Community Acquired Methicillin Resistant *Staphylococcus Aureus*

John S. Hammes, M.D.

Abstract

Community acquired Methicillin Resistant *Staphylococcus aureus* (ca-MRSA) is an important cause of illness among active duty forces in general and among Special Operations personnel in particular. It is increasingly common and has the potential to continue to spread to affect a large proportion of the population. This pathogen may cause degradation in operational readiness, time lost from training, and potentially disabling damage to soft tissues and joints. This article has several purposes. It will describe background and significance of ca-MRSA related disease, describe the clinical manifestations of ca-MRSA disease, explain how the bacterium causes illness, and explain the measures needed to treat and prevent the spread of ca-MRSA infections.

Learning Objectives

1. Describe background and significance of ca-MRSA related disease.
2. Review the microbiologic, clinical and diagnostic features of ca-MRSA disease.
3. Explain the measures needed to treat and prevent the spread of ca-MRSA infections.

Background and significance

Why is ca-MRSA important? It is the rare pathogen which is virulent (i.e., has great disease causing potential), is highly contagious (has the ability to disseminate widely) and is resistant to most commonly used antibiotics.[1]

Ca-MRSA has become increasingly common both in civilian and military environments. More specifically, as many as 70% of community isolates of *Staphylococcus aureus* in Houston and Atlanta are resistant to methicillin and similar beta-lactam antibiotics.[2,3] While resistant strains of Staphylococcus aureus have been described since early in the antibiotic era, important changes in the origins, genes, ability to cause disease, and management of this germ have taken place in the last 10 years. For example, early MRSA bacteria and infections appeared to result from widespread use of antibiotics, particularly in healthcare settings. When it occurred in the community, it was typically a result of spread from a hospital or nursing home. However, present day ca-MRSA appears to be microbiologically different from what may be viewed as traditional, older MRSA.

The epidemiology of ca-MRSA should be of significant interest to military healthcare providers. Traditional MRSA often caused disease among immune-compromised and/or hospitalized hosts. Ca-MRSA most often causes disease among relatively young persons. The spread of ca-MRSA can usually be traced to close contacts such as family members, athletic teammates, or barracks dwellers. In fact, along with small children, athletes, and inmates of correctional facilities, military personnel are an identified population at risk for ca-MRSA infection.[1] In addition to recent experience reviewed below, outbreaks of ca-MRSA have been reported from Naval Special Warfare Center (NSWC) in 2002[4] and multiple other military sites, to include the U.S. Naval Submarine Force. Of 1888 MRSA isolates found at Naval Medical Center San Diego (all obtained from Branch Medical Clinics and the tertiary hospital facility) between 1990 and 2004, 65.4% were ca-MRSA.[5] It is possible that some of these cases were from dependents / retirees, but clearly this pathogen has military relevance

To underscore the significance of ca-MRSA, we reviewed medical attritions from four classes at Basic Underwater Demolition School (BUD/S) at NSWC in San Diego during a nine month period in 2006 (see figure 1) Of students rolled back or dropped from training due to medical causes, 11% of these were due to ca-MRSA cellulitis, and abscesses. The most serious of these involved bursae or joints and resulted in hospitalizations for intravenous antibiotics and surgical incision and drainage (I&D). In addition to serious illnesses and hospitalizations, ca-MRSA infections have resulted in over four hundred hours lost from training due to initial sick-call visits and follow up for repeat I&D and packing.

The two principal manifestations of infection with ca-MRSA are cellulitis and abscesses (95% of cultures in a study by Crum et al.) In the same analysis, the majority of sites infected involve the extremities, which is consistent with our experience at NSWC.[5]

In other large studies, skin and soft tissue infections remain the most common sites for infection with ca-MRSA. Indeed, most reports suggest that a majority – 70 to 90% of infections with ca-MRSA involve the skin and soft tissues. While hospital acquired-MRSA (ha-MRSA) also frequently involves skin and soft tissues, it appears to be more likely to result in infection of the bloodstream, respiratory tract, and urinary tract than ca-MRSA, according to a study of cultures obtained in Sacramento, California.[6] Clinical manifestations will be described further in a subsequent section of this article. While these infections may cause substantial morbidity, thus far, mortality has been exceedingly uncommon. Deaths, if they occur, are usually related to necrotizing pneumonia and associated overwhelming sepsis.[7]

