Methicillin-Resistant *Staphylococcus aureus*: The Latest Health Scare

For decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has been the most commonly identified multidrug-resistant pathogen in many parts of the world, including the United States. Recently, it has become the focus of intense media attention. Some of this attention stems from a recent article in the *Journal of the American Medical Association* that provided estimates of MRSA infections annually in the United States.[1] (The occurrence of the word "staph" increased by 10-fold in the 2 weeks after this report.[2]) In addition, both health care safety initiatives (eg, Joint Commission National Patient Safety Goals, Institute for Healthcare Improvement) and consumer groups (eg, American Association of Retired Persons, StopHospitalInfection.org) have begun ca lling for hospitals to do more to reduce MRSA infections. Legislation related to hospital infections, including measures targeting MRSA control and public reporting of MRSA infections, is being introduced in many states and at the federal level.[3-5] Finally, increasing reports of MRSA occurring in community settings, eg, day care centers, schools, and sports teams, along with several reports of deaths in previously healthy children and young adults, have also prompted fears that we are now facing a new "superbug."

Historical Background

Staphylococcus aureus is one of the most successful and adaptable human pathogens. Its remarkable ability to acquire antibiotic resistance has contributed to its emergence as an important pathogen in a variety of settings. In the preantibiotic era, *S aureus* infections were associated with very high mortality. When penicillin was first introduced in the early 1940s, much of its success was in the treatment of *S aureus* bloodstream infections. However, as early as 1942 the first strains of penicillin-resistant *S aureus* were detected in hospitals (Table 1). These subsequently spread into the community; by 1960, most *S aureus* strains both in hospitals and in the community were resistant to penicillin. Shortly after the introduction in 1959 of methicillin, a semisynthetic penicillin, resistance to it emerged; the first hospital outbreak of MRSA was reported in 1963.[6] Initially spreading widely in Europe, India, and Australia, MRSA strains were detected in the United States in the late 1960s.[7] By the 1980s, MRSA had become firmly established in US hospitals, and rates of MRSA infection have since continued to increase. In large US hospitals, MRSA rates (the proportion of all *S aureus* isolates that are MRSA) increased from 4% in the 1980s to 50% in the late 1990s. According to National Nosocomial Infections Surveillance data, the increase in MRSA rates in intensive care units was even greater, reaching 60% in 2003.[8]

Nosocomial MRSA is remarkable for its clonal pattern of spread. Currently, 5 major MRSA clones account for approximately 70% of MRSA isolates in hospitals in the United States, South America, and Europe. The major cause of this clonal spread is infection control lapses by health care professionals. The traditional risk factors for MRSA acquisition include previous hospitalization, antibiotic use, residence in long-term care facilities, and long-term hemodialysis. Increasing use of vancomycin to treat MRSA led to the emergence of *S aureus* with intermediate resistance to vancomycin (VISA) and then vancomycin-resistant *S aureus* (VRSA) in the 1990s.[9,10] Fortunately, VISA and VRSA infections have been sporadic, and intense infection control measures have ensured that they did not circulate widely in health care settings.

In the early 1980s, several instances of community-onset MRSA were reported in the upper Midwest. Because many of these early cases involved intravenous drug users or people with serious underlying disease, it was thought that the infections were acquired during contact with health care personnel. However, in the 1990s serious MRSA infections were reported in patients with no prior contact with the health care system, heralding the onset of community-acquired MRSA (CA-MRSA) outbreaks. The seriousness of CA-MRSA was highlighted by a report in 1999 of 4 deaths in children infected with CA-MRSA in Minnesota and South Dakota.[11] Since then, many reports have described CA-MRSA infections, particularly in children, and CA-MRSA is a growing problem worldwide. Clusters of CA-MRSA have been reported in correctional facilities,[12] professional sports teams,[13] high school athletes,[14] day care centers,[15] healthy newborns,[16] military personnel,[17,18] and tattoo recipients.[19] The term "health care–acquired MRSA" (HA-MRSA) has been used to differentiate the earlier hospital strains of MRSA from these newer CA-MRSA strains.

