

Perspective

Methicillin-Resistant *Staphylococcus aureus* Infections

Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection is epidemic in the community, differs from nosocomial MRSA in virulence, mechanisms, and antibiotic susceptibility, and exhibits diverse and often unique pathologic characteristics. The community-acquired MRSA USA 300 strains are transmitted largely by person-to-person contact and cause characteristic soft-tissue abscesses and, less commonly, other sometimes unusual and serious infections including a necrotizing pneumonia, and other necrotic infections such as necrotizing fasciitis, pelvic thrombophlebitis, and septic phlebitis. This MRSA 300 family remains susceptible to drugs active against nosocomial MRSA (ie, vancomycin, linezolid, daptomycin) and is often susceptible to trimethoprim-sulfamethoxazole, doxycycline, and clindamycin. Recent epidemiologic data indicate that nosocomial MRSA (eg, mainly USA 100) strains are also present in the community and that MRSA USA 300 strains are present in hospital settings, with both families found in intermediate frequency in health care-associated settings (eg, nursing homes, dialysis centers). More work is needed to identify effective barrier precautions to limit their spread. This article summarizes a presentation on MRSA made by John G. Bartlett, MD, at the 11th Annual Clinical Update for the Ryan White HIV/AIDS Program Clinicians held in August 2008 in Washington, DC. The original presentation is available as a Webcast at www.iasusa.org.

Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) has no clear specific relationship with HIV disease as yet, although higher frequencies of *S aureus* infection are observed in persons at risk of acquiring HIV, including injection drug users and, in recent studies, men who have sex with men (MSM). MRSA is a general public health problem widely encountered in health care practices, and there is now a global epidemic involving a newly emerged form referred to as the USA 300 strains. This article contains frequent references to MRSA strains such as USA 100, 200, and 300, each of which represents a family of related strains that have distinct lineage and evolution. The article's main focus is on USA 300 strains, which appear to have evolved in the 1960s from phage type 80/81.

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Background

MRSA was first identified in the 1960s, reflecting the response of *S aureus* to widespread exposure to penicillins. This includes a group of related *S aureus* strains, many of which are referred

to as the USA 100 strains, that became rampant in hospital settings around 1983. A new family of strains, the USA 300 strains, emerged in the community setting around 2000 and appear related to the old phage type 80/81; they are now referred to as a "super bug."

The USA 300 strains differ from the earlier strains in several ways (Table 1), including presence of the cytotoxin Panton-Valentine leukocidin (PVL) and different methicillin resistance elements. Infections characteristically caused by the hospital-acquired USA 100 strains include wound infections, line-associated bacteremia, ventilator-associated pneumonia, and other common nosocomial infections. Infections with the community-acquired USA 300 strains include skin and soft-tissue infection, community-acquired pneumonia including a distinctive type of necrotizing pneumonia, and necrotizing fasciitis.

Active antibiotics for the nosocomial MRSA strains are usually limited to vancomycin, linezolid, and daptomycin. There is broader susceptibility with the USA 300 strains that often includes trimethoprim-sulfamethoxazole (TMP-

Table 1. Characteristics of Methicillin-Resistant *Staphylococcus aureus* USA 100 and USA 300 Strains and Infections

	USA 100	USA 300
Where originated	Hospital	Community
When	~1983	~2000
Panton-Valentine leukocidin	Absent	Present
Methicillin resistance elements	Mec I-III	Mec IV
Active antibiotics	Vancomycin, linezolid, daptomycin	PLUS trimethoprim-sulfamethoxazole, doxycycline, clindamycin
Infections	Wound, ventilator-associated pneumonia, line infections, other plastic- or metal-associated infections	Skin and soft tissue, community-acquired necrotizing pneumonia, necrotizing fasciitis

SMX), minocycline, and clindamycin. The USA 300 strains continue to dominate the community-acquired forms of *S aureus* infections but now are being found with increasing frequency in hospital settings and are increasingly resistant to antibiotics including tetracycline and clindamycin.