Pathogenesis

Staphylococcus aureus organisms in general have demonstrated a unique ability to adapt and survive in a great variety of environments (just like Special Operations Forces!) Molecular and genetic analyses of this germ have shown that it may have a wide variety of molecules known as adhesins, which mediate adherence to and colonization of target tissues. This helps to explain how ca-MRSA may be easily transmitted among groups of people as well as its tendency to recur in the same patient over time.[8] Isolates of ca-MRSA have been analyzed and found to carry a specific gene known as mec A. This gene encodes a protein which does not bind well to Beta-lactam agents such as penicillin, and helps to confer resistance to these drugs. Penicillin and other beta-lactam agents work by inhibiting the bacterial cell wall synthesis. This has a lethal effect on bacteria, especially on Gram-positive ones. The mec A gene is carried on what is known as a staphylococcal chro-

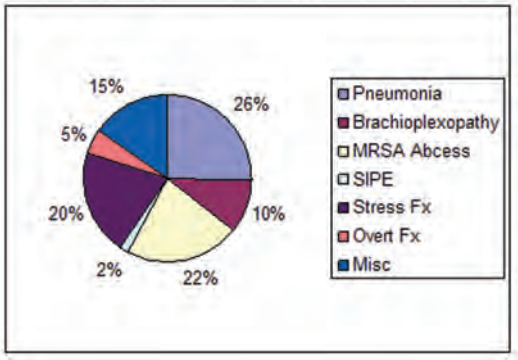

Fig. 1

mosomal cassette (SCC). The significance of this is that the gene and SCC can be used to conduct epidemiologic studies of outbreaks and identify that ca-MRSA is involved. Additionally, ca-MRSA isolates typically possess genes which code for a cytotoxin known as Panton-Valentin leucocidin. This factor is thought to give ca-MRSA the ability to destroy tissue and is associated with rapid formation of abscesses and tissue destructive pneumonias.[9]

On a more practical level, "5Cs" have been implicated in the transmission of ca-MRSA. These include **C**rowding, skin **C**ontact, **C**ompromised skin, sharing **C**ontaminated items, and lack of **C**leanliness.[1] Crowding is an obvious consequence of military training and operational environments. Potentially infected personnel are also placed in close contact with each other as a result of team building and other exercises. Trainees at NSWC and other special operations training environments are frequently exposed to abrasions and other trauma which may compromise the skin. Similarly, it is not unusual for trainees to share items such as towels, wetsuits, masks, and other gear items. Ca-MRSA has been cultured from patient examination tables, computer keyboards, a pulse oximeter, and patient chairs, which attests to the importance of proper infection control measures in clinic spaces.[9]

DIAGNOSTIC CONSIDERATIONS

The typical presentation of a patient with ca-MRSA skin or soft tissue infection is a rapidly appearing area of induration and erythema which may or may not develop into an obvious swollen, abscess-like lesion (figures 2 and 3). These infections may also resemble a spider bite (figure 4) and patients not infrequently present with the complaint that they feel that they were bitten by a spider. While patients may be febrile, our experience at NSWC suggests it is rare, with less than five patients in over 100 presenting with temperature greater than 98.6 degrees Fahrenheit. While abscess/cellulitis are the most frequent manifestations of ca-MRSA, it is important to note that patients may present with sepsis, necrotizing (rapidly progressive and destructive) pneumonia, pyomyositis, necrotizing fasciitis, and other serious invasive infections, even among healthy individuals. Abscess lesions may drain spontaneously if left untreated, and may present with serosanguinous purulent material emanating from the lesion.