Differences Between HA-MRSA and CA-MRSA

A review article by Kowalski et al[20] contrasted the features of CA-MRSA and HA-MRSA. To summarize, HA-MRSA and CA-MRSA strains carry different types of the gene complex known as staphylococcal chromosome cassette mec (SCC mec), which contains the mecA gene that confers methicillin resistance. Health care–acquired MRSA

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TABLE 1. **Timeline of *Staphylococcus aureus* Infection and Resistance**

Year	Event
1940	Penicillin introduced
1942	Penicillin-resistant *Staphylococcus aureus* appears
1959	Methicillin introduced; most *S aureus* strains in both hospital and community settings are penicillin resistant
1961	Methicillin-resistant *S aureus* appears
1963	First hospital outbreak of methicillin-resistant *S aureus* (MRSA)
1968	First MRSA strain in US hospitals
1970s	Clonal spread of MRSA globally, very high MRSA rates in Europe
1982	4% MRSA rate in the United States
1980s, early 1990s	Dramatic decreases in MRSA rates due to search-and-destroy programs in Northern Europe
	By 1999, <1% MRSA rate in the Netherlands; that rate has been sustained to date despite increasing MRSA rates in other parts of the world
1996	Vancomycin-resistant *S aureus* (VRSA) reported in Japan
1997	Approximately 25% MRSA rate in US hospitals; vancomycin use increases; vancomycin-intermediate *S aureus* (VISA) appears; serious community-acquired MRSA (CA-MRSA) infections reported; pediatric deaths reported
2002	First clinical infection with VRSA in the United States
2003	MRSA rates continue to increase; approximately 60% MRSA rate in intensive care units; outbreaks of CA-MRSA (predominantly USA 300 clone) reported in numerous community settings and also implicated in hospital outbreaks
2006	>50% of staphylococcal skin infections seen in emergency departments caused by CA-MRSA
	HA-MRSA rate continues to increase
	Distinction between HA-MRSA and CA-MRSA on epidemiological basis becomes increasingly difficult
2007	"The Year of MRSA?"
	Report of active, population-based surveillance for invasive MRSA done in 2004-2005 estimates 95,000 invasive MRSA infections and 19,000 deaths from MRSA per year
	Continued reports in the medical literature and the lay press about severe CA-MRSA infections
	Several states pass or are considering legislation regarding control of MRSA and public reporting of MRSA rates
	Strategies to control MRSA, including public reporting of MRSA infections, are hotly debated; "staph" and MRSA become household words

strains carry SCC mec types I, II, and III and tend to be multidrug resistant. They typically cause bloodstream and postoperative wound infections along with nosocomial pneumonia in hospitalized patients.

In contrast, CA-MRSA strains carry SCC mec type IV and V and usually cause skin and soft tissue infections in community-dwelling children and adults. The most common clinical presentations are furuncles, superficial abscesses, and boils that are often mistakenly attributed to spider bites. Like HA-MRSA, CA-MRSA also spreads clonally, and the USA 300 clone is the predominant strain circulating in the United States.[21] Although resistant to methicillin and other β-lactam antibiotics (eg, penicillin, cephalosporins, carbapenems), CA-MRSA often remains sensitive to many other classes of antibiotics, including trimethoprim-sulfamethoxazole and tetracyclines. Resistance to macrolides, clindamycin, and fluoroquinolones varies by region. In addition to skin infections, cases of severe necrotizing pneumonia (including postinfluenza pneumonia) and necrotizing fasciitis caused by CA-MRSA have been described.[22,23] Many cases of necrotizing pneumonia and some soft tissue infections have been characterized by rapid progression to septic shock and death. Most CA-MRSA strains carry the Panton-Valentine leukocidin gene. This gene could play a role in the pathogenesis of more severe infection, especially pneumonia.[24] Community-acquired MRSA strains are also associated with production of other toxins, such as staphylococcal enterotoxin A, B, C, and H, which are capable of causing illness resembling toxic shock syndrome in animal models[25,26] and could play a role in severe human infections.

