

# Preface

For many years after the discovery of antibiotics, microbial resistance was largely ignored. Now, however, the prevalence of antibiotic-resistant microorganisms, both in the community and in hospitals, has reached a level that impacts treatment efficacy. New, more potent agents have been introduced, but resistant microbes continue to be selectively enriched. Unfortunately, the problem of drug-resistant microorganisms extends beyond bacteria: it is also of major concern with the management of viral diseases, such as that caused by Human Immunodeficiency Virus, and with parasitic diseases such as malaria. Meanwhile, it is becoming increasingly difficult to identify new compound classes and more active derivatives of existing agents, especially since many pharmaceutical companies have abandoned efforts to find and develop new antimicrobials.

*Antimicrobial Resistance and Implications for the Twenty-First Century* serves as a status report on resistance. This set of comprehensive, up-to-date reviews by international experts covers problems being observed among a variety of bacteria (*Streptococcus pneumoniae*, enterococci, staphylococci, Gram-negative bacilli, mycobacteria species), viruses (HIV, herpesviruses), and fungi (*Candida* species, fusarium, etc.). The chapters explore molecular mechanisms of drug resistance, epidemiology of resistant strains, clinical implications, and future directions, including strategies for restricting the acquisition of resistance. The work is intended for experts and students in the fields of infectious disease, microbiology, and public health. While our goal is to stimulate basic research on resistance, the work should also help international bodies, such as the World Health Organization, formulate effective plans to combat the acquisition and dissemination of resistant strains. We hope that the documentation provided in *Antimicrobial Resistance and Implications for the Twenty-First Century* can be used by public health and medical communities to exert the political pressure needed to limit the indiscriminate use of antimicrobials and to provide the incentives needed to find new antimicrobials and treatment strategies.

# Chapter 2

## Emergence of MRSA in the Community

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### 2.1 Introduction

*Staphylococcus aureus* has been recognized as a cause of human infection for over a hundred years, and its role in causing diseases such as sepsis and abscesses was first described by Ogston in the late nineteenth century (Ogston, 1882). *S. aureus* can colonize human hosts without causing disease, and infections with *S. aureus*, especially antimicrobial-resistant strains such as methicillin-resistant *S. aureus* (MRSA), now pose a large and growing health burden.

*S. aureus* has emerged as one of the major pathogens of public health significance in the new millennium, and MRSA is on the rise. Over the last 20 years, the percentage of *S. aureus* infections in hospitalized US patients that are resistant to methicillin has continually increased from 2% in 1975 to 34% in 1992 and 64% in 2003 (Klevens et al., 2006; Panlilio et al., 1992). Skin and soft tissue infections, which annually account for an estimated 11.6 million visits to medical providers in the United States (four visits for every 100 persons) (McCaig et al., 2006), are most commonly caused by *S. aureus*; the majority of abscesses cultured in emergency departments in the United States are now MRSA (Cohen et al., in press; Moran et al., 2005, 2006). The percentage of skin infections caused by MRSA in a emergency department in Los Angeles has increased from 29 to 64% from 2001 to 2004 (Moran et al., 2005).

Penicillin was first introduced to treat patients with bacterial infections in 1941, and resistance to penicillin was first reported in *S. aureus* within 1–2 years (Kirby, 1944). These resistant strains were first found in hospitals after the Second World War, where patients were exposed to this new antimicrobial agent (Barber and Rozwadowska-Dowzenko, 1948). *S. aureus* had quickly acquired the ability to produce penicillinase, an enzyme that inactivates penicillin. An “epidemic strain” of antimicrobial-resistant *S. aureus*, which was characteristically lysed by bacteriophage 80 and 81, was noted to cause hospital outbreaks in Australia, Canada, and the United States in the 1950s. This strain was reported to more commonly cause disease in hospitalized children and otherwise healthy young adults (Fekety and Bennett, 1959).

In Copenhagen in the late 1960s, the first large-scale study of penicillin-resistant *S. aureus* discovered that not only were the majority of *S. aureus* found

in hospitals resistant to penicillin but also the resistance gene had spread to a majority of *S. aureus* strains in community settings (Jessen et al., 1969). Within a decade, a majority of community *S. aureus* strains in the United States were penicillin-resistant (Ross et al., 1974). New drug development found a solution with semisynthetic penicillins (such as methicillin, oxacillin, and nafcillin) that resisted penicillinases produced in the majority of *S. aureus* strains.

The first *S. aureus* isolates resistant to methicillin were obtained from patients in England within months of methicillin introduction in 1959 (Jevons, 1961). Reports of MRSA in the United States soon followed (Barrett et al., 1968). As with penicillin-resistant *S. aureus*, MRSA strains were first seen in hospitals, prompting concerns that MRSA would soon spread outside the hospital. Nearly 50 years later, we are now seeing the emergence of MRSA in the community; however, the source of the resistant strains does not appear to be the hospital. It appears that both the absolute number of MRSA infections and the proportion of MRSA infections that are community-associated are increasing. At three urban children's hospitals in the United States, the percentage of MRSA infections associated with the community have increased as much as 60% in the 3 or 4 years after 2000 (Buckingham et al., 2004; Mishaan et al., 2005; Ochoa et al., 2005).

Community-associated MRSA (CA-MRSA) has unique characteristics that separates it from methicillin-susceptible *S. aureus* (MSSA) and MRSA in healthcare settings. CA-MRSA typically has different epidemiological risk factors, clinical manifestations, and microbiological characteristics than healthcare-associated MRSA (HA-MRSA). In this chapter we discuss the epidemiology and mechanisms of resistance of CA-MRSA, an approach to management of CA-MRSA infections, recommendations for prevention of MRSA in the community, and future directions for research.

## **2.2 Epidemiology and Mechanisms of Resistance in MRSA in the Community**

### ***2.2.1 Epidemiology and Clinical Presentation of MRSA***

In 1999, the Centers for Disease Control and Prevention (CDC) published a report concerning four children from 12 months to 13 years of age who had died from MRSA infections (Centers for Disease Control and Prevention, 1999). None of the children had risk factors for HA-MRSA, which included recent hospitalization or surgery, residence in a long-term care facility, or a history of injecting drug use. Although CA-MRSA had been recently reported in children (Adcock et al., 1998; Herold et al., 1998), most documented US MRSA infections up to that point were associated with healthcare settings or in adult injecting drug users (Levine et al., 1982; Saravolatz et al., 1982). These four cases highlighted the fact that not only could patients develop MRSA disease outside the hospital, but also that CA-MRSA disease could be severe and fatal. In addition to the four pediatric deaths, CA-MRSA infections were reported in other populations, such as prisoners (Centers for

Disease Control and Prevention, 2001). In response to these reports, CDC began active surveillance of all culture-confirmed MRSA infections in the United States to study the epidemiology and drug resistance patterns of MRSA isolates in the community (Fridkin et al., 2005).

Numerous reports have noted that CA-MRSA can present with different clinical manifestations than HA-MRSA and, typically, causes less severe disease for the majority of infections. Most *S. aureus* infections are of the skin and soft tissue and often start out as a small papule or pustule. MRSA and other *S. aureus* skin and soft tissue infections may be misdiagnosed as “spider bites” due to their characteristic presentation. Possible reasons for this are that patients may detect a spontaneous, red bump and assume that it is a spider bite and that clinicians may note necrotic features of the lesions and associate this with a brown recluse spider bite. Patients and medical providers may misdiagnose MRSA skin infections as spider bites even in the absence of having seen a spider or having brown recluses endemic to the local community. In addition, brown recluse spiders have been implicated as the cause of skin lesions across the United States and Canada, despite the fact that these spiders are found only in the southern and central Midwestern United States (Vetter and Bush, 2002).