An important initial consideration in approaching a patient with a new skin or soft tissue infection should be index of suspicion. While these diseases were often caused by Group A Streptococcus species or Methicillin Sensitive *Staphylococcus aureus* in the past, clinicians should be aware that the prevalence of ca-MRSA has rapidly increased in the USA.[10] As noted above, military personnel (particularly in the close quarters of a training environment) are a population at risk. Providers should have a low threshold for obtaining a swab of site material for culture and sensitivity testing from abscesses and other skin infections. While the sensitivity of culturing swabbed sites may be imperfect (70.9% in one study), culturing may prove useful if the infection spreads or proceeds to worsen rapidly or if it is unresponsive to a course of prescribed antibiotics. A slide latex agglutination test for detection of MRSA is highly sensitive and specific and is currently used in hospitals and laboratories in more than 17 countries.[11]

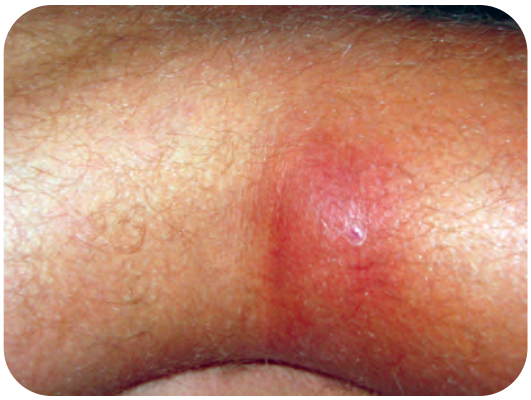

Figure 2. Ca-MRSA abscess of posterior leg with associated cellulitis

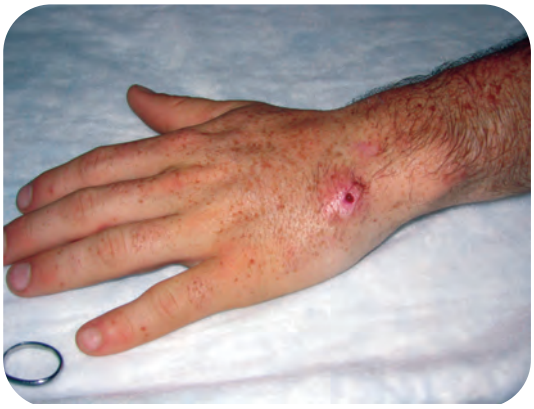

Figure 3. Ca-MRSA abscess of hand status-post incision and drainage

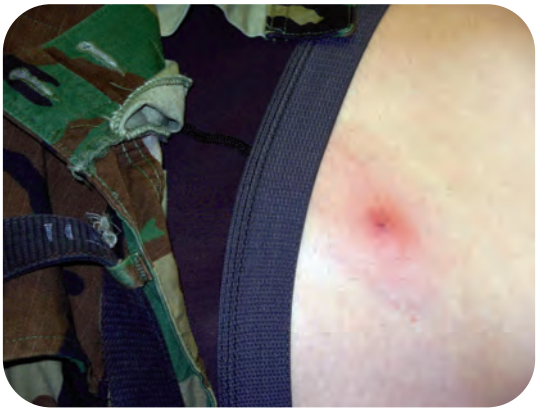

Figure 4. . Ca-MRSA abscess with characteristic spider bite appearance.

We and others have also identified otitis media and externa associated with ca-MRSA. Patients treated for otitis with conventional antibiotics who present with persistent otorrhea should have discharge swabbed and sent to a laboratory for culture and sensitivity testing.[12]

Management

The first step in appropriate treatment of ca-MRSA related disease involves a high index of suspicion and adequate recognition of the presentation. In one study from Atlanta, Georgia, two thirds of ca-MRSA cases were treated inadequately initially, probably because the providers did not recognize that the causative germ was resistant to beta-lactam antibiotics.[10] Ca-MRSA is typically also resistant to macrolide antibiotics such as erythromycin and azithromycin, as well as fluoroquinolone antibiotics such as ciprofloxacin.[13]

The following sections discuss the use of different agents in the treatment of suspected or proven ca-MRSA. However, these therapies have not been compared in vigorous clinical trials, and so it is not known what the ideal therapy is. General consensus favors the empiric therapies described below, as well as incision and drainage for abscesses.

The good news about ca-MRSA is that it is treatable. In contrast with older nosocomial strains of MRSA, it is usually sensitive to a larger number of antibiotics. Ca-MRSA is resistant to cephalosporins such as cephalexin and penicillin derived antibiotics such as dicloxacillin. However, most ca-MRSA is susceptible to tetracyclines such as minocycline and to trimethoprim-sulfamethoxazole. Many ca-MRSA strains are susceptible to clindamycin, but development of resistance to this drug during therapy may occur.[14] Rifampin is also generally an effective agent against ca-MRSA. Table 1 describes specific medications, their dosages, and most common side effects.

