSTIs) were on the rise.[15,18,19]

The USA300 strain of MRSA and others that arose in the community including the USA400 strain, are quite different from typical HA-MRSA strains.[14,15] The USA300 strain occurs in diverse regions of the United States,[20] while the USA400 strain has been found in several outbreaks and "endemic" CA-MRSA infections in the US Midwest.[21] There is consistent evidence that the CA-MRSA strains are susceptible to a group of oral antibiotics such as tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX), and clindamycin, whereas HA-MRSA is most often resistant to these and several other

antimicrobial agents, as would be expected with pathogens that arise in a setting of heavy antimicrobial use.[14,15]

From a genetic perspective, HA-MRSA strains tend to carry the staphylococcal cassette-chromosome *mec* (SCC*mec*) types I, II, or III, which convey genes for resistance to lincosamides, macrolides, tetracyclines, other antibiotics, and heavy metals,[22,23] while CA-MRSA strains more often carry types IV or V, which are smaller and contain fewer resistance genes.[23,24] Furthermore, the Panton-Valentine leukocidin (*PVL*) gene is common in CA-MRSA strains, but is typically absent from most HA-MRSA isolates.[25] These differences suggest that the CA-MRSA isolates are not simply HA-MRSA strains that have disseminated into the community and evolved along a different path.[14,15] There is growing evidence that CA-MRSA strains, such as USA300, are more virulent than those occurring in the hospital setting, and perhaps what is more disturbing, they lead to more serious illness in individuals who are otherwise healthy.[14,15] Of concern are recent reports that some CA-MRSA strains, especially USA300, ST80, and ST30, have now become common in hospitals and institutional settings in certain regions of the world.[14,15] Thus it may no longer, as useful to make a great distinction between CA-MRSA and HA-MRSA strains; rather, it may be important to determine whether or not infections are due to the newer strains such as USA300, regardless of clinical setting.

Virulence Factors

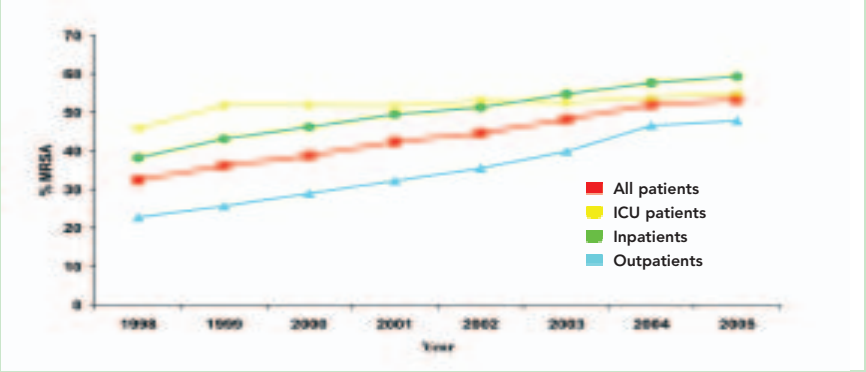
Evidence has suggested that some virulence factors and toxins produced by USA300 and similar strains favor bacterial survival.[15,18] Virulence factors may allow pathogens to adhere to surfaces and invade or avoid the immune system, while causing toxic effects to the host.[26] A component of the infection process associated with *S aureus* may be related to the production of exotoxins, several of which have been characterized.[8] A number of superantigens have been identified—TSST-1 (toxic shock syndrome toxin-1), SEB (staphylococcal enterotoxin serotype B), and SEC (staphylococcal enterotoxin serotype C).[8] Along with PVL, these toxins are associated with toxic shock syndrome, purpura fulminans, and necrotizing MRSA pneumonia.[8,27] The superantigens induce massive cytokine release from T cells and macrophages. The ensuing hypotension and shock are believed to be the result of tumor necrosis factor α and β (TNF-α and TNF-β)–mediated activity.[8]