CA-MRSA infection is defined as an MRSA infection with onset in the community in an individual lacking established HA-MRSA risk factors. For MRSA active surveillance conducted through the CDC-sponsored Active Bacterial Core Surveillance program, an MRSA infection is considered to be community-associated if *S. aureus* isolates are cultured in an outpatient or less than 2 days after hospitalization and if the patient has had no hospitalization, surgery, dialysis, or residence in a long-term care facility within the previous year; no permanent indwelling catheter or percutaneous medical device; and no previous history of MRSA (Fridkin et al., 2005). When case definitions based on risk factors are extended to newborns, admission of a neonate to the hospital at birth has been disregarded as a risk factor for HA-MRSA since nearly all neonates are hospitalized at birth (Buckingham et al., 2004). From studies using these definitions, several demographic characteristics of CA-MRSA have been identified.

### 2.2.1.1 Geographic Characteristics

Cases of CA-MRSA infection have been reported worldwide (Boyce et al., 2005) and regional differences exist within countries. The percentage of MRSA that was community-associated varied from 8 to 20% in three states in the United States (Fridkin et al., 2005); however, prevalence of MRSA in some populations may be higher. MRSA strains present in the community vary by continent, region, and country, but the strains seen worldwide have many microbiological characteristics in common, such as presence of genes for Panton–Valentine leukocidin toxin (Harbarth et al., 2005; Ma et al., 2005; Mulvey et al., 2005; Vandenesch et al., 2003). Although there are microbiological similarities in MRSA strains from different countries, these similarities, such as the development of resistance to methicillin, may have arisen independently in each country or region (Ma et al., 2005).

### 2.2.1.2 Age Characteristics

As discussed earlier, some of the first reports of MRSA infection without traditional healthcare-associated risk factors were in children (Centers for Disease Control and Prevention, 1999; Herold et al., 1998). In two urban areas in the United States where MRSA surveillance was in place from 2001 through 2002, CA-MRSA was more common among children less than 2 years of age than in other age groups (Fridkin et al., 2005). Age differences exist in nasal colonization rates as well. Prevalence of *S. aureus* nasal colonization is highest in children 6–11 years of age, and MRSA nasal carriage is highest in individuals 60 years or older (Kuehnert et al., 2006).

### 2.2.1.3 Racial, Ethnic, and Socioeconomic Characteristics

Rates of CA-MRSA vary between racial and ethnic groups. Compared with Australians of European descent, high rates of CA-MRSA have been noted in Maori and Pacific Islanders in Australia (Hill et al., 2001). Similarly, Pacific Islanders in Hawaii have much higher rates of CA-MRSA infection than Hawaiians of Asian descent. In one investigation of MRSA in Hawaii, Pacific Islanders comprised 76% of patients with CA-MRSA but only 35% of patients who received care in the facility under investigation (Estivariz et al., 2007). In some urban centers in the United States, African Americans have incidence rates higher than whites (Fridkin et al., 2005). Pediatric patients hospitalized with CA-MRSA infection in an urban center in the United States were more likely to be African American than patients hospitalized with community-associated MSSA infections (Ochoa et al., 2005; Sattler et al., 2002).

The racial and ethnic differences that are seen in CA-MRSA may be due to intrinsic genetic factors associated with different races and ethnicities; however, further study is needed (Fine et al., 2005). Geographic isolation of some groups, such as Pacific Islanders in Hawaii, may also contribute to increased rates of MRSA infection (Estivariz et al., 2007). Concurrent diseases such as diabetes may also be a factor (Estivariz et al., 2007). A more likely explanation for the differences may be socioeconomic factors, such as limited access to healthcare and crowded housing conditions, which are more common in some racial groups (Estivariz et al., 2007). Surveillance of CA-MRSA infections shows that the disease occurs across all income categories (Fridkin et al., 2005); however, a study in Minnesota found that the median household income for patients with MRSA infection was lower than the median income for state residents overall (Naimi et al., 2003).

### 2.2.1.4 Sex Characteristics

Although the trends are not consistent across age groups, men and women have different rates of MRSA infection and nasal colonization. Male infants are more likely than female infants both to be colonized by *S. aureus* and to have *S. aureus*

skin infections (Enzenauer et al., 1984, 1985; Thompson et al., 1963, 1966). The cause of this difference is unknown and has not been demonstrated in adults. MRSA nasal carriage is more common among females compared to males, but among non-Hispanic whites and Mexican Americans, males are more likely than females to have nasal colonization of *S. aureus* (Kuehnert et al., 2006). Outbreaks involving men have been repeatedly reported; however, it is not clear if this represents a reporting bias or a higher incidence of disease among men (Centers for Disease Control and Prevention, 2003a,b).

### 2.2.1.5 Urban, Suburban, and Rural Characteristics

CA-MRSA is found in both urban and rural settings. The four pediatric deaths in 1999 from MRSA were reported in rural areas of North Dakota and Minnesota, and different strain types of CA-MRSA continue to cause disease in rural western United States (Stevenson et al., 2005) and among rural native populations in Alaska (Baggett et al., 2003), the Midwestern United States (Groom et al., 2001), and the Northern Territory in Australia (Maguire et al., 1996). A study in Minnesota found that the percentage of MRSA infections that were community-associated were higher outside urban areas (Naimi et al., 2003). Recent investigations have shown increases in prevalence of CA-MRSA in rural settings, possibly associated with increases in methamphetamine use (Cohen et al., in press).

## 2.2.2 Transmission of CA-MRSA

As late as the 1960s, transmission of MRSA was not well understood. Early studies of transmission of *S. aureus* among newborns in a hospital nursery suggested that *S. aureus* was transmitted from patient to patient on the hands of nursery staff and not by airborne particles (Mortimer et al., 1962; Wolinsky et al., 1960). In the hospital, healthcare workers can become transiently colonized after contact with colonized or infected patients and subsequently transmit the MRSA to other patients (Mulligan et al., 1993). While staphylococci can be spread through contaminated fomites, environmental spread does not appear to be the most common method of transmission (Mortimer et al., 1962). As in earlier studies of *S. aureus* in the hospital, CA-MRSA is now considered to be transmitted primarily person-to-person and less commonly through environmental contamination.

When considering transmission of MRSA in the community, it may be helpful to categorize individuals into one of three states: (1) infected with MRSA, (2) colonized with MRSA, or (3) susceptible to MRSA. An individual may move in and out of each of these states, but individuals colonized with MRSA are more likely than non-colonized individuals to develop infection (Ellis et al., 2004, von Eiff et al., 2001). Colonized and infected individuals can also contaminate the environment, allowing environmental surfaces, shared items, and hands to serve as transient vehicles for transmission.

### 2.2.2.1 The Colonized State

Colonization with *S. aureus* is common in humans. Although colonization may occur in many parts of the body (including the axillae, perineum, groin, rectum, skin, and umbilical stump in neonates), the anterior nares are the most consistent site of colonization. Colonization of the nares can lead to contamination of the hands and other parts of the body, and likelihood of colonization can increase after contact with an infected individual (Adcock et al., 1998).