Antimicrobial	Usual Dosage	Common Side Effects
Trimethoprim-Sulfisoxazole 160/800mg (Septra DS)	1 DS tablet every 12 hours	Nausea/Vomiting, Diarrhea, Rash
Minocycline	100mg every 12 hours	Photosensitivity, Nausea/Vomiting
Doxycycline	100mg every 12 hours	Anorexia, Nausea, Dysphagia, Rash
Rifampin	600mg once daily	Stomache upset, Discolored Urine
Clindamycin	300-450mg every 6 hours	Nausea/Vomiting, Diarrhea

All patients with furuncles or abscesses should have them drained. Drainage may be problematic, in that abscesses may be septated and may require significant pressure to break up septations and assure complete drainage. These procedures are often quite painful and poorly tolerated by patients. In our experience at NSWC, pre-medication with morphine sulfate 2 to 4mg or with fentanyl 50 to 100mcg may help mitigate pain and ensure complete drainage of ca-MRSA related abscesses, although this is anecdotal. Furuncles less than 5cm in diameter may respond to drainage alone, but we routinely provide coverage with antibiotics, particularly if there is surrounding erythema or induration. If an abscess is large, it should be packed with a Penrose drain or with material such as iodoform gauze, and undergo daily evaluation to ensure that the abscess is not re-accumulating.

In severe or invasive infections or in infections which do not respond quickly to the above therapies, patients should be admitted to a medical treatment facility and be treated with vancomycin or linezolid. Also, if patients present with evidence of sepsis or the systemic inflammatory response syndrome (fever, low blood pressure, tachycardia, hyperventilation, confusion) expeditious administration of vancomycin (and possibly other antibiotics) should occur. Rapid referral for hospitalization and surgical consultation should be made in these cases.

Preventive Measures

Proper hygiene remains a cornerstone for preventing transmission of this infectious illness. This involves hand washing, covering draining skin lesions, not sharing potentially contaminated items, and avoidance of crowding and close contact whenever possible. Medical providers play an important role in these measures, in that they may be the first and only personnel to educate infected service members. Colonized and infected patients may be important reservoirs for ca-MRSA and contribute to the spread and recurrence of disease. It is incumbent upon medical providers in the military system to advise commanders regarding appropriate hygiene practices. Rates of colonization with ca-MRSA in various settings have suggested rates of 4 to 8% of an at-risk population, but it is unclear whether swabbing and culturing the nares is an effective way to decrease colonization and limit outbreaks.[15] However, this could be of benefit in monitoring the effectiveness of a community-based MRSA prevention program.

Reports of de-colonization with hexachlorophene or chlorhexidine gluconate with mupirocin have resulted in mixed success.[16] Anecdotally, we have seen significant reductions in ca-MRSA infections at

NSWC since providing and requiring use of chlorhexidine gluconate 4% in barracks showers. This is used as a body wash and is enforced by inspection of barracks showers and direction by instructor staff.

While the impact of hand washing on prevention of ca-MRSA in the general population has not been studied, multiple studies have shown a benefit to hand washing in preventing multiple types of infectious illnesses. An increasing trend in the use of alcohol based waterless hand cleaners has occurred. This has been due to their ease of use and some information that they may result in decreased rates of infection. Specifically, a study of alcohol based hand cleaner in a hospital setting resulted in a 46% reduction in the number of nosocomial MRSA cases per 1000 patient-days.[17] Caution should be used in generalizing this result to a military population since hospitalized patients and healthy service members are different hosts.

Summary

Ca-MRSA is an increasingly important cause of morbidity in military populations, particularly in training settings. It is highly contagious and destructive of tissue. Skin and soft tissue involvement are the most common manifestations, but other serious illness may occur. Incision and drainage of abscesses and antibiotics for soft tissue infections are the mainstays of treatment. Several oral antibiotics are effective, but beta-lactam antibiotics such as penicillins or cephalosporins are not. A high index of suspicion for ca-MRSA is important, and patients with infections not responding to initial therapy should have wounds cultured and antibiotics changes to provide appropriate coverage. Intravenous vancomycin and hospitalization should be considered for patients with serious infection or systemic illness. Hygiene and avoiding sharing personal items are cornerstones of prevention, and use of antibacterial soaps such as chlorhexidine are also likely helpful.