Recent clinical reports have drawn attention to the possible role of PVL in virulence, either directly or as a marker for closely associated pathogenic factors. PVL is a 2-component staphylococcal pore-forming membrane cytotoxin that operates by targeting mononuclear and polymorphonuclear cells.[1,26] PVL induces severe inflammatory lesions, capillary dilation, chemotaxis, polymorphonuclear karyorrhexis, and tissue necrosis.[26] Its association with necrotizing pneumonia is particularly disturbing. A French study by Gillet et al compared 16 cases of community-acquired pneumonia caused by PVL-positive *S aureus* with 36 cases of PVL-negative *S aureus* pneumonia.[27] The median age of those with PVL-positive disease was 14.8 years, as compared with 70.1 years for those with PVL-negative infections (P = .001), and the crude mortality rate among the PVL-positive group was 75% as compared with 47% in the PVL-negative group (P = .11).[27] However, when the analysis was restricted to patients with no serious comorbidities, the mortality was 75% in the PVL-positive group and 36% in the PVL-negative group (P = .05).[27] While none of the PVL-positive patients had risk factors for infection, 56% of those with PVL-negative disease had one or more factors.[27] Bacterial infection in many PVL-positive patients was preceded by influenza-like syndrome.[27] Interestingly, only one of the 16 PVL-positive isolates was methicillin-resistant, but unfortunately the investigators failed to type the strains of *S aureus*.[27] Overall, a mortality rate of approximately 70% has been associated with community-acquired pneumonia caused by PVL-positive CA-MRSA.[28]

Gonzalez et al reviewed the cases of 14 previously healthy adolescents who developed severe staphylococcal sepsis between September of 2002 and January of 2004.[9] Although no deaths from this illness had occurred in the 3 years prior to that time at this reporting institution, 3 patients died in the group reviewed despite the fact that the *S aureus* strains associated with the infections were susceptible to at least 2 of the antibiotics given (gentamicin and vancomycin).[9] Bone and joint infections occurred in 93% of these patients, and 57% had pyomyositis of muscles adjacent to the infected bone and joints.[9] Vascular complications occurred in 29% of the patients.[9] Genes for PVL were present in all isolates, including the 2 that were methicillin-susceptible (MSSA), and all isolates were identical or closely related to the predominant clone found in Houston, Texas—USA300 ST8.[9] *PVL* genes have been detected in 93% of strains associated with furunculosis, 55% associated with cellulitis, 50% associated with cutaneous abscess, and 13% of strains associated with finger-pulp infection, although they are not found in more superficial infections.[3,29] It has been hypothesized that the rapid spread of the USA300 MRSA strain has been facilitated by the presence of PVL, and this is currently under investigation.[19]

Others have found what appears to be a very high likelihood of progression to infection among MRSA-colonized patients. For example, a study by Ellis et al of the natural history of CA-MRSA among soldiers indicated that 38% of those colonized with CA-MRSA at the initial examination subsequently developed infection, and that nearly all of the infections were caused by a single PVL-positive strain.[24] A little more than half (55.6%) of the total isolates (including both baseline isolates from nasal screening cultures and clinical isolates) belonged to one genotype that appeared similar to USA300, but 8 of 9 available clinical CA-MRSA isolates were of this single genotype.[24] Elsewhere, investigators have found that approximately 25% of patients colonized with PVL-positive strains of CA-MRSA go on to develop infection.[30]

Figure 1. MRSA trends: cumulative data from 1998 to March 2005.



From Styers D, et al. *Ann Clin Microbiol Antimicrob.* 2006;5:2. Available at BioMed Central.

Who Gets CA-MRSA?

If traditional risk factors do not appear to predispose individuals to CA-MRSA, then what does? Who does get CA-MRSA? A number of studies have been conducted to characterize those whose infections are caused by CA-MRSA, and the answers are both surprising and disquieting. Fridkin et al conducted a population-based surveillance study in Atlanta and Baltimore and a hospital-laboratory–based sentinel surveillance in Minnesota, from which were found 1647 cases of CA-MRSA.[2] In Atlanta, the incidence of MRSA infections was 25.7 per 100,000 residents, while for Baltimore the incidence was 18. Risk was significantly greater for those aged 2 years and younger rather than older persons in both cities (relative risk [RR], 1.51; 95% confidence interval [CI], 1.19-1.92), and was also significantly higher for blacks rather than whites of all ages in Atlanta (age-adjusted RR, 2.74; 95% CI, 2.44-3.07).[2] A high percentage of these infections (77%) were SSTIs, while 6% of cases were invasive (defined as presence of bacteremia, meningitis, septic arthritis, or osteomyelitis)[2] (see Figure 2).