The epidemiological differences between these strains are becoming increasingly blurred. Community-acquired MRSA strains are making their way into health care settings, and several outbreaks of nosocomial infections with these strains have been reported.[27-30] They are also becoming increasingly drug resistant[31] and are spreading rapidly within defined populations and in select geographical regions, particularly in large urban centers. In some metropolitan areas, CA-MRSA accounts for as high as 80% of all *S aureus* infections seen in emergency departments.[21]

Prevalence of *S aureus* and MRSA

Staphylococcus aureus is a common colonizer of the skin and the nose. A 2001-2002 population-based study in the United States showed that the prevalence of nasal colonization with *S aureus* and with MRSA was 31.6% and 0.84%, respectively,[32] meaning that there are approximately 2.3 million MRSA-colonized people in the United States. Women, people older than 65 years, those with diabetes mellitus, or those who have been in long-term care in the preceding year are more likely to be colonized with MRSA. Two nasal *S aureus* carriage patterns can be distinguished: persistent and intermittent. The density of *S aureus* in the nose is highest in persistent carriers, as is its colonization of other body sites, including the hands, axillae, and perineal regions.

Although the relationship between colonization and infection is not completely understood, both are associated with intrinsic host factors, as well as the strain of *S aureus*. Nasal colonization with *S aureus* is a risk factor for subsequent infection. Both higher rates of *S aureus* nasal carriage and subsequent higher rates of infection have been

associated with many underlying diseases or conditions, including insulin-dependent diabetes mellitus, long-term dialysis, intravenous drug abuse, repeated injections for allergies, liver cirrhosis, liver transplant, human immunodeficiency virus infection, and hospitalization. Also correlated with higher *S aureus* infection rates are activities leading to skin lesions such as contact sports. The common factor between these conditions seems to be the repeated violation of the skin or mucosa as anatomical barriers.

Impact of MRSA

Patients colonized with MRSA are more likely to develop infections than patients colonized with methicillin-sensitive *S aureus* (MSSA).[33] Methicillin-resistant *S aureus* infections lengthen hospital stays (by an average of 10 days) and are associated with a 2.5-fold higher mortality rate and increased health care costs.[34,35] A diagnosis of *S aureus* infection accounts for an estimated 292,000 hospitalizations per year in the United States.[36] In 2005, approximately 94,000 persons were diagnosed as having invasive (ie, serious) MRSA infections, an estimated 19,000 of whom died. Of these MRSA infections, 86% were health care acquired and 14% were community acquired.[1] The annual cost of treating MRSA in hospitalized patients in the United States has been estimated to be between $3.2 and $4.2 billion.[37]

Transmission and Control of MRSA

In health care settings, MRSA is transmitted from patient to patient primarily via health care professionals' hands. It can survive on surfaces for days to weeks; hence, contaminated patient care equipment can play a role in transmission.[38] The factors that promote transmission of MRSA in community settings have been called the *5 Cs* and are summarized in Table 2. Although the strategies to control HA-MRSA and true CA-MRSA share many features, they differ in some respects. Rates of infection with both these organisms can be reduced by good antibiotic stewardship, which will prevent the selection of MRSA from among a population of *S aureus*. Good hand hygiene practices will limit person-to-person transmission and decrease the pool of persons who are colonized. In health care settings, active surveillance cultures to identify patients with MRSA, contact precautions (use of gown and gloves while caring for these patients), and good environmental cleaning have been proposed as additional strategies to limit MRSA transmission[39,40] In selected patients, decolonization could help reduce infection. However, widespread use of decolonization is not recommended because it is expensive, its benefit is usually short lived (most patients become recolonized during the next few months), and it carries the risk of promoting resistance to agents, such as mupirocin, that are used in decolonizing regimens.