References

1. Hawkes M, Barton M, Conly J et al. (2007). Community-Associated MRSA: Superbug at our Doorstep. *Canadian Medical Association Journal*. 176(1) 54-56.
2. Kaplan SL, Hulten KG, Gonzalez BE et al. (2005). Three-Year Surveillance of Community-Acquired *Staphylococcus Aureus* Infections in Children. *Clinical Infectious Diseases.* 40(12):1785-91.
3. King MD, Humphrey BJ, Wang YF et al. (2006). Emergence of Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* USA 300 Clone as the Predominant Cause of Skin and Soft-Tissue Infections. *Annals of Internal Medicine*. 144(5) 309-317.
4. Campbell KM, Vaughn AF, Russell KL et al. (2004). Risk Factors for Community-Associated Methicillin-Resistant *Staphylo coccus Aureus* Infections in an Outbreak of Disease Among Military Trainees in San Diego, California, in 2002. *Journal of Clinical Microbiology*. 42(9), 4050-4053.
5. Crum NF, Lee RU, Thornton SA, et al. (2006). Fifteen-Year Study of the Changing Epidemiology of Methicillin-Resistant *Staphylococcus Aureus*. *The American Journal of Medicine.* 119(11) 943-951.
6. Huang H, Flynn NM, King JH et al. (2006). Comparisons of Community-Associated Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and Hospital-Associated MRSA Infections in Sacramento, California. *Journal of Clinical Microbiology*. 44(7) 2423-2427.
7. Frazee BW, Salz TO, Lambert L, Perdreau-Remington F. (2005). Fatal Community-Associated Methicillin-Resistant *Staphylococcus Aureus* Pneumonia in an Immunocompetent Young Adult. *Annals of Emergency Medicine*. 46(5), 401-404.
8. Moreillon P, Que Y, Glauser MP in Mandell, (2005). *Bennett & Dolin: Principles and Practice of Infectious Diseases*, 6th ed. Churchill Livingstone.
9. Johnston CP, Cooper L, Ruby W et al. (2006). Epidemiology of Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* Skin Infections Among Healthcare Workers in an Outpatient Clinic. *Infection Control and Hospital Epidemiology*. 27(10) 1133-113.
10. Moellering RC. (2006). The Growing Menace of Community-Acquired Methicillin-Resistant *Staphylococcus Aureus. Annals of Internal Medicine*. 144(5) 368-70.
11. Retrived 12 July 2007 from http://www.denka-seiken. co.jp/english/products/bacteriology/staphylococcusAureus.html.
12. Al-Shawwa BA, Wegner D. (2005). Trimethoprim-Sulfamethoxazole Plus Topical Antibiotics as Therapy for Acute Otitis Media With Otorrhea Caused By Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* in Children. *Archives of Otolaryngology and Head and Neck Surgery*. 131: 782-784.
13. Cohen PR. (2005). Cutaneous Community-Acquired Methicillin-Resistant Staphylococcus Aureus Infection in Participants of Athletic Activities. *Southern Medical Journal*. 98(6) 596-602.
14. Kowalski TJ, Berbari EF. (2005). Osmon DR. Epidemiology, Treatment, and Prevention of Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* Infections. Mayo Clinic Proceedings 80(9) 1201-1208.
15. Palavecino E. (2004). Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* Infections. *Clinics in Laboratory Medicine* 24 403-418.
16. Simor AE, Phillips E, McGeer A et al. (2007). Randomized Controlled Trial of Chlorhexidine Gluconate for Washing, Intranasal Mupirocin, and Rifampin and Doxycycline Versus No Treatment for the Eradication of Methicillin-Resistant *Staphylococcus Aureus* Colonization. *Clinical Infectious Diseases*. 44(2):178-85.
17. Lai KK, Fontecchio S, Melvin Z, Baker S. (2006). Impact of Alcohol-Based, Waterless Hand Antiseptic on the Incidence of Infection and Colonization With Methicillin-Resistant *Staphylococcus Aureus* and Vancomycin-Resistant Enterococci. *Infection Control and Hospital Epidemiology.* 27(10)1018-1021.