REVIEW

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The emergence of methicillin-resistant *Staphylococcus aureus* in the community

ABSTRACT

Infections with methicillin-resistant *Staphylococcus aureus* (MRSA), long endemic in hospitals and nursing homes, are now being reported in the community as well. While we await further epidemiological and microbiological study of this emerging pathogen, current clinical practice requires a reconsideration of the empiric use of beta-lactam agents for the seriously ill patient with a gram-positive infection.

KEY RULE

The true incidence of community-acquired MRSA is difficult to ascertain, owing to different criteria used in different reports. Most community-onset MRSA infections are epidemiologically linked to traditional health care settings, and the overall incidence is still low.

Patients with community-acquired MRSA infections tend to be younger than those with nosocomial MRSA infections.

Risk factors for MRSA infections include hospitalization in the past year, residence in a long-term care facility, a recent surgical procedure, intravenous drug use, dialysis, an indwelling vascular catheter, and exposure to broad-spectrum antibiotics.

A 42-YEAR-OLD MAN suffered a laceration to his hand after sliding into third base during a softball game. Three days later, swelling, erythema, and a fluid collection developed on the palmar surface. He underwent operative debridement, and cultures revealed methicillin-resistant *Staphylococcus aureus*.

The patient did not work in a health care setting nor did any household member. He had not been prescribed an antibiotic in the past year. His last contact with the health care system was 2 years before, when he underwent an exploratory laparotomy for diverticulitis.

NO LONGER JUST IN HOSPITALS

S aureus, a ubiquitous and virulent pathogen, causes significant morbidity and mortality from a variety of infectious syndromes ranging from skin and soft-tissue infections to bloodstream infections and endocarditis.

Treating *S aureus* infections with antibiotics has become increasingly complex because the organism can develop resistance mechanisms that give it a selective advantage. Methicillin resistance was first demonstrated in *S aureus* shortly after the semisynthetic penicillins were introduced in 1960, and it had become widely recognized by the early 1980s.[1] Methicillin-resistant *S aureus* (MRSA) is now endemic in many institutions and is a leading cause of nosocomial infection. Now, MRSA infections are being reported outside the hospital as well.

This review discusses the phenomenon of community-associated MRSA infections and its implications for daily practice.

TABLE 1

Definitions of methicillin-resistant *Staphylococcus aureus* (MRSA)

Nosocomial MRSA: An MRSA infection:
Isolated after 48 hours of admission to the hospital, or
At time of admission if a resident of a long-term care facility, or
In a patient recently discharged from the hospital

Community-onset MRSA: An MRSA infection that began incubating outside of the health care setting

Community-acquired MRSA: An MRSA infection that began incubating outside of health care setting without health care risk factors*

*Risk factors for MRSA infection
Hospitalization in the past year
Residence in a long-term care facility
Surgical procedure
Intravenous drug use
Dialysis
Indwelling vascular catheter
Exposure to broad-spectrum antibiotics

REDEFINING 'COMMUNITY-ACQUIRED'

Prolonged nasal carriage of MRSA has been demonstrated

Infections that manifest within 72 hours of admission to the hospital have traditionally been designated "community-acquired," while those that develop after 72 hours in the hospital, in residents of long-term care facilities, or within 2 weeks of a hospital stay have been considered nosocomial.

But the trend in health care is for shorter hospital stays and greater use of ambulatory care centers, and patients are moving in and out of the hospital more frequently. These changes make it harder to apply traditional definitions to classify infections.

Various terms have been suggested to describe MRSA infections identified outside of a traditional health care setting, including "community-acquired," "community-onset," and "community-associated." To call an MRSA infection "community-acquired" may be arbitrary, given that prolonged nasal carriage of MRSA has been demonstrated.[2] Therefore, it can be problematic to determine whether an MRSA isolate is truly community-acquired and not hospital-acquired.

The difficulty in defining community-acquired MRSA infection is demonstrated by a meta-analysis in which Salgado et al[3] found that at least eight different definitions have been used in the literature.

In view of these vagaries, a clearer approach has been suggested in which MRSA infections are categorized as nosocomial or community-onset.[3,4] Patients with community-onset MRSA infections can then be further subdivided into those who have health care-associated risk factors (TABLE 1) and those who do not. Those without risk factors are, from an epidemiological perspective, perhaps the ones with true community-acquired MRSA infections.