TABLE 2. **Factors Associated With Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Transmission (The *5 Cs*)**

Crowded living conditions
Frequent skin-to-skin ***C***ontact
Compromised skin
Sharing ***C***ontaminated personal items such as towels and razors
Lack of ***C***leanliness

In July 2004, Mayo Clinic Rochester expanded its MRSA control program. In addition to isolating patients known to be carriers of MRSA and electronically flagging their records so that isolation procedures could be reinstituted on readmission, staff members began to screen high-risk patients for MRSA and preemptively isolated them until negative culture results were obtained. In the 36 months after institution of this program, rates of MRSA rates decreased by 25% (ie, from 42% to 29% of *S aureus* isolates) (unpublished data). Several Scandinavian countries have reduced MRSA infection rates to less than 2% through intensive infection control programs and have successfully maintained these low rates over the past several years.[41,42]

Physicians can help control the spread of CA-MRSA in communities by encouraging hand hygiene, maintaining a high degree of suspicion for MRSA as an etiologic agent when treating skin and soft tissue infections, knowing local rates of CA-MRSA (public health departments might be able to provide these data), emphasizing the importance of hygiene to patients with MRSA, and discouraging the sharing of personal items such as towels and razors. Draining lesions should be kept covered, and return to team sports should be limited until the lesion has healed or can be adequately covered. Flu shots (especially in children) could be helpful in reducing the risk of postinfluenza bacterial pneumonia with MRSA.

Treatment Options

Selection of initial antibiotic regimens should be guided by the local prevalence of MRSA, the presence of health care–associated risk factors, and the severity and type of clinical presentation. For severe infections, intravenous vancomycin should be included in initial empiric therapy. Microbiological data and antibiotic susceptibility testing should be used to guide subsequent therapy. First approved in 1958, vancomycin became standard therapy for MRSA in the 1960s. Its advantages include its good safety profile, the long experience with its use, and its relatively infrequent dosing regimen. Disadvantages include the need for intravenous administration and monitoring of levels in critically ill patients and in those with changing renal function. In addition, the molecule is large, limiting its pen-

etration into tissues. Recently, there have been reports of vancomycin failure due to either relative vancomycin resistance or MRSA infections in sites that have poor vancomycin penetration.[43,44]

Overall, vancomycin remains standard treatment for MRSA; however, some alternatives have recently received Food and Drug Administration approval and could be good options in selected patients, including linezolid (a synthetic oxazolidinone), tigecycline (a derivative of minocycline), and daptomycin (a cyclic lipopeptide). Daptomycin should be avoided in the treatment of MRSA-associated pneumonia because it is inactivated by pulmonary surfactant. Additional agents that appear promising include dalbavancin, a semisynthetic lipoglycopeptide that can be dosed once a week, and ceftobiprole, an investigational cephalosporin.

For soft tissue CA-MRSA infections, surgical drainage is crucial, with antibiotics serving as adjunctive therapy. Severe infections should be managed with intravenous antibiotics as aforementioned. Oral antibiotics can be used for less severe infections in the outpatient setting. For initial empiric therapy, oral trimethoprim-sulfamethoxazole is a good choice. Other alternatives include minocycline, clindamycin, or a macrolide antibiotic, depending on local susceptibility patterns.

In summary, MRSA is a growing public health problem. Initially, it was feared that HA-MRSA, long a cause of health care–associated infections, would escape into community settings. Instead, in the past few years, CA-MRSA strains that are genetically different from HA-MRSA have appeared, are now circulating widely in many communities, and are causing a wide variety of infections, ranging from minor skin infections to rapidly progressive, life-threatening ones. Ironically, these more virulent CA-MRSA strains have been imported from the community into health care settings and have been responsible for outbreaks of infections in hospitals. Infection control measures have been successful in limiting the spread of MRSA in many parts of the world, and most hospitals in the United States are increasing MRSA control activities to improve patient safety and quality of care.

Currently, the health care industry is under increasing scrutiny by both the public and governmental agencies. Medicare and other groups have threatened not to reimburse for hospital-acquired infections. Legislation is being considered or has already been passed in some states mandating the reporting of health care–acquired infection rates and separate reporting of MRSA rates. The spread of MRSA and other drug-resistant organisms can be limited by infection control measures. It is time that we, as health care professionals, incorporate proven infection control measures such as hand hygiene and the use of appropriate personal protective equipment (gowns and gloves) into our daily patient care routines. The next influenza pandemic might or might not happen in our lifetime. The MRSA pandemic is here.

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