Initial Reports of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections

A widely publicized story of a MRSA epidemic in the St. Louis Rams football team and transmission through physical contact with another team raised awareness in 2000 of the importance of the USA 300 strains in the community. The hospital strains such as USA 100 or 200 have considerable heterogeneity of types, whereas isolates of the USA 300 strain are remarkably similar. Initial pulsed-field gel electrophoresis (PFGE) studies in outbreaks showed that USA 300 strains were present not only in the professional football team but in college football teams, fencers, children, prison inmates, and MSM from various locations across the country. The classic MRSA lesion in these outbreaks is known as the “spider bite” abscess (Figure 1). An outbreak in a Los Angeles jail before wide recognition of the prevalence of this problem prompted authorities to call in an exterminating company, which informed them, after inspection, that spiders were not among the many problems present.

Moran and colleagues shed light on the magnitude of the problem with community-acquired MRSA (Moran et al, *N Engl J Med*, 2006). Isolates were analyzed from 422 cases of soft-tissue infection at 11 emergency departments in the United States. Lesions consisted of abscess in 81% of cases, wounds in 11%, and cellulitis with exudate in 8%. MRSA was found in 60% (n = 249) of cases and was the most common organism in 10 of 11 centers. Methicillin-susceptible *S aureus* (MSSA) accounted for 17% of cases (n = 71), and *Streptococcus* species for 8% (n = 30); lesions were sterile in 9% of cases (n = 38). Virtually all of the MRSA isolates (99%) were identified as USA 300, and



Figure 1. Classic “spider bite” abscess caused by methicillin-resistant *Staphylococcus aureus* USA 300.

most were strain type 0114. More than 98% had the Mec IV resistance mechanism and *pvl* genes. Antibiotic susceptibilities showed 100% were sensitive to TMP-SMX, 100% to rifampin, 95% to clindamycin, 92% to tetracycline, 60% to quinolones, and 6% to macrolides.

A major message from this study is that MRSA has supplanted MSSA as the dominant *S aureus* in community-acquired infections. Treatment consisted of incision and drainage plus antibiotic treatment in 60% of cases and incision and drainage alone in 19%. A beta-lactam antibiotic was used in 64% of cases in which antibiotic therapy was used, including 57% of MRSA cases treated with an antibiotic. Assessment of outcome at 15 days to 21 days by telephone showed resolution of infection in 96% of cases, with no correlation of outcome according to treatment with an antibiotic, an inactive antibiotic, or no antibiotic. There is widespread agreement that the cutaneous abscess needs drainage, but indications for antibiotics to supplement drainage are unclear. A prospective study sponsored by the National Institutes of Health is currently evaluating the issue of use of antibiotics in MRSA cutaneous abscesses.

The necrotizing infections associated with the USA 300 MRSA strains are often remarkable and devastating. Although health care practitioners have had experience with necrotizing fasciitis for decades, most of these infections have been caused by group A streptococci or anaerobic bacteria. Staphylococci were not previously among likely pathogens, but they are now the major cause. With regard to necrotizing pneumonia, the author’s own experience with 4 young, previously healthy adult patients at The Johns Hopkins Hospital 4 years ago shows how devastating this community-acquired disease can be: 2 young, previously healthy women underwent amputations of both legs as a result of septic shock, 1 man died, and the fourth survived but only after 103 days in the intensive care unit.

An initial Centers for Disease Control and Prevention (CDC) report on community-acquired pneumonia caused by MRSA presented details on 10 cases in Louisiana and Georgia during the influenza season of 2006 and 2007 (*MMWR Morb Mortal Wkly Rep*, 2007). The infection was lethal in 6 of 10 patients at an average of 3.5 days after onset of symptoms. In addition to these new staphylococcal syndromes, communi-

ty-acquired MRSA has been associated with septic thrombophlebitis and pediatric “pelvic syndromes” (eg, septic arthritis of the hips, pelvic abscess).

The particular virulence factors underlying the types of infections caused by these strains remain disputed. Although the presence of *pvl* genes in the USA 300 strains suggest that PVL could be a virulence factor, debate remains over whether it is the major determinant of the greater virulence of these strains. For example, 2 experienced research groups performed well-designed studies that were published in 2 highly reputable scientific journals and came to very different conclusions. One group stated that PVL is a key virulence factor in pulmonary infections, as supported by showing that a nasal challenge of just PVL in mice causes lethal pneumonia (Labandeira-Rey et al, *Science*, 2007). However, the second group repeated this experiment and concluded that although PVL may be a marker for community-acquired MRSA, it is not an important virulence determinant and might even be protective (Voyich et al, *J Infect Dis*, 2006).