This definition will probably undergo further revision as more studies are done. To that end, the Centers for Disease Control and Prevention (CDC)[5] has proposed that MRSA infections be considered community-acquired if all of the following criteria are met:

- The diagnosis of MRSA infection is made in the outpatient setting or by culture within 48 hours after admission to the hospital;
- The patient has no medical history of MRSA infection or colonization;
- The patient has not been admitted to a hospital, nursing home, skilled nursing facility, or hospice in the past year nor has undergone dialysis or surgery; and
- The patient has no permanent indwelling catheters or percutaneous medical devices.

In this paper, we use the term *community-onset* MRSA for any infection due to an isolate that began incubating outside the health care setting, regardless of risk factors. *Community-acquired* MRSA will be used to describe community isolates from patients without health care-associated risk factors (TABLE 1).

MOLECULAR BIOLOGY OF RESISTANCE

S aureus gains resistance to methicillin by acquiring and incorporating a genetic element called the staphylococcal cassette chromosome *mec*A (SCC*mec*A). The mecA determinant renders the organism resistant to all beta-lactam antibiotics by encoding for a penicillin-binding protein with a reduced affinity for beta-lactams.[6]

Nosocomial MRSA tends to possess one of three types of SCC*mec*A: I, II, or III. These elements are large, and genes in types II and III code not only for methicillin resistance but also for resistance to multiple non-beta-lactam antibiotics. Only rarely is this genetic material transferred from one strain to another, as only a handful of ancestral strains are responsible for clinical isolates worldwide.[7]

In contrast, community-acquired MRSA strains possess a novel cassette, SCC*mec*A IV. This particular genetic element is small and can be transferred horizontally.[8] Strains that harbor it are usually resistant to beta-lactams but are susceptible to clindamycin and fluoroquinolones.

The origin of SCC*mec*A IV is still being elucidated. Strains that harbor it may have evolved into their present forms in the hospital and subsequently found the community environment more favorable. Another possibility is that a hospital strain of MRSA underwent deletion of other genes in the less antibiotic-pressured environment of the community, the end result being a smaller, more transferable element.[9] Alternatively, this trait may have been selected for in a preexisting, susceptible, community strain in the face of antibiotic pressure.[10] Yet another possibility is that SCC*mec*A IV was transferred to a sensitive strain of *S aureus* from a coagulase-negative strain of *Staphylococcus*.[11]

Another characteristic of community-acquired MRSA is the presence of the Panton-Valentine leukocidin (PVL) gene, which encodes for a toxin that acts as a virulence factor and is thought to contribute to disease presentation.[9,12,13] The PVL gene is not as unique to community-acquired MRSA as SCC*mec*A type IV is, as it has been described in methicillin-sensitive community isolates. However, some researchers have consistently found this gene in many of the described isolates.[14]

EPIDEMIOLOGY

The medical community first became aware of the emergence of community-acquired MRSA in 1982, when an outbreak occurred among intravenous drug users in Detroit.[15] Multiple outbreaks have been reported since then[16–19]; the populations all share the characteristic of geographical, institutional, or physical proximity.

It is not clear if these outbreaks are unique to community-acquired MRSA strains or if there is a reporting bias such that outbreaks of methicillin-susceptible *S aureus* are not equally represented in the literature.

Younger patients

Of interest is that community-acquired MRSA infections appear to be more common in younger patients. In a prospective cohort study by Naimi et al,[20] patients with community-associated MRSA infections were younger than health care-associated MRSA patients, with a median age of 23 years vs 68 years. Even after two pediatric hospitals were excluded from the study, the median age of community-onset MRSA patients was 30 years vs 70 years for health care-associated MRSA patients.[20]

Risk factors identified

Several studies examined the risk factors for community-onset MRSA. Salgado et al,[3] in their meta-analysis, found the risk factors for community MRSA to be recent hospitalization, a recent outpatient visit, recent nursing home admission, recent antibiotic exposure, chronic illness, injection drug use, and close contact with a person with risk factors for MRSA acquisition.[3] Johnson et al[21] found community-onset MRSA bacteremia to be associated with multiple hospital admissions and residence in a long-term care facility. Jernigan et al[22] found the history of an admission to a hospital or a nursing home and underlying chronic illness to be associated with colonization with MRSA among patients in an ambulatory setting.