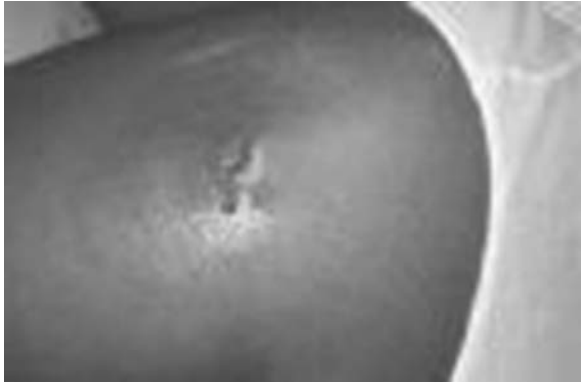
The majority of individuals are either transiently or persistently colonized by *S. aureus* at some point during their life. Staphylococcal carriage studies have found that 16–36% of individuals are persistently colonized, 15–70% are intermittently or occasionally colonized, and 6–47% are never colonized (VandenBergh et al., 1999; Williams, 1963). This has been colloquially referred to as “The Rule of Thirds”: one third of individuals are persistently colonized, one third occasionally, and one third never. However, the Rule of Thirds likely underestimates the number of individuals who are persistently colonized.

In a representative sample survey, nearly a third (an estimated 32.4%) of the United States population carried *S. aureus* in their nares in 2001 and 2002, but less than 1% were carriers of MRSA at that time (Kuehnert et al., 2006). Rates of MRSA colonization based solely on nasal carriage have been as low as less than 1% in certain populations (Hussain et al., 2001; Kuehnert et al., 2006; Sa-Leao et al., 2001), but this may underestimate the carriage on other body parts or intermittent colonization. MRSA nasal carriage can be much higher in certain populations, and children may have higher rates of colonization than adults (Shopsin et al., 2000). In 2001, MRSA nasal colonization in a healthy pediatric population was less than 1%, but the prevalence had increased to 9.2% by 2004 (Creech et al., 2005). The MRSA nasal carriage rate for patients admitted to a public urban hospital in the United States was 7.3% in 1996–1998 (Hidron et al., 2005).

### 2.2.2.2 The Infected State

*S. aureus* causes a broad spectrum of disease. MRSA also causes infections in many parts of the body and has manifestations similar to MSSA (Herold et al., 1998). Those that are infected can be treated but become susceptible again since there is no natural lasting immunity to *S. aureus*. Severity of disease can vary by site of infection, and CA-MRSA may also cause recurrent infections. In one study, approximately one quarter of patients with CA-MRSA infection were hospitalized for their infection (Fridkin et al., 2005), but this percentage may be higher among those with severe or invasive disease (Naimi et al., 2001).

Multi-state surveillance for CA-MRSA infections in the United States shows that skin and soft tissue are the most common sites of infection, causing between 77 and 84% of disease (Fridkin et al., 2005; Naimi et al., 2001) (Figure 2.1). The majority of skin and soft tissue infections are abscesses or cellulitis, but up to one quarter are superficial infections such as impetigo (Naimi et al., 2001). In addition to skin and soft tissue infections, MRSA causes wound infections, sinus infections, urinary tract infections, and pneumonia. Invasive syndromes, such as bacteremia, meningitis,



**Fig. 2.1** MRSA skin and soft tissue infection in prison inmate (CDC, 2005; photo credit Bruno Coignard, MD and Jeff Hageman, MHS).

osteomyelitis, bursitis, and arthritis, are uncommon manifestations (approximately 5%) of MRSA infection (Fridkin et al., 2005). MRSA pneumonia has been reported as a bacterial super-infection after influenza infection in both adults and children (Bhat et al., 2005; Podewils et al., 2005). MRSA can be a cause of otitis media in children (Santos et al., 2000) and accounted for as much as 12% of cases of otorrhea in one series (Hwang et al., 2002). MRSA has also been a reported cause of pyomyositis (Kaplan, 2005a) and Waterhouse–Friderichsen syndrome in children (Adem et al., 2005). Recently, cases of CA-MRSA necrotizing fasciitis have been reported (Miller et al., 2005).

### 2.2.2.3 The Susceptible State

The development of MRSA infection in an individual is related to both the virulence of the bacteria and the susceptibility of the host. Host factors that increase susceptibility to MRSA include a weakened immune response, a non-intact skin barrier, and a genetic predisposition to infection. Specifically, defects in chemotaxis (such as in Wiskott–Aldrich and Chediak–Higashi syndromes), phagocytosis, and humoral immunity can cause an increased risk for staphylococcal infection. MRSA skin infections may be more common in persons with HIV, but this is more likely due to behavioral risk factors than immune suppression by HIV (Lee et al., 2005). Other factors leading to increased transmission of MRSA in susceptible hosts have been elucidated by evaluating outbreaks of MRSA in the community.

### 2.2.2.4 Outbreaks of MRSA in the Community

Since the early 1980s when MRSA was recognized as a pathogen that can cause outbreaks in the community in groups such as intravenous drug users, outbreaks of CA-MRSA have been reported in a number of diverse groups: Native American, Alaskan Native, and Pacific Islander communities (Baggett et al., 2003, 2004; Estivariz et al., 2007; Groom et al., 2001; Hill et al., 2001); prisoners (Centers for Disease Control and Prevention, 2001, 2003b); amateur and professional sports participants, such as



football players, wrestlers, rugby players, fencers, and divers (Begier et al., 2004; Centers for Disease Control and Prevention, 2003a; Kazakova et al., 2005; Stacey et al., 1998; Wang et al., 2003); child care attendees (Adcock et al., 1998); military personnel (Campbell et al., 2004; Zinderman et al., 2004); men who have sex with men (Lee et al., 2005); methamphetamine and injecting drug users (Cohen et al., in press; Fleisch et al., 2001); survivors of natural disasters (Centers for Disease Control and Prevention, 2005); recipients of tattoos (Centers for Disease Control and Prevention, 2006); and isolated religious communities (Coronado et al., 2006). MRSA can cause infections in animals and pets and has been reported to cause infections in humans who have contact with infected animals (Weese et al., 2005).