In a study conducted among rural populations in Idaho and Utah, Stevenson and colleagues found significantly greater rates of HA-MRSA in communities that had a high incidence of CA-MRSA.[16] However, a higher proportion of CA-MRSA (65%) than of HA-MRSA (49%) infections were SSTIs.[16] In patients with co-existing factors, such as comorbidities or prior antibiotic use, where it could not be determined whether the strain was CA-MRSA or HA-MRSA, SSTIs constituted 60% of infections.[16] Another study, conducted in Los Angeles, found that 114 of 157 patients hospitalized for *S aureus* infections, or 73%, had community-associated infections. Of these, 62% were MRSA, 38% were MSSA, and 86% of the overall clinical infections were SSTIs. Factors associated with CA-MRSA infections were younger age, recent contact with a person who had an SSTI, and use of illicit nasal drugs.[31] Likewise, a French study found that CA-MRSA infections were more likely to occur in children and young adults.[3] Again, most of the infections were SSTIs; however, 2 cases of necrotizing pneumonia occurred, and both resulted in death of the infected child.[3]

Outbreaks of CA-MRSA infection have also occurred among participants in team sports. In Colorado, a cluster of 5 MRSA infections was found among members of a fencing club and their immediate family members. Four patients developed multiple skin abscesses, and one developed paraspinal myositis with bacteremia. Overall, 3 patients required hospitalization and received intravenous antibiotic therapy.[7] Investigators noted that the fencing club lacked showers; sharing of clothing, masks, and weapons was common; and a sensor wire used to determine points scored was not routinely cleaned.[7] CA-MRSA infections have also been noted among football players and wrestlers. Infections occurred in 10 football players on a Pennsylvania college football team, and 70% of these infected players required hospitalization. Risk factors for CA-MRSA infection included skin trauma from turf burns, shaving, and sharing of unwashed bath towels.[7] Two college football players in Los Angeles also experienced MRSA skin infection that required hospitalization, and one required surgical debridement and skin grafts. These players reported frequent skin trauma and failure to cover wounds 50% of the time.[7] In Indiana, 2 high school wrestlers developed MRSA skin infections.[7]

Professional football players have also been affected by USA300, PVL-positive CA-MRSA infections. During the 2003 season, 9% of the players on the St. Louis Rams developed MRSA skin infections associated with turf abrasions. Risk of infection included players who played lineman or linebacker positions and also those with higher body mass index. Although nasal carriage of MRSA was not found during the outbreak investigation, contamination of whirlpools and taping gel was evident.[20] The lack of nasal colonization may be related to antimicrobial treatment that had eliminated nasal carriage of MRSA.[20] Interestingly, football players tend to be heavy antibiotic users—up to 10 times the amount used by the general population, and it is possible that this factor played a role in the emergence of MRSA in this setting.[20]

Other groups that share close quarters have been affected by MRSA infections. In 2002, CA-MRSA outbreaks occurred among prisoners of the Los Angeles County Jail, where 928 inmates were diagnosed with MRSA infections. Initially they were assumed to be secondary to spider bites, but subsequent examination demonstrated no insect infestation.[6] (Misdiagnosis of MRSA as infection caused by brown recluse spiders is quite common, even in areas where these spiders are not found[32,33]).

In this case, 66 inmates were hospitalized for MRSA infection, all with initial SSTIs, but 10 went on to develop invasive disease, including bacteremia, endocarditis, or osteomyelitis.[6] Resistance to fluoroquinolones was noted among some of these strains.[6] Frequent MRSA infections have also been reported in correctional facilities in Georgia and Texas.[6]

Outbreaks of MRSA infections have similarly been noted among military recruits, postpartum women, men who have sex with men, and isolated populations including Native Americans, Native Alaskans, Native Hawaiians, Aboriginals, and Pacific Islanders.[4,6,24,34,35]

Reservoirs and Modes of Transmission

Asymptomatic colonization with *S aureus* is much more common than active infection, since humans serve as a natural reservoir for this microbe.[14] Higher carriage rates of *S aureus*, compared to the general population, are associated with intravenous drug users, insulin-dependent diabetes, patients with dermatologic conditions, patients with indwelling intravascular catheters, and healthcare workers.[14,36] A study by Charlebois et al of the urban poor in San Francisco found that 23% of individuals were colonized nasally with *S aureus*. Twelve percent of isolates were methicillin-resistant, making the overall prevalence of nasal colonization with MRSA in this population 2.8%.[37] When soldiers in basic training were evaluated for prevalence of *S aureus* colonization, carriage of CA-MRSA was 3%, similar to the finding of the Charlebois study, and 56% of these were PVL-positive USA300 strains. An additional 28% were colonized with MSSA.[24] Colonization with CA-MRSA was a risk factor for subsequent SSTI infection, 38% of MRSA-colonized soldiers developing soft-tissue infections, whereas only 3% of participants colonized with MSSA developed such infections.[24]