Staphylococcus aureus is an organism with more than 60 virulence factors including cytotoxic peptides thought to be important by some. Identifying individual factors that account for the changing behavior of the diverse pathogenic processes attributed to MRSA may be impossible. By comparison, group A streptococci also can cause severe infections but remain relatively simple in both virulence factors and antibiotic sensitivities. For example, *S pyogenes* remains sensitive to penicillin despite having been exposed extensively to the drug for more than 5 decades.

Current Epidemiology

A large-scale CDC surveillance study described the incidence and burden of invasive MRSA in the United States (Klevens et al, *JAMA*, 2007). The study was hospital-based and involved sentinel laboratories covering approximately 16.5 million patients, approximately 5.6% of the US population. MRSA was isolated from blood or other normally sterile site from 8987 cases with com-

munity onset. The site of disease acquisition was classified as community onset in 28%, whereas 58% were health care-associated onset, and 14% were nosocomial onset. Bacteremia accounted for 75% of infections and pneumonia for 13%. Mortality was 13%. PFGE typing showed USA 300 strains accounted for 16% of hospital-acquired cases, 22% of health care-associated cases, and 67% of community-acquired cases. Note the “health care-associated” category is a relatively new, hybrid form of epidemiologic classification representing patients recently discharged from the hospital (within 30 days), patients admitted from chronic care facilities, and those who are part of the hospital network, for example, outpatients of dialysis centers.

These data indicate the lack of restrictions on where the older versus newer MRSA strains are to be found. The USA 100 strains can be found in community-acquired infections, and the USA 300 strains are now found in nosocomial infections, and both strains are found at intermediate frequencies in health care-associated sites. On the basis of this report, an estimated 94,360 invasive MRSA infections occur each year, with 18,650 associated deaths. The incidence was estimated at 32 cases per 100,000 population, with geographic variation including rates of 20 per 100,000 population in Portland and 118 per 100,000 in Baltimore.

Treatment

Vancomycin remains the standard treatment for serious MRSA infections. It is the second most commonly used antibiotic in hospitals, and approximately 16 tons of the drug are used every year. In 50 years of use, only 6 clinical MRSA strains with vancomycin resistance have been identified. However, recent reports provide cause for concern. Tenover and Moellering (*Clin Infect Dis*, 2007) showed several concerns about vancomycin: 1) heteroresistance in MRSA, in which small numbers of organisms with high vancomycin minimal inhibitory concentrations (MICs) are present within large populations of organisms that show vancomycin resistance de-

spite resistance of a subpopulation; 2) “MIC creep,” in which an increase has occurred in recent years in numbers of both MRSA and MSSA clinical isolates with vancomycin MICs of 2 µg/mL or greater (strains now considered only intermediately sensitive to vancomycin) (Wang et al, *J Clin Microbiol*, 2006); and 3) prolonged MRSA bacteremia in many patients despite adequate vancomycin treatment as indicated by trough levels of 15 mcg/mL to 20 mcg/mL.

The standard regimen of intravenous vancomycin is 1 g every 12 hours or, preferably, 15 mg/kg to 22 mg/kg every 12 hours. Although this regimen may suffice for many staphylococcal infections, drug levels should be considered and monitored in serious staphylococcal infections with a goal of reaching trough levels of 15 µg/mL to 20 µg/mL in pneumonia, 20 µg/mL in central nervous system infection, 10 µg/mL to 20 µg/mL in endocarditis, and 10 µg/mL to 15 µg/mL in bacteremia. In cases of vancomycin failure, options are linezolid (600 mg every 12 hours), daptomycin (6-8 mg/kg/day), clindamycin (600 mg every 8 hours), or TMP-SMX (10/50 mg/kg/day). A new drug was just recommended for approval by the US Food and Drug Administration Advisory Panel (November 20, 2008). This may provide another option.

For USA 100 strains, use of linezolid or daptomycin is likely to be required in vancomycin failures; linezolid is the only available oral agent for these infections and is preferred for pneumonia (see below). For USA 300 strains, sensitivity testing should be performed to determine that a tetracycline (preferably minocycline), clindamycin, or TMP-SMX can be used. However, more recent experience suggests the USA 300 strains are becoming more resistant to tetracycline and clindamycin.