The PVL gene may make MRSA more virulent

These and other studies highlight the increasingly recognized association between institutional health care, methicillin resistance, and the community.

Incidence is hard to determine, but it is low

Several investigators have sought to determine the incidence or prevalence of community-acquired MRSA (**TABLE 2**).[3,10,22–24] Comparing one study with another is difficult, owing to different health care risk factors and different

TABLE 2

Prevalence of community-acquired MRSA in selected studies

INVESTIGATORS	SETTING	HEALTH CARE RISKS?*	PREVALENCE
Salgado et al[3]	Meta-analysis	Yes	1.3%
Charlebois et al[10]	Community-based high-risk population	No	6.1%
Jernigan et al[22]	10 hospitals in Minnesota	No	1.4%–6.2% of isolates
Naimi et al[23]	Metropolitan children's hospital	No	0.259% of admissions
Herold et al[24]	Chicago metropolitan area	No	0.017% incidence

*The absence of health care risk factors implies community-acquired MRSA as defined in the text.

patient settings. In general, however, the overall prevalence of community-onset MRSA is low, and the prevalence of true community-acquired MRSA is even lower.

For instance, in a population-based study of community-onset *S aureus* bacteremia, Morin and Hadler[25] found that all patients with MRSA had identifiable health care risk factors.

In the meta-analysis by Salgado et al,[3] the prevalence of community-acquired MRSA was as low as 0.2%.

S aureus that is resistant to erythromycin may also be resistant to clindamycin

In the prospective cohort study by Naimi et al,[20] in which strict inclusion criteria were used per the CDC definition, only 12% of patients were found to have had true community-acquired MRSA infections.

Molecular techniques show promise

Studies that combine traditional epidemiology with molecular techniques show promise in truly elucidating the current burden of disease. Two bear mention here.

Charlebois et al[10] reviewed community MRSA isolates from patients in their health care network. They performed pulsed-field gel electrophoresis, multiplex polymerase chain reaction (PCR) for SCC*mec*A type, and multilocus sequence typing on all isolates. They found that most MRSA strains in the community were traceable to a hospital or long-term care setting. However, almost all true community-acquired MRSA strains, while genetically diverse, carried SCC*mec*A type IV.

Vandenesch et al[14] examined community MRSA strains from multiple countries. Patients with ties to hospitals or nursing homes were excluded, and thus the cases included can be considered community-acquired MRSA. Molecular testing included PCR for both SCC*mec*A type IV and the PVL gene. All of the isolates contained the SCC*mec*A type IV.

These two studies suggest that the absence of health care-associated risk factors and the presence of SCC*mec*A type IV may best define community-acquired MRSA. This definition may not be valid over the long term, however, as these strains are being identified in hospitalized patients.[26,27]

ANTIMICROBIAL SUSCEPTIBILITY

By definition, MRSA is not susceptible to beta-lactam antibiotics and cephalosporins.

Although nosocomial strains of MRSA tend to be resistant to multiple antibiotics, community-acquired MRSA tends to be susceptible to clindamycin, the fluoroquinolones, trimethoprim-sulfamethoxazole, and the aminoglycosides. In fact, this unique susceptibility pattern has been one tool to help recognize community strains.

Naimi et al[23] found that 93% of the 348 community-acquired MRSA strains in their series in Minnesota were susceptible to clindamycin.

Similarly, Herold et al[24] found that 76% of MRSA isolates from children at their institution between 1993 and 1995 were susceptible to clindamycin. Only 6 of 25 isolates were not susceptible to two or more antibiotics.

In contrast, only 38% of nosocomial MRSA isolates identified in the past calendar year at The Cleveland Clinic Foundation were susceptible to clindamycin (G. Hall, personal communication).