More is known about the prevalence of *S aureus* strains in patients admitted to hospitals. A study conducted at an inner city hospital in Atlanta, Georgia, found a high prevalence of *S aureus* nasal colonization at the time of admission. More than 7% of patients were found to be colonized with MRSA and 16% were colonized with MSSA.[38] Among HIV-positive patients, the prevalence of MRSA was 17% compared with 6% in HIV-negative patients. Only 7 patients (13%) colonized with MRSA, were either admitted with or subsequently developed a confirmed MRSA infection, although 5 of these 7 patients developed bacteremia. Thirty percent of the MRSA isolates were identified as USA300, and overall colonization with USA300 in this population was 2.2%.[38] Nearly all USA300 isolates carried the SCC*mec*IV and *PVL* genes.[38]

Risk factors for the acquisition of CA-MRSA appear to be associated with what has come to be known as the "Cs" of CA-MRSA transmission: Contact, Crowding, Contaminated items (and environmental surfaces), Compromised skin integrity, and Cleanliness (or lack thereof). Familial outbreaks also suggest that close contact and possibly shared items are key mechanisms of transmission.[39]

Surveillance and Detection

In 2002, an outbreak of CA-MRSA infections affected patients in the labor and delivery, nursery, and maternity wards of a large New York City hospital. Genetic analysis indicated that the strain involved was USA400.[21] None of the infected patients had evidence of infection on admission to the hospital.[21] Surveillance data that had been gathered from a total of 4345 isolates of *S aureus* collected in 1999, 2001, and 2003 were analyzed, and indicated that 44% of isolates were methicillin-resistant.[21] Only 11 isolates, however, possessed the same genetic pattern as the outbreak strain, and 9 of these 11 had SCC*mec*IV.[21]

Prevention and Management of Infection

Prevention

Prevention of infection and outbreaks of MRSA or MSSA is relatively well investigated in the hospitals and other healthcare settings such as nursing homes and dialysis units,[40] although some infection control issues remain controversial or untested in diverse settings.[40-42] To prevent spread of MRSA within hospitals, it is recommended that those at higher risk for MRSA carriage be screened at admission and isolated if found to be colonized.[38] Surfaces in examination rooms should be cleaned with commercial disinfectants or diluted bleach (1 tablespoon to 1 quart of water), and wound dressing and other materials that come into contact with pus, nasal discharge, blood, and urine should be disposed of carefully.[5] Healthcare providers need to wash their hands between contacts with patients[5] and should don fresh gowns and gloves for contact with each patient.[43,44]

Prevention of MRSA infection in community settings is essential, as illustrated by MRSA outbreaks among athletes, military personnel, and prisoners.[5-7] The Centers for Disease Control and Prevention (CDC) has developed guidelines for the prevention of CA-MRSA infection among members of competitive sports teams. The CDC recommends that athletes and others in close contact avoid sharing equipment and towels; additionally, common surfaces such as benches that could become contaminated with MRSA or MSSA should be carefully cleaned on a regular basis.[7] Wounds should be covered, and individuals with potentially infectious skin lesions should be excluded from practice and competitions until the lesions have healed or are covered. Good hygiene, such as frequent showering and use of soap and hot water, should be encouraged among athletes, military recruits, prisoners, and all persons who live or work in similarly close contact with each other.[7]

Other preventative measures at this point are still investigational. An *S aureus* conjugate vaccine has been studied in hemodialysis patients, who are at relatively high risk of contracting *S aureus* bacteremia.[45] In a double-blind, randomized trial conducted in 1804 patients on hemodialysis, the vaccine provided partial immunity to subjects and

reduced *S aureus* bacteremia rates for a period of from 3 to 40 weeks after vaccination, but immunity waned after 40 weeks.[45] This vaccine is not approved by the US Food and Drug Administration (FDA) and is not commercially available; unfortunately, there have been no further major advances in the development of a safe and effective vaccine against *S aureus*.

Rapid identification of MRSA may be another important step in the control and treatment of MRSA infection. Recently, an easy to use, real-time polymerase chain reaction (PCR) assay has been developed for the detection of MRSA nasal carriage. Identification, with a specificity of 98.4%, a positive predictive value of 95.3%, and a sensitivity and negative predictive value of 100% can be made in less than one hour.[46] This may offer an advantage over standard tests, which currently take 48 hours to perform.[46] This new test is able to identify the major SCC*mec* types I, II, III, and IV, as well as the IV subtypes a, b, and c.[46] Although the role of these tests in clinical practice and infection control has yet to be defined, tests may help prevent unnecessary isolation of patients or identify MRSA carriers when used as part of a more global screening strategy. An assay for the rapid identification of PVL has been developed as well,[47] and use of this type of test could help provide more targeted antimicrobial therapy in the future.