Although these groups are diverse, they have common factors that may underlie the transmission of MRSA in the community. Based on investigations of community outbreaks, five factors that contribute to transmission of MRSA in the community have been characterized as the “Five Cs”:

1. *Crowding*. Outbreaks have occurred in populations living in crowded quarters such as prisons and military barracks. Living in a house with more than one person per bedroom has been independently associated with developing a CA-MRSA skin or soft tissue infection (Cohen et al., in press).
2. *Contact, skin-to-skin*. Participants in contact sports may have frequent skin-to-skin contact, which may act as a method of transmitting MRSA skin and soft tissue infection. Outbreaks among professional and college football teams have been attributed to frequent skin-to-skin contact (Begier et al., 2004; Kazakova et al., 2005). Similarly, wrestlers who have significant skin-to-skin contact have experienced outbreaks of MRSA infection (Centers for Disease Control and Prevention, 2003a). High-risk sexual behavior (Lee et al., 2005) and sexual contact with someone with a skin infection (Cohen et al., in press; Lee et al., 2005) have both been associated with CA-MRSA skin and soft tissue infections. These factors have been described both in rural and urban communities.
3. *Cut or compromised skin*. Breaks in the skin can be a portal for MRSA bacteria to enter the body. For example, in an outbreak of MRSA infections among a college football team, MRSA infections were associated with abrasions from artificial grass (“turf burns”) and cosmetic body shaving (Begier et al., 2004). In an outbreak among military recruits, most of the MRSA skin and soft tissue infections were on exposed skin of the arms, legs, and knees, where abrasions are common during field training (Zinderman et al., 2004). Skin picking behavior has also been associated with MRSA skin and soft tissue infections (Cohen et al., in press). Injection drug use, where the skin is compromised by insertion of contaminated needles, has been associated with MRSA infections (Miller et al., 2005; Young et al., 2004), but injection may not be the only method by which MRSA is transmitted among drug users (Cohen et al., in press).
4. *Contaminated surfaces and shared items*. Although environmental transmission of MRSA may not be the most common mode of transmission, the environment may have played a role in some outbreaks of MRSA in the community. Outbreaks have been associated with whirlpools (Begier et al., 2004) MRSA-contaminated sauna benches (Baggett et al., 2004) (Figure 2.2). An outbreak

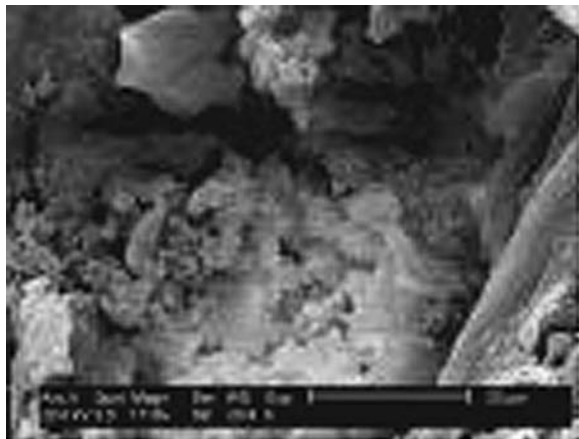
among fencers was unusual because there is typically little skin-to-skin contact in that sport; however, investigators surmised that the cluster of cases was due to shared fencing equipment (Centers for Disease Control and Prevention, 2003a). In a correctional facility in Mississippi, sharing personal items such as linens was associated with infection (Centers for Disease Control and Prevention, 2001), while sharing bars of soap was implicated in an outbreak among members of a college football team (Nguyen et al., 2005).

5. *Cleanliness.* Cleanliness includes both personal bathing and laundering of clothing, linens, and towels, all of which has been noted as potential contributing factors to CA-MRSA infection among prison inmates (Centers for Disease Control and Prevention, 2001). Investigations of MRSA transmission in prisons suggest that lack of access to basic hygiene is a contributing factor (Centers for Disease Control and Prevention, 2003b). Homelessness has also been associated with MRSA skin and soft tissue infections (Young et al., 2004).

In addition to the “Five Cs,” previous use of antimicrobial agents has also been shown to be a factor in the development of CA-MRSA (Baggett et al. 2003, Kazakova et al., 2005).

6. *Antimicrobial agent use.* The prior use of antimicrobial agents has been associated with MRSA infections in the healthcare setting and may also be a contributing factor in the community. Use of antimicrobial agents may predispose individuals to the acquisition of resistant organisms, such as MRSA strains. An outbreak of CA-MRSA skin infections in southwestern Alaska found that patients with the skin infections received significantly more antimicrobial agents in the year before the outbreak compared to community members without skin infections (Baggett et al., 2004). Nasal MRSA colonization, which can precede MRSA infection, was more common in new military recruits who had received antimicrobial agents within 6 months of arriving at training camp than those who had received no recent antibiotics (Ellis et al., 2004). In an outbreak of MRSA

**Fig. 2.2** Scanning electron micrograph (magnification 1719 $\times$ ) of *Staphylococcus*-like organisms on samples of wood collected from steam baths responsible for a furunculosis outbreak in rural Alaska (CDC, 2004; photo taken by Janice Carr, Division of Healthcare Quality Promotion).



in a closed religious community in the United States, investigators found use of antimicrobial agents was associated with infection (Coronado et al., 2006).

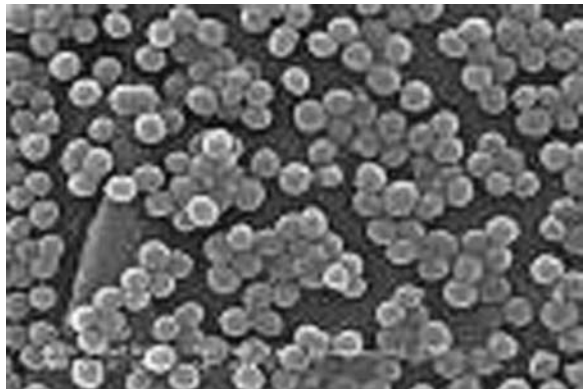
It is important to note that in a study at an urban emergency department in the United States, most patients with MRSA skin infections had none of these characteristic risk factors associated with recent reports of CA-MRSA outbreaks (Moran et al., 2005).

### 2.2.3 Microbiology and Mechanisms of Resistance

*S. aureus* is a non-motile, non-spore-forming Gram-positive coccus that appears as characteristic grape-like clusters (Figure 2.3). The bacteria are catalase-positive, facultative aerobes that are usually unencapsulated. They can survive on fomites in the environment for months. Antimicrobial resistance and virulence factors in *S. aureus* help explain the clinical presentations and the transmission of CA-MRSA. Microbiologic differences of MRSA isolated from patients with CA- and HA-MRSA infections have been identified based on molecular typing, antimicrobial susceptibility testing, and identification of methicillin resistance and toxin genes (Table 2.1). However, these differences are becoming less distinct as MRSA strains that emerged in the community develop resistance to additional classes of antimicrobial agents and enter healthcare settings.

#### 2.2.3.1 Mechanisms of Resistance

Penicillin resistance in *S. aureus* is conferred by a plasmid-associated gene (*blaZ*) that codes for a  $\beta$ -lactamase. Methicillin resistance is usually conferred by an altered chromosomally encoded penicillin-binding protein (PBP-2a) that causes resistance to all  $\beta$ -lactam antimicrobial agents (including penicillin) and cephalosporins. The staphylococcal chromosomal cassette contains the gene for this altered penicillin-



**Fig. 2.3** Scanning electron micrograph of *S. aureus* (CDC, 2005; Photo taken by Janice Carr, Division of Healthcare Quality Promotion).

**Table 2.1** Microbiological differences initially noted between community- and healthcare-associated MRSA in the United States.

	Community-associated	Healthcare-associated
Pulsed-field gel electrophoresis (PFGE) type	USA300, USA400 commonly; USA1000, USA1100 less commonly	USA100, USA200
Staphylococcal chromosomal cassette or <i>mec</i> type	<i>SCCmec</i> Type IV	<i>SCCmec</i> Types I, II, III (most commonly Type II)
Accessory gene regular ( <i>agr</i> ) allele	<i>agr3</i>	<i>agr2</i>
Panton–Valentine leukocidin (PVL) toxin production	Common	Rare
Antimicrobial susceptibility <sup>a</sup>	Generally susceptible to antimicrobials other than $\beta$ -lactams and erythromycin	Generally resistant to multiple agents
Chloramphenicol	Usually susceptible	Often resistant
Clindamycin	Usually susceptible	Often resistant
Erythromycin	Usually resistant	Usually resistant
Fluoroquinolone	Variable	Usually resistant
trimethoprim /sulfamethoxazole (TMP-SFZ)	Usually susceptible	Usually susceptible

<sup>a</sup> Antimicrobial susceptibility patterns may change.