Caution should be used in interpreting clindamycin susceptibility in patients whose *S aureus* strain is resistant to erythromycin. If the mechanism of erythromycin resistance is an inducible macrolide-lincosamide-streptogramin (MLS) resistance, then cross-resistance to clindamycin (a lincosamide) may also be present. MLS resistance is a manifestation of the activity of a ribosomal methylase. To identify MLS resistance, an erythromycin induction test (a D test) must be done. This entails placing two disks, one impregnated with clindamycin and the other with erythromycin, 15 to 20 mm apart on a standardized suspension of *S aureus*. If there is a D-shaped distortion of the zone of inhibition on the erythromycin side of the clindamycin disk, inducible MLS resistance exists. In one report, 50% of MRSA isolates that were erythromycin-resistant and clindamycin-susceptible were found to have inducible clindamycin resistance.[28]

Most authorities would also be wary of treating significant *S aureus* infection with fluoroquinolones, in view of reports of clinical failure of ciprofloxacin for methicillin-susceptible *S aureus*. Whether this class of antibiotic could be useful in the treatment of fluoroquinolone-sensitive community-acquired strains of MRSA remains to be determined.

CLINICAL MANIFESTATIONS

In general, community-acquired MRSA causes a spectrum of disease similar to that of community strains of methicillin-susceptible *S aureus*. Skin and soft-tissue infections are the most frequent manifestations and are the presentation in approximately 80% of cases.[19,20,23,24]

However, severe disease has also been described, presenting as deep soft-tissue infections with shock and as necrotizing pneumonia. The MRSA isolates responsible for these deep tissue infections all had SCC*mec*A type IV, and some had the PVL gene as well.[9,29]

IMPLICATIONS FOR CLINICIANS

The emergence of MRSA in the community has multiple implications for clinicians.

- A thorough history remains invaluable in selecting antibiotic therapy. Available epidemiologic data demonstrate that most patients at risk for community-onset MRSA have discernible clinical risk factors (TABLE 1).
- MRSA is causing a small but increasing number of true community-acquired infections. Some patients have presented with very severe manifestations. Establishing a microbiological diagnosis becomes even more important when usual antimicrobial prescribing habits are confronted by such rising rates of resistance.
- Although beta-lactams are appropriate for most community-onset skin and soft-tissue infections, they may not be effective in all cases (see below). Careful source control in the form of drainage or debridement of a suppurative focus and timely follow-up are necessary.

Antibiotic selection

Antibiotic selection is also influenced by this changing epidemiology.

A thorough history remains invaluable in selecting antibiotic therapy

Empiric vancomycin therapy should be considered for a patient who presents severely ill with a syndrome that could be caused by *S aureus*. Therapy can subsequently be tailored once the culture and sensitivity results come back from the laboratory.

The options for multidrug-resistant MRSA remain limited. However, **clindamycin** and **trimethoprim-sulfamethoxazole** remain options for community-acquired MRSA in the appropriate clinical situation.[30] For example, an isolated skin or soft-tissue infection in an otherwise healthy patient found to be due to a strain of *S aureus* with the community-acquired MRSA phenotype could be treated in this fashion. As mentioned above, careful follow-up is important for these infections. Serious beta-lactam-resistant infections are usually treated with **intravenous vancomycin**.

Newer agents for the treatment of beta-lactam-resistant, gram-positive infections have been developed.

Linezolid, an oral agent from the oxazo-

lidinone class, is effective in treating MRSA infections. However, it is expensive and has the potential for toxicity (thrombocytopenia, anemia, and peripheral neuropathy) with prolonged use, which limits its use.[31]

Daptomycin, a cyclic lipopeptide, has recently been approved for treating gram-positive skin and soft-tissue infections. However, it is also expensive and must be given intravenously, limiting its use in outpatients.[32]

Quinupristin-dalfopristin, another intravenous agent, is an option for MRSA, although toxicity and expense are of concern with this antibiotic as well.[31]

SUMMARY

As the daily practice of medicine continues to change, our understanding of health care-associated infections also must change. The emergence of resistant pathogens such as MRSA among ambulatory patients is forcing us away from the traditional distinctions between nosocomial and community infections. Ambiguity still exists regarding the definition of community-acquired MRSA, and this makes it difficult to define its prevalence.

While we await further epidemiological and microbiological study of this emerging pathogen, current clinical practice requires a reconsideration of the empiric use of beta-lactam agents for the seriously ill patient with a gram-positive infection.

Despite these developments, an appropriate history and physical examination remain the best tools for the busy clinician in the approach to infectious syndromes.

The distinction between nosocomial and community-acquired infections is blurring

CASE REVISITED

The patient recovered from his surgery and received 4 weeks of therapy with vancomycin. He did not suffer any long-term sequelae from this.

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