Wound Care of Infected Patients

Once an infection has been established, wound cultures should be obtained whenever feasible. Ideal samples for culture include pus or grossly infected tissue. Cultures from ulcers are of dubious utility, as bacteria isolated from the skin may be due only to colonizing strains and not pathogens. Antibiotic therapy may not be needed in all cases of SSTIs when adequate surgical drainage can be achieved. One investigation demonstrated that in children with *S aureus* infections who had abscesses measuring less than 5 cm in diameter and no systemic signs of infection (eg, fever), incision and drainage resulted in cure most of the time even when antibiotics ineffective against the pathogenic strain were prescribed.[48] Another small investigation randomized patients with relatively uncomplicated skin infections to treatment with incision and drainage, either with or without antibiotics. This investigation demonstrated similar cure rates in the antibiotic-treated and placebo groups.[49] Nevertheless, when incision and drainage is used without antibiotics or when inappropriate antibiotics are prescribed, sometimes failures do occur.[50,51] Therefore, when antibiotics are not prescribed, patients should have follow-up care (ie, a follow-up appointment or phone call) and be instructed to seek medical care if symptoms worsen or do not resolve. If antibiotics are prescribed, empiric choices should be made with an awareness of the likelihood of an *S aureus* infection being caused by MRSA. Additionally, local patterns of antibiotic susceptibility among CA-MRSA should be used to help direct empiric therapy against this pathogen.

Antibiotic Therapy

Vancomycin has been a mainstay of treatment for serious infections that are resistant to β-lactams, because traditionally there have been no good alternatives.[52] However, in the treatment of MSSA, vancomycin has been associated with a slower clinical response and longer duration of bacteremia compared to β-lactams.[15] Vancomycin may also have other limitations; treatment failures are known to occur with vancomycin, even when the minimum inhibitory concentrations (MICs) are well within the susceptibility range.[15,53] The relatively recent emergence of vancomycin-resistant and vancomycin-intermediate susceptible *S aureus* (VRSA and VISA) is also of concern, as heavy vancomycin use may drive the emergence of these strains and even further limit the utility of this antibiotic.[15]

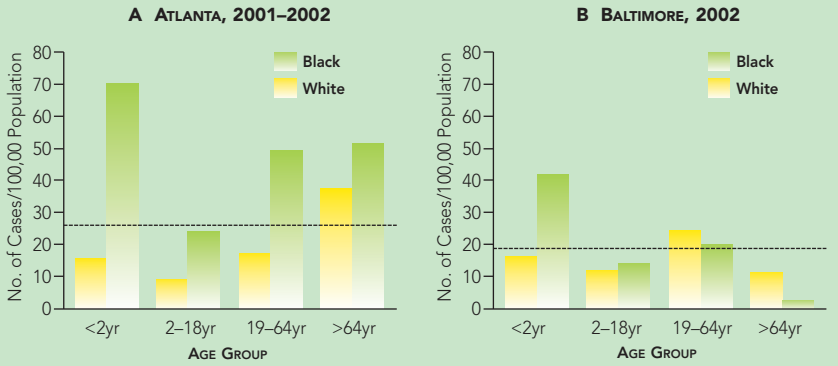
A number of older antibiotics are active in vitro against most CA-MRSA strains, but clinical studies on the efficacy and safety of older agents such as tetracyclines are few. Some tetracycline-resistant strains are susceptible to doxycycline and minocycline. However, some doxycycline- and minocycline-susceptible isolates carry inducible efflux genes against tetracyclines, which may limit their clinical efficacy.[54,55] Nevertheless, doxycycline and minocycline have been successfully used to treat MRSA infections in relatively small case series.[15,56]

There has been much interest in the use of TMP-SMX for the treatment of *S aureus*, given that this antibiotic is active in vitro against most CA-MRSA strains. However, data on clinical efficacy are limited. The largest published trial on the use of TMP-SMX for *S aureus* is a randomized clinical trial conducted among intravenous drug users with *S aureus* infection, the majority of whom were bacteremic; TMP-SMX demonstrated a lower clinical cure rate for *S aureus* infection compared with vancomycin (85% vs 98%).[57] Interestingly, no clinical failures occurred among patients with MRSA. As for the use of TMP-SMX for less severe SSTIs, many have successful anecdotal experience or consider it a viable treatment option.[15,19,58]

Fluoroquinolones have variable activity against CA-MRSA strains; however, in many locales fluoroquinolone resistance among MRSA strains has been reported to be very high (>40%-50%).[2,31,59] Therefore, fluoroquinolones are probably not useful unless the organism targeted is known to be susceptible to earlier generation fluoroquinolones, including ciprofloxacin. Susceptibility to ciprofloxacin indicates that low-level or partial fluoroquinolone resistance is probably not present.