For pulmonary infections involving USA 300 strains linezolid is usually preferred because of its superior lung penetration and better 28-day survival in MRSA nosocomial pneumonia compared with vancomycin (Wunderink et al, *Chest*, 2003). A highly controversial area is that of indications for antibiotics for the common cutaneous abscess. There is widespread agreement that in-

cision and drainage are key in most such infections, but there is no consensus on indications for antibiotics or on the drug to use, except that cephalexin and dicloxacillin (once the favored agents) are now considered “wrong” choices unless the strain is known to be MSSA.

Important factors to consider with vancomycin include the potential for nephrotoxicity and the need to monitor drug levels with treatment of serious infections. Linezolid occasionally causes marrow toxicity and serious optic toxicity. Daptomycin has been associated with elevated levels of creatine kinase, although the clinical consequences of this seem rare. The optimal dosing of daptomycin is still not clear, and it should not be used in pneumonia because of poor lung penetration. TMP-SMX is associated with rash, and its use may be problematic because of a potential for severe reactions. Clindamycin is associated with *Clostridium difficile* colitis and presents potential problems with resistance.

Control Efforts

All cutaneous abscesses should be covered. Colonization sites for staphylococci are the nose, skin, intestines, genital tract, and objects. The nose harbors MSSA in approximately 30% of individuals and MRSA in approximately 2% to 5%. Fomites such as towels were implicated in the MRSA USA 300 epidemic in the St. Louis Rams players. Studies in MSM have indicated a genital or perirectal source; in a survey in San Francisco hospitals, MSM had a relative risk for MRSA infection of 13.2 that was unrelated to HIV infection; affected sites included buttocks, genitals, and perineum (Diep et al, *Ann Intern Med*, 2008).

Given the potential sources of infection, it is reasonable to attempt barrier precautions in the health care setting, including use of mupirocin for the nose and chlorhexidine soap and hexachlorophene cleanser for the body. The effects of a strategy of universal screening for MRSA and barrier precautions were assessed in a recent study in surgical wards in a Swiss teaching hospital (Harbarth et al, *JAMA*, 2008). Surgical patients underwent randomization

to rapid screening (polymerase chain reaction testing) for the presence of MRSA in the nose. The intervention for MRSA carriers found through screening included contact isolation, adjusted antibiotic prophylaxis, a computerized MRSA alert, and use of mupirocin ointment and chlorhexidine body wash. The investigators found no differences in rates of MRSA surgical site infection or nosocomial acquisition with the screening and intervention.

On the other hand, a study of screening and barrier precautions in 3 affiliated hospitals in Chicago did show benefit (Robicsek et al, *Ann Intern Med*, 2008). In this study, patients underwent surveillance for MRSA using polymerase chain reaction testing, with isolation and barrier precautions used for MRSA carriers and decolonization attempted using mupirocin and chlorhexidine wash. The strategy of universal screening and infection control in those colonized was studied in sequence with no intervention, followed by intervention restricted to the intensive care unit, and then universal screening.

Compared with a control period during which the rate of MRSA infection was 8.9 per 10,000 patient-days, the infection rate was similar (7.4) with the intensive care unit–based strategy and statistically significantly reduced (3.9) with the universal strategy. The aggregate MRSA disease prevalence density was reduced by greater than 70% with universal screening. The point to emphasize is that screening, covering lesions, and decontamination with mupirocin and chlorhexidine all make sense, but evidence that they work is limited in number and variable in results. We now have universal screening for MRSA in Veterans Administration hospitals and in some states with a legislated requirement, but we do not know what strategies are effective in controlling this organism in health care settings, and these mandated and unfunded policies represent extensive resources.

Conclusion

Staphylococcus aureus features incredibly diverse pathogenic and resistance mechanisms, and MRSA has emerged

as the major bacterial pathogen of the 21st century to date. The primary mode of transmission of community-acquired MRSA is human-to-human contact. Management of the infections includes drainage of abscesses, but the criteria for antibiotics are often unclear. Many strains of the USA 300 family are sensitive to TMP-SMX, clindamycin, and/or minocycline. Serious infections and most nosocomial MRSA strains are best treated with vancomycin, aiming for trough levels of 15 mcg/mL to 20 mcg/mL in serious infections. Screening for nasal carriage combined with use of barrier techniques is often employed to contain spread of the organism, but there is no consensus on the utility of this intervention. The history of MRSA strongly indicates that even if the organism is controlled, the victory will be temporary.

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Suggested Reading

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