References: Naimi et al. (2003), Baba et al. (2002), Fey et al. (2003) and Weber (2005).

binding protein (*SCCmec*). *SCCmec* can be mobilized for transfer between organisms in vitro (Katayama et al., 2000), although this is thought to be a rare occurrence (Chambers, 2001). *SCCmec* contains two genes [(cassette chromosome recombinase A and B (*ccrA* and *ccrB*)] that encode recombinases that integrate the cassette into its chromosomal locus.

Five types of *SCCmec* have been described; Types II and IV are the primary types seen in the United States. Genotypes associated with community transmission almost exclusively contain *SCCmec* Type IV; it is the smallest of the five types. *SCCmec* Type IV has been identified in MRSA strains from CA-MRSA infections in the United States and worldwide. MRSA strains associated with healthcare transmission in the United States most commonly contain *SCCmec* Type II and less commonly Types I and III. *SCCmec* Type IV is also typical in some healthcare-associated strains, such as USA800. Types II and III often carry genes conferring resistance to other antimicrobial agents (such as aminoglycosides, tetracyclines, erythromycin, and clindamycin), whereas Type IV typically does not. This difference in community- and healthcare-associated *SCCmec* types leads to different

antimicrobial agent susceptibility patterns between healthcare- and community-associated MRSA infections. However, these patterns are likely to change over time.

### 2.2.3.2 Mechanisms of Virulence

Virulence factors enhance the ability of bacteria to cause infection by evading the host's defenses, increasing adherence to tissues, or spreading through tissues. Examples of virulence factors in *S. aureus* include production of coagulase, toxins, and proteins intrinsic to the cell wall. *S. aureus* produces coagulase, which interacts with fibrinogen causing plasma to clot. This clumping creates a loose polysaccharide capsule that can interfere with phagocytosis. The combination of these virulence factors may cause localization of an infection, such as in an abscess, a common clinical manifestation of CA-MRSA infection.

Panton–Valentine Leukocidin (PVL) is a cytotoxin (coded by the *lukS-PV* and *lukF-PV* genes) first identified in methicillin-susceptible *S. aureus* (Panton and Valentine, 1932). PVL kills leukocytes by creating pores in the cell membrane of affected cells or by activating apoptosis pathways. Pore formation leads to increased cell wall permeability and leakage of protein from the cell causing cell death and tissue necrosis. PVL genes have been associated with severe abscesses, necrotizing pneumonia, and increased complications in osteomyelitis (Lina et al., 1999, Martinez-Aguilar et al., 2004). Genes encoding PVL are more commonly found among strains of MRSA originating in the community and not strains traditionally associated with health care settings (Naimi et al., 2003). The presence of PVL may explain the clinical manifestations of abscesses and skin and soft tissue infections in CA-MRSA infections.

In addition to PVL, other toxins may be produced by *S. aureus*:  $\alpha$ -toxin, which causes tissue necrosis and acts on cell membranes; exfoliatin A and B, which cause skin separation in diseases such as bullous impetigo and staphylococcal scalded skin syndrome; enterotoxins A, B, C<sub>1</sub>, C<sub>2</sub>, D, and E, which can cause vomiting and diarrhea associated with food poisoning; and toxic shock syndrome toxin 1 (TSST-1), which induces production of interleukin-1 and tumor necrosis factor leading to shock. Peptidoglycans, which comprise 50% by weight of the cell wall of staphylococci, can have endotoxin properties as well. Other cell wall polymers, such as teichoic acid, and cell surface proteins, such as protein A, fibronectin-, and collagen-binding proteins, may also be virulence factors for *S. aureus*. Recent sequencing of the most common molecular type of CA-MRSA (USA300) suggests that encoded gene products might enhance the ability of the strain to live on the host's skin (Diep et al., 2006).

### 2.2.3.3 Antimicrobial Susceptibility Testing

Antimicrobial agent susceptibility testing is commonly used in clinical laboratories to guide the clinical treatment of *S. aureus* infection. The most standardized

and accurate methods of antimicrobial agent susceptibility testing are disk diffusion tests and broth microdilution tests. In disk diffusion tests, a disk impregnated with an antimicrobial agent is placed on an agar plate containing a lawn of bacteria to test whether the antimicrobial agent inhibits the growth of bacteria. (However, the vancomycin disk diffusion test does not detect vancomycin intermediate *S. aureus* isolates.) One variation of the disk diffusion test is the E-test, a plastic strip with a gradient of antimicrobial agent concentrations used to determine the minimal inhibitory concentration (MIC) to specific antimicrobial agents. Broth microdilution tests determine the lowest concentration of antimicrobial agents that inhibit bacterial growth in a broth medium using a standard inoculum size. In an agar screen test, a standardized suspension of the microorganism is inoculated directly onto an agar plate impregnated with an antimicrobial agent. Rapid automated instrumentation, such as with devices offered by Vitek<sup>TM</sup>, Microscan<sup>TM</sup>, and others, are most commonly used in laboratories to determine the susceptibility pattern of *S. aureus*.

Clindamycin resistance may be constitutive or inducible, and testing for this resistance can impact clinical treatment decisions. Resistance to clindamycin is closely tied to resistance to erythromycin, the latter of which is encoded by two different genes: *msrA* and *erm* (Siberry et al., 2003). The *msrA* gene encodes an adenosine triphosphate (ATP)-dependent efflux pump that confers resistance to erythromycin but not clindamycin. The *erm* (or erythromycin ribosomal methylase) gene confers constitutive resistance to erythromycin and either constitutive or inducible clindamycin resistance. MRSA isolates with inducible clindamycin resistance are resistant to erythromycin and sensitive to clindamycin on routine testing, but can be induced to express resistance to clindamycin *in vitro*.

Rates of inducible clindamycin resistance among strains of MRSA vary widely across the United States, from less than 10% (Sattler et al., 2002) to greater than 90% (Frank et al., 2002). Inducible clindamycin resistance has become less common among MRSA isolates from an urban pediatric population in the United States (Chavez-Bueno et al., 2005). Inducible clindamycin resistance can be identified with the D-zone test, a double disk diffusion test in which the zone of inhibition is measured around both erythromycin and clindamycin disks (Fiebelkorn et al., 2003). The “D” is formed when the zone of inhibition around the clindamycin disk is blunted on the side adjacent to the erythromycin disk. A positive D-zone test indicates inducible clindamycin resistance. The Clinical and Laboratory Standards Institute (CLSI), formerly the National Committee for Clinical Laboratory Standards (NCCLS), recommends performing a D-zone test on all erythromycin-resistant, clindamycin-susceptible *S. aureus* isolates before reporting clindamycin susceptibility results (Clinical and Laboratory Standards Institute, 2006).