Among commercially available agents, moxifloxacin and gemifloxacin have the best in vitro activity against *S aureus*, but there are few clinical data on the use of these agents for the treatment of CA-MRSA infection.

Figure 2. Incidence of community-associated MRSA disease in Atlanta and Baltimore, according to race and age group.[2]



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Clindamycin has been used successfully to treat CA-MRSA disease,[48,60,61] but resistance to this agent has been encountered,[15] in some areas, resistance is greater than 10% to 15%,[2,31] and was as high as 93% in a Taiwanese series.[62] Inducible clindamycin resistance is also a concern. Some strains that are reported as clindamycin susceptible and erythromycin resistant can develop resistance when exposed to lincosamides (such as clindamycin), macrolides (such as erythromycin), and streptogramins (such as quinopristin/dalfopristin). This inducible resistance can be detected via the use of the D-test, which, if positive, is considered to be diagnostic for inducible resistance.[63] The clinical implications of a positive D-test are controversial, but many believe that clindamycin should not be used to treat D-test–positive strains, although successes have been seen treating mild disease.[60] Nevertheless, most experts believe that confirming whether a strain is D-test–negative is critical when considering treating an *S aureus* infection with clindamycin, especially a serious syndrome.[63] The ability of clindamycin to inhibit PVL expression, however, is a distinct advantage of this compound,[64] although the clinical benefit of this inhibition is not well delineated.

Several relatively new antimicrobials may also have roles in the treatment of MRSA. For example, linezolid, like clindamycin, inhibits the production of toxins,[64] including inhibition of toxin production by clinical isolates.[65] Unlike many of the older generic agents that have been resurrected as treatments for MRSA, there is considerable clinical experience with linezolid, and results have been published. In clinical trials, linezolid was found to be equivalent to vancomycin for the treatment of hospital-acquired pneumonia.[66] In retrospective clinical trial subgroup analyses of patients with HA-MRSA nosocomial and ventilator-associated pneumonia, linezolid was found to be associated with higher cure rates and lower mortality compared with vancomycin.[67,68] These analyses have been criticized due to their retrospective methods and use of subgroup analyses; thus, caution has been expressed about the risk of over-interpreting these findings.[69] Nevertheless, there may be biologic plausibility for the advantages of linezolid over vancomycin for the treatment of pneumonia. Limitations of vancomycin in the treatment of pulmonary infections have been noted and are ascribed to the relatively low concentrations this compound achieves in the epithelial lining fluid (ELF), a space in which concentrations are believed to correlate well with clinical outcomes.[70,71] Conversely, linezolid penetrates well into the ELF, with concentrations similar to that of serum (compared with ELF concentrations of approximately one sixth that of serum for vancomycin).[70,72] In 2005, the American Thoracic Society listed linezolid as an alternative to vancomycin in the treatment of MRSA ventilator-associated pneumonia.[73] Other trials have shown that linezolid has efficacy comparable to vancomycin in treating MRSA.[15,74] And, in a situation analogous to a pulmonary MRSA infection study, linezolid was found to be not only equivalent to vancomycin in the treatment of surgical site and complicated skin infections, but also had a significantly higher cure rate compared to vancomycin in a subgroup analysis of MRSA-infected patients.[75,76] Linezolid may be limited by its bacteriostatic rather than bactericidal action against *S aureus*. In infections where this is arguably an important factor,[77] such as endocarditis, linezolid may not be an appropriate choice when other options exist.[15,74,77]