#### 2.2.3.4 Molecular Typing of MRSA

Typing MRSA strains has been used in the past to link cases in a cluster and to locate sources of specific outbreaks. Using the antimicrobial agent susceptibility profile to determine genetic relatedness of strains of *S. aureus* is unreliable. Since this typing

method has low discriminatory power, pulsed-field gel electrophoresis (PFGE) is one of the most frequently used methods of typing strains; pulsed-field types are commonly recognized in the United States and around the world. Spa (*Staphylococcus* protein A) typing, multi-locus sequence typing (MLST), multi-locus variable-number tandem-repeat analysis (MLVA), or a combination of typing methods can also be used to differentiate among isolates.

In the United States, a limited number of MRSA strains have been implicated in most community outbreaks. Most CA-MRSA disease in the United States is now caused by pulsed-field type USA300, but other genotypes (USA400, USA1000, and USA1100) also cause disease (McDougal et al., 2003). A highly conserved USA300 strain (USA300-0114) has been implicated in multiple outbreaks across the United States in diverse populations that are not epidemiologically related, such as athletes, prisoners, and children (Kazakova et al., 2005).

#### **2.2.3.5 Molecular Origins of MRSA**

The microbiological differences between strains of MRSA isolated from CA-MRSA and HA-MRSA infections give us clues as to the origins of MRSA in the community. Some experts postulate that CA-MRSA strains are descendants of healthcare-associated strains that leaked from hospitals into the community. However, CA-MRSA and HA-MRSA are so microbiologically different that it is unlikely that CA-MRSA strains descended directly or recently from healthcare-associated strains. Instead, the *mecA* gene was likely acquired by MSSA strains established in the community, possibly from coagulase-negative staphylococci or HA-MRSA strains (Chambers, 2001). This theory is bolstered by the finding that MSSA and MRSA strains in a series of community-associated *S. aureus* infections in an urban city in the United States had indistinguishable PFGE patterns and differed only by *SCCmec* (Mongkolrattanothai et al., 2003).

### **2.3 Considerations in Management of *S. aureus* Infection in the Community**

Given that most skin and soft tissue infections are treated empirically, a majority of CA-MRSA infections may be treated with antimicrobial agents to which the bacteria are not susceptible in vitro (Naimi et al., 2001). Treatment should be based on the susceptibility profile of the organism and may differ with severity of the infection. Even though wound, skin, and soft tissue MRSA infections are generally less severe than invasive MRSA infections, they account for nearly 90% of all MRSA infections (Fridkin et al., 2005) and comprise the majority of the burden of MRSA disease.

### ***2.3.1 Management of Severe or Invasive MRSA Infections***

Severe or invasive MRSA infections include sepsis, pneumonia, endocarditis, osteomyelitis, and the progression of localized infections such as of the skin or soft tissue. MRSA should be considered in cases of community-acquired pneumonia, particularly those following influenza-like illness (Hageman et al., 2006). Many patients with severe or invasive MRSA infections require parenteral antimicrobial therapy; vancomycin remains a first-line treatment. Prompt empiric treatment with antimicrobial agents can be essential in treating severe or invasive disease; however, a culture should be obtained before starting antimicrobial therapy if possible. In some cases, other antimicrobial agents such as ceftriaxone, gentamicin, or rifampin may be added to ensure optimal coverage of other potential pathogens. In addition to antimicrobial agent therapy, incision and drainage is mandatory for drainable skin and soft tissue infections and should be considered for severe or deep infections, such as septic joints.

### ***2.3.2 Management of MRSA Skin or Soft Tissue Infections***

Few MRSA skin and soft tissue infections will progress to severe or invasive disease, but early diagnosis and treatment is important to prevent progression and limit further spread. MRSA should now be considered a potential causative organism in all community-associated skin and soft tissue infections. MRSA may be the most common bacterial cause of certain skin and soft tissue infections in some areas (Cohen et al., in press; King et al., 2006; Moran et al., 2006). Local data on prevalence of MRSA and susceptibilities to alternative antimicrobial agents should be used to guide treatment decisions. Although data from controlled trials are limited, steps that may be considered part of management of CA-MRSA skin and soft tissue infections are as follows (Gorwitz et al., 2006):

1. *Incision and drainage should be routine for skin lesions that are able to be drained.* Incision and drainage has been the primary mode of treatment for skin and soft tissue abscesses for many centuries, and the introduction of antimicrobial agents should not change that practice. Incision and drainage may become more important as MRSA and other antimicrobial agent-resistant organisms cause more diseases. Studies that assess whether antimicrobial treatment with incision and drainage is more effective than incision and drainage alone have not shown a clear benefit to adding antimicrobial agents for uncomplicated disease (Gorwitz et al., 2006). Clinicians may consider prescribing antimicrobial agents if the skin and soft tissue infection (1) is severe, rapidly progressing, or greater than 5 cm (Lee et al., 2004); (2) has spread systemically; (3) is in a location that may be difficult to drain completely; (4) does not respond to incision and drainage alone; or (5) is in a patient with extremes of age or other co-morbidities (e.g., diabetes mellitus, neoplastic disease, or HIV infection).



2. *Collect diagnostic specimens for culture.* Incision and drainage should be performed for all drainable skin lesions; cultures should be obtained from patients with both draining and non-draining, purulent lesions. Obtaining isolates not only helps guide treatment of individual patients but also monitors the antimicrobial agent susceptibility patterns in the community. Cultures are also important when clinicians or public health officials suspect that the patient may be part of a cluster or outbreak of cases.
3. *Provide careful and thorough wound care.* MRSA skin and soft tissue infections are transmissible through contact with draining lesions. After incision and drainage, wounds should be adequately covered, bandages should be appropriately disposed of, and hand hygiene should be continued to prevent further spread of MRSA.
4. *Ensure adequate follow-up.* Clinicians should ensure that all culture and antimicrobial susceptibility testing results are reviewed to identify cases of MRSA. Patients should be monitored for response to treatment and educated about symptoms that suggest treatment failure, i.e., worsening of local symptoms, development of systemic symptoms, or lack of improvement of symptoms in 48 h.
5. *Use appropriate antimicrobial agents.* Although practice patterns are changing as medical providers learn about CA-MRSA, a large percentage of pediatric and adult patients with MRSA skin infections still receive an antimicrobial agent to which the bacteria are not susceptible in vitro (Lee et al., 2004; Moran et al., 2006). Local antimicrobial susceptibility data for outpatient *S. aureus* skin and soft tissue infections should guide empiric treatment decisions. Ideally, antimicrobial susceptibility testing results from the individual patient should be used to select definitive therapy of infections that are yet to resolve or have not resolved by the time culture results are available. Empiric therapy for MRSA may be warranted in areas where prevalence of MRSA in the community is high. A prevalence of 10–15% of methicillin resistance in community *S. aureus* strains has been suggested by some experts (Kaplan, 2005b).