Quinupristin/dalfopristin, another relatively new agent for Gram-positive infections, has proved disappointing for treatment of pneumonia in studies that have shown it to be inferior to vancomycin.[78] Furthermore, quinupristin/dalfopristin appears to be less effective in the presence of constitutive expression of macrolide-lincosamide-streptogramin (MLS) resistance, which is found in some MRSA strains.[15,78,79] The need to give this agent intravenously via a central line (to decrease infusion-related adverse events) also limits its utility. Daptomycin has bactericidal activity against *S aureus* and has been approved for treatment of complicated SSTIs due to susceptible Gram-positive pathogens.[15,80] The agent has impressive in vitro activity against high inocula of *S aureus*,[81] although the clinical advantage of this activity is not well delineated. Daptomycin should not be used in the treatment of pneumonia, as pulmonary surfactant inactivates this agent and it has been found to be inferior to comparators in clinical investigations of pneumonia.[15,67,68,82]

Table 1. CDC Recommendations on Clinical Management of CA-MRSA SSTIs

- ➤ **Consider MRSA in diagnosis of SSTIs**
- ➤ **"Spider bite" may be MRSA**
- ➤ **Consider MRSA in event of syndromes such as**
  - **Sepsis**
  - **Osteomyelitis**
  - **Septic arthritis**
  - **Severe pneumonia**
  - **Pneumonia following flu-like illness**
- ➤ **Culture & test susceptibility of abscesses/purulent SSTIs**
- ➤ **Incise & drain furuncles, abscesses, septic joints**
- ➤ **Initiate empiric antibiotic therapy if infection is**
  - **Severe**
  - **Progressing rapidly**
- ➤ **Initiate empiric antibiotic therapy in the presence of**
  - **Cellulitis**
  - **Systemic illness**
  - **Immune suppression**
  - **Serious comorbidities**
  - **Very young and elderly patients**
  - **Lack of response to incision/drainage**

Adapted from CDC Experts' Meeting. Available at: http://www.ccar-ccra.com/english/pdfs/CAMRSA_ExpMtgStrategies.pdf

However, daptomycin appears efficacious in the treatment of bloodstream infections and right-sided endocarditis caused by *S aureus*,[83] and recently received approval for this use.

For multidrug-resistant infections caused by MRSA that require parenteral therapy, vancomycin, linezolid, daptomycin, and quinupristin/dalfopristin are the only agents that are reliably active against many HA-MRSA infections.[15] TMP-SMX, tetracyclines, clindamycin, and fluoroquinolones may be alternatives if susceptibility of the infecting strain to these agents is documented. However, compared with many of the newer agents, clinical experience with these agents is relatively scant.[15]

Optimizing Outcomes

The CDC has suggested a number of strategies to improve the clinical management of MRSA in the community; recommendations focus on SSTIs. The guidelines suggest that MRSA should be considered in the differential diagnosis of any SSTIs that are compatible with *S aureus* infections, such as skin abscesses. A complaint of "spider bite" should raise alarms, as many patients, when queried about their spider bites, admit they never saw a spider and do not even live in an area that has spiders whose bites can cause similar lesions; many of these patients are ultimately diagnosed with CA-MRSA infections.[33,84,85] MRSA should also be considered when other syndromes compatible with *S aureus* infection are present, such as sepsis syndrome, osteomyelitis, septic arthritis, and severe pneumonia or pneumonia following an influenza-like illness.[84] Many have argued that all patients with abscesses or purulent skin lesions should have specimens collecte for culture and susceptibility testing.[84] Currently, there is no evidence to suggest that genetic typing and identification of toxin genes has a role in clinical practice.[84]

Incision and drainage of all furuncles and abscesses is standard primary therapy. Antimicrobial therapy is critical, although it may be deferred in select patients who successfully undergo incision and drainage, have very limited disease, and are not immunocompromised.[84] Other factors to consider for determining treatment are the presence of systemic illness, underlying immune suppression, or serious comorbidities such as HIV infection or diabetes mellitus. Extremes of age should also be considered, as well as the possibility that an abscess may not drain properly due to its location or that there may be a lack of response to incision and drainage alone[84] (see Table 1).

Empiric antibiotic decisions should be based on knowledge of local susceptibility patterns of MRSA strains isolated from outpatients and inpatients. When an oral antibiotic with activity against MRSA is desirable, clindamycin, tetracyclines, TMP-SMX, and linezolid may be considered; rifampin may also be used, but only in combination with other agents.[84]

Conclusion

Many have asked how high the prevalence of CA-MRSA must be to trigger use of antibiotics with reliable activity against MRSA for empiric treatment of community-acquired SSTIs and infections likely caused by *S aureus*. The answer is, that for virtually all locales in the United States, the time is now. The prevalence and severity of MRSA in community infections is currently high enough in the United States and many locales worldwide to require new patterns of treatment. The role of newer, rapid diagnostic tests may have a role in clinical practice, although this requires further study. Better surveillance and a better understanding of the efficacy of various treatment regimens for SSTIs are needed as well. An effective *S aureus* vaccine would also be an important advance. Because few new antibiotic classes that are active against MRSA are on the horizon, antimicrobial resistance will likely remain a constant and increasing threat. It is essential to make these important changes now—implementing appropriate and judicial use of antibiotics, targeting likely pathogens early with antimicrobial agents when antibiotic therapy is needed, maintaining surveillance of microbial development and epidemiology, and preventing infection wherever possible.