The choice of antimicrobial therapy for MRSA infections depends on a number of factors: Is the therapy empiric or directed? Is the MRSA disease severe or invasive versus non-invasive? Options for therapy with commonly recommended antimicrobial agents are listed below:

1. *Clindamycin.* Clindamycin is bacteriostatic and, by binding to the bacterial ribosomal 50S subunit, inhibits protein synthesis. Clindamycin is available in both oral and parenteral formulations. Resistance to clindamycin in *S. aureus* can be either constitutive or inducible. Inducible clindamycin resistance, as discussed earlier, can be detected with the D-zone test. If using clindamycin, it is important to consider whether a *S. aureus* isolate possesses inducible clindamycin resistance. Although some *S. aureus* infections in which the isolate possesses inducible clindamycin resistance improve on clindamycin therapy (Frank et al., 2002), clindamycin is not recommended for any infection in which the infecting isolate is known to possess inducible resistance. If inducible resistance is detected after empiric clindamycin therapy has been initiated, the decision to

modify therapy should be based on the patient's clinical response. A theoretical benefit of clindamycin treatment of *S. aureus* infections is inhibition of protein synthesis in toxin-mediated bacterial syndromes; however, no data have shown this benefit for *S. aureus* strains producing the PVL cytotoxin.

2. *Daptomycin*. Daptomycin is a cyclic lipopeptide that binds to bacterial membranes, causing a loss of membrane potential and inhibiting protein, DNA, and RNA synthesis. It was approved in 2003 in the United States for treatment of complicated MRSA skin and soft tissue infections in adults. Daptomycin is only available as an intravenous medication. Daptomycin is inactivated by surfactant and is not recommended for treating *S. aureus* pneumonia (Carpenter and Chambers, 2004).
3. *Linezolid*. Linezolid is an oxazolidinone with both parenteral and oral formulations. Its antibacterial effects are from inhibition of ribosomal protein synthesis. This mechanism of action is unique, so there is no cross-resistance with other known antimicrobial agents. Linezolid was approved in 2000 in the United States for treatment of complicated MRSA skin and soft tissue infections and MRSA pneumonia in both children and adults. Linezolid is expensive compared to other antimicrobial agents and side effects such as reversible myelosuppression have been reported. In order to limit development of resistance, clinicians may choose to reserve linezolid for more severe infections and infections that do not respond to other antimicrobial therapy. Consultation with an infectious disease specialist may be helpful.
4. *Mupirocin*. Mupirocin is a topical antimicrobial agent that works by inhibiting bacterial protein and RNA synthesis. Mupirocin is recommended for the topical therapy of impetigo, but not for other *S. aureus* or MRSA skin and soft tissue infections. Mupirocin is also available in an intra-nasal formulation for nasal decolonization.
5. *Quinupristin-dalfopristin*. Quinupristin-dalfopristin is an intravenous-only streptogramin antibacterial agent that inhibits peptide bond formation in the 50S ribosome. It is approved by the United States Food and Drug Administration for the treatment of complicated MRSA skin and soft tissue infections.
6. *Rifampin*. Rifampin is an antimicrobial agent thought to inhibit RNA polymerase. Rifampin should not be used as a single agent because *S. aureus* can develop resistance to rifampin rapidly when used alone (Strausbaugh et al., 1992). Rifampin has been used in combination with other antimicrobial agents (Iyer and Jones, 2004) and may be useful in decreasing nasal carriage because it reaches high levels in mucosal surfaces.
7. *Tetracyclines*. Tetracyclines are bacteriostatic antimicrobial agents. Doxycycline is approved for treatment of *S. aureus* infection in the United States, and minocycline is also used. There is little information in the literature about treatment of MRSA or serious staphylococcal infection with tetracycline. Tetracyclines should be avoided in pregnant women and children less than 8 years of age due to impaired tooth and bone growth.
8. *Tigecycline*. In 2005, the United States Food and Drug Administration approved intravenous tigecycline for the treatment of MRSA. Tigecycline inhibits protein translation by binding to the 30S ribosomal subunit. Tigecycline has activity

against a wide range of bacteria, but it is too early to tell how this antimicrobial agent should be used in the treatment of MRSA.

9. *Trimethoprim/sulfamethoxazole (TMP/SFX)*. TMP/SFX is available in both oral and intravenous formulations and blocks the production of folic acid. TMP/SFX is a common treatment for *S. aureus* skin and soft tissue infections, because MRSA isolates are often susceptible to TMP/SFX. However, other bacteria that cause skin infections, such as  $\beta$ -hemolytic streptococci (groups A and B), are typically resistant to this agent. For clinical syndromes in which streptococcal infection is likely, such as cellulitis without abscess, substitution or addition of an agent with streptococcal coverage should be considered. TMP/SFX is not recommended for women in their third trimester of pregnancy or for infants less than 2 months of age.
10. *Vancomycin*. Vancomycin is commonly used as first-line therapy for severe and invasive disease and as a second-line therapy when other treatment fails. Vancomycin is a glycopeptide that inhibits cell wall biosynthesis. It is only used in the intravenous form because it is not well absorbed from the gastrointestinal tract. Another glycopeptide, teichoplanin, is available in some countries outside the United States but is not routinely recommended as a first- or second-line agent in the treatment of MRSA. A number of isolates of vancomycin-resistant and vancomycin-intermediate *S. aureus* have been reported and are discussed later.

Prevalence of resistance to other antimicrobial agents, such as fluoroquinolones and macrolides, is relatively high or can rapidly develop among *S. aureus* strains. These agents are not optimal choices for empiric treatment of community-associated skin and soft tissue infections:

1. *Fluoroquinolones*. MRSA strains can easily develop fluoroquinolone resistance. Newer fluoroquinolones, such as moxifloxacin and levofloxacin, have increased activity against *S. aureus*, but increasing resistance suggests that fluoroquinolones may not be an optimal choice for empiric treatment of community-associated skin infections.
2. *Macrolides and azalides*. Resistance to macrolides (e.g., erythromycin and clarithromycin) and azalides (e.g., azithromycin) is common among MRSA isolates (Fridkin et al., 2005), so they are not recommended for empiric treatment of infections possibly caused by MRSA.

### ***2.3.3 Strategies to Eliminate S. aureus Colonization***

Decolonization has been suggested as a treatment for recurrent or persistent MRSA infections but has not been proven an effective intervention for the management of MRSA infection. Decolonization may also be useful to halt ongoing transmission in a closely associated, well-defined cohort. Decolonization regimens have been effective in reducing colonization in the short term, but recolonization is common (Laupland and Conly, 2003; Perl et al., 2002). Carriage at sites other than the nares

and reports of resistance to mupirocin may also limit the effectiveness of nasal decolonization (Loeb et al., 2003). If decolonization is used, the medical provider should confirm that the patient is colonized with MRSA. Proposed regimens for decolonization include intranasal mupirocin twice a day for 5–10 days and antiseptic body wash, such as with chlorhexidine, for the same duration (Stevens et al., 2005). Decolonization with systemic oral antimicrobial agents such as TMP/SFX, tetracyclines, and clindamycin has also been suggested.

## **2.4 Prevention of MRSA in the Community**

Effective prevention strategies for CA-MRSA need to include public health officials, medical providers and infection control practitioners, and patients and community members.

### ***2.4.1 Public Health Officials***

1. *Enhance surveillance.* Both prospective and retrospective surveillance may be important to identify cases of MRSA in the community. Surveillance can also be used as an opportunity to collect isolates and to educate both patients and providers. Contacts of patients with MRSA infection should be notified to identify new cases and to ensure that they are receiving proper treatment.
2. *Initiate public health investigations when appropriate.* When MRSA is detected in a group of individuals in the community who are linked epidemiologically, public health officials should consider whether to investigate the causes of the cluster. When considering whether to investigate, public health officials should weigh the number and clustering of time and space of cases, the setting of the cluster, the severity of illness, the presence of ongoing transmission, and the likelihood that an intervention could be successfully implemented.

### ***2.4.2 Medical Providers and Infection Control Practitioners***

1. *Use appropriate treatment.* As discussed earlier, abscesses should be drained and antimicrobial treatment should be chosen based on local antimicrobial susceptibility patterns. Since CA-MRSA infections have been associated with previous antimicrobial use, antimicrobials should be used appropriately and judiciously to prevent development of resistance. Since skin and soft tissue infections may start out innocuously, patients may attempt to care for their wounds without medical treatment. Inadequate self-care has been associated with developing skin infections and may contribute to transmission in an outbreak (Centers for Disease Control and Prevention, 2001).

2. *Educate patients and providers on diagnosis, treatment, and prevention.* Clinicians should ask patients with MRSA infections if other contacts and household members also have suspicious lesions or infections.
3. *Consider decolonization.* Testing for MRSA colonization may be useful in public health investigations. Decolonization may be useful along with other measures, when there is ongoing transmission in members of a closely associated, well-defined cohort. If decolonization is being considered for the prevention of MRSA transmission in a discrete population, then all members of the population should be decolonized simultaneously.
4. *Continue effective healthcare infection control measures.* The control of MRSA in the community needs to include infection control measures in healthcare settings, since many of these patients interface with the medical system. Recommendations for preventing MRSA infections in the healthcare setting include (1) isolating or cohorting patients with MRSA, (2) wearing gloves and gowns during contact with MRSA patients, (3) using appropriate antimicrobials for treatment, and (4) ensuring appropriate hand hygiene (Siegel et al., 2007). Hospitals may also educate staff on MRSA transmission and treatment, increase the number of infection control personnel, and ensure environmental cleaning (Nijssen et al., 2005). Contaminated surfaces in healthcare locations should be cleaned with an approved hospital detergent/disinfectant or a 1:100 solution of diluted bleach (1 tablespoon bleach in a 1 quart water) (Schulster and Chinn, 2003). Targeted interventions to prevent MRSA infection can be successful; however, many interventions use multiple approaches and it is often unclear which activities led to the successful prevention of disease (Wootton et al., 2004). The proportion of *S. aureus* infections caused by MRSA has remained very low in the Netherlands, which has been attributed to vigilant active surveillance and strict patient isolation (Vandenbroucke-Grauls, 1996). Preventive measures in the hospital vary from institution to institution, and surveillance cultures may not effectively measure the success of infection control policies (Nijssen et al., 2005). Passive surveillance of hospitalized patients with MRSA may fail to identify asymptomatic patients who are colonized with MRSA. No study has conclusively shown that patient isolation or cohorting of patients with similar disease is alone sufficient to reduce nosocomial spread of MRSA (Cepeda et al., 2005). However, isolation and cohorting should still be used since they have been part of successful campaigns to stop transmission (Cooper et al., 2004).

### ***2.4.3 Patients and Members of the Community***

1. *Educate patients on treatment and prevention.* Patients should be encouraged to keep wounds covered, to maintain good personal and hand hygiene, and to avoid sharing potentially contaminated items. In addition to patients, individuals in high-risk groups, such as incarcerated individuals, those involved in contact sports, and injecting drug users, should also be educated on prevention measures. Prevention recommendations may need to be tailored for each individual group.

This education is critical to ensure that patients get correct treatment and stop the spread of infection in the community.

2. *Care for and contain wounds.* Wounds should be covered with clean, dry dressings. Patients with open skin wounds, such as draining skin and soft tissue infections that cannot be covered, may need to be excluded from activities that could lead to transmission. Specifically, sports participants with draining lesions that are unable to be adequately contained during sports play may need to be excluded until the lesion can be adequately contained.
3. *Encourage personal hygiene,* especially hand hygiene. Use soap and water or alcohol-based hand gels to clean hands, and encourage regular bathing. Do not share personal items that may transmit infection. Launder contaminated clothes and linens with detergent, soap, or bleach, and dry thoroughly (Sehulster and Chinn, 2003).
4. *Maintain a clean environment.* Facilities where patrons and staff have close contact (e.g., homeless shelters) or shared equipment or surfaces (e.g., gyms) should consider environmental interventions to prevent transmission of MRSA. Since surfaces contaminated with *S. aureus* have been implicated in outbreaks (Baggett et al., 2004), targeted cleaning may be warranted on areas and equipment where known cases had recent contact. A barrier such as clothes or a towel should be used when in contact with shared equipment or surfaces, such as at a gymnasium.

## 2.5 Future Directions

Why has MRSA emerged in the community? An increase in use of antimicrobial agents, more virulent strains, and transmission of methicillin-resistance genes may be contributing to the spread of MRSA in the community (Weber, 2005). MRSA will continue to evolve, and we will need to adhere to known methods for the control of *S. aureus* while we identify other treatment and prevention strategies. Research will continue to elucidate why some people are more susceptible to MRSA than others and what host factors are linked to MRSA infection.

Vancomycin is a primary treatment for severe, invasive MRSA infections that fail to respond to other antimicrobial agents. *S. aureus* developed resistance first to penicillin and then to semisynthetic penicillins, such as methicillin, oxacillin, and nafcillin; similarly, recently identified isolates of *S. aureus* have developed resistance to vancomycin. Clinical isolates of *S. aureus* with intermediate resistance to vancomycin (MICs of 8–16 mug/ml) were first reported in Japan in the late 1990s (Hiramatsu et al., 1997). Intermediate resistance to vancomycin in strains of *S. aureus* may be due to the development of thicker cell walls in the bacteria.

Resistance to vancomycin is conferred by the presence of a *vana* operon, which is thought to be transferred from vancomycin-resistant enterococci (Weigel et al., 2003). In 2002, reports of *S. aureus* resistant to vancomycin (MICs  $\geq 32$  mug/ml) came from two states (Michigan and Pennsylvania) in the United States (Centers

for Disease Control and Prevention, 2002a,b); four subsequent cases have occurred in Michigan and New York (Centers for Disease Control and Prevention, 2004). All these vancomycin-resistant *S. aureus* (VRSA) patients have risk factors for healthcare-associated disease.

New mechanisms of preventing *S. aureus* infection are also on the horizon. Passive immunizations for high-risk patients (namely premature infants and adults with blood stream infections) are being evaluated. Active vaccination may target staphylococcal toxins or the bacterial cell wall through peptidoglycans, lipids, or associated cell wall proteins (Gotz, 2004; Shinefield and Black, 2005). Other treatments and antimicrobial agents are being developed. Intravenous immunoglobulin can neutralize toxins such as PVL, but this has not been sufficiently tested as a treatment for PVL-positive MRSA infections.

The epidemiology of the MRSA infection continues to evolve. Many described strains of CA-MRSA are now the cause of disease and outbreaks in healthcare settings, such as in maternal and neonatal wards (Bratu et al., 2005; Healy et al., 2004; Saiman et al., 2003), in patients receiving prosthetic joints (Kourbatova et al., 2005), and in patients with healthcare-associated bloodstream infections (Seybold et al., 2006). We will need to be vigilant in our identification and treatment of MRSA infections in the future to prevent further spread and development of new resistant strains.

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