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Notes

Community-Acquired MRSA: Right Here, Right Now

CE Posttest

Select the single-letter response that best answers the question or completes the sentence.

1) When compared to hospital-associated MRSA strains, community-acquired MRSA strains are generally associated with:
a. Susceptibility to a broader range of antibiotics, but lower PVL prevalence
b. Similar antibiotic susceptibility, but greater prevalence of PVL
c. Susceptibility to a broader range of antibiotics, and higher PVL prevalence
d. Susceptibility to a narrower range of antibiotics, and similar prevalence of PVL

2) True or False: The 2003 MRSA outbreak in the St. Louis Rams football team members was associated with high rates of nasal colonization.

3) In the study by Gillet on community-acquired pneumonia caused by *S aureus*, the investigators found:
a. There were no differences in age or mortality between PVL-positive and PVL-negative patients
b. PVL- positive patients were younger and had a lower crude mortality compared to PVL-negative patients
c. PVL-positive patients were older with higher crude mortality compared to PVL-negative patients
d. PVL-positive patients were younger and had higher crude mortality compared to PVL-negative patients

4) In a 2004 study of patients hospitalized with *S aureus* infections, what percent were, according to Miller and colleagues, found as being community-associated infections?
a. 46%
b. 54%
c. 60%
d. 73%
e. 82%

5) Which risk group(s) is/are associated with higher MRSA carriage rates?
a. IV drug users
b. Insulin-dependent diabetics
c. Patients with dermatologic conditions
d. Health care workers
e. Patients with indwelling catheters
f. HIV positive patients
g. Options d, e, and f
h. All of the above

6) True or False: The clinical implications of a positive D-test for clindamycin are clearly understood.

7) True or False: Use of trimethoprim-sulfamethoxazole (TMP-SMX) for community-associated MRSA infections is supported by several randomized clinical trials.

8) True or False: Clinical trials have shown that quinopristin/dalfopristin is less effective than vancomycin.

9) Antibiotics that act primarily through inhibition of bacterial protein synthesis include:
a. Clindamycin
b. Linezolid
c. Vancomycin
d. Daptomycin
e. Options a and b
f. Options a, b, and c

10) True or False: The USA300 MRSA strain refers to a community-acquired pathogen characterized by PGEF patterns.

Community-Acquired MRSA: Right Here, Right Now

Released: August 4, 2006 Expires: August 4, 2007

A passing score of 70% or higher on the posttest awards the participant a maximum of 1.0 *AMA PRA Category 1 Credit™* or 1.0 contact hour (0.1 CEUs) of continuing pharmacy education credit. To claim continuing education credit, individuals must complete the self-study activity, posttest, and evaluation and mail this form, postmarked by August 4, 2007 to:

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University of Kentucky Colleges of Pharmacy and Medicine
Continuing Education Office
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Lexington, KY 40507-1428

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Posttest Answers (circle the correct answer)

1.	a	b	c	d			
2.	True	False					
3.	a	b	c	d			
4.	a	b	c	d	e		
5.	a	b	c	d	e	f	h
6.	True	False					
7.	True	False					
8.	True	False					
9.	a	b	c	d	e	f	
10.	True	False					

Evaluation	Poor		Satisfactory		Excellent
1. Extent to which the objectives were achieved:	1	2	3	4	5
2. Potential impact on your practice:	1	2	3	4	5
3. Detail of information presented:	1	2	3	4	5
4. Extent to which commercial bias appeared:	1	2	3	4	5

5. Suggestions for future CE topics:

_____

_____

_____

ISMR Update

INTERNATIONAL SOCIETY ISMR OF MICROBIAL RESISTANCE

Community-Acquired Methicillin-Resistant *Staphylococcus aureus*: Right Here, Right Now

CME Opportunity
From the 2006 MRSA
Education Summit

Med EDirect

25 Lindsley Drive, Suite 208
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