Why is community-associated MRSA spreading across the world and how will it change clinical practice?

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ABSTRACT

Meticillin-resistant Staphylococcus aureus (MRSA) emerged in 1960 and over the following 40 years was a problem confined largely to the healthcare setting. In the late 1990s the first US reports of so-called community-associated MRSA (CA-MRSA) infections appeared. CA-MRSA infections were defined as occurring in patients who had no identifiable predisposing risk factors, such as healthy children and young adults. CA-MRSA is associated with a novel genetic profile and phenotype; it is remarkably fit and capable of spreading within communities, it is virulent and is often susceptible to multiple narrow-spectrum antimicrobials other than β-lactams. CA-MRSA infections involve predominantly skin and soft tissue; however, necrotizing pneumonia and necrotizing fasciitis have been described. At present, several reports suggest that CA-MRSA may be replacing the hospital-acquired MRSA strains (HA-MRSA), with potentially catastrophic consequences. Given the rapid spread and the high virulence of CA-MRSA, global strategies are needed. Prompt, appropriate treatment, guided by the site and type of infection and risk factors for HA-MRSA or CA-MRSA, increases the chances of a successful outcome and is urgently needed.

1. Introduction

Meticillin-resistant Staphylococcus aureus (MRSA) was discovered in 1960, within a year of the introduction of semi-synthetic anti-staphylococcal penicillins. Over the following 40 years MRSA was a problem confined largely to hospitalized patients and to occasional outpatients who had readily identifiable predisposing risk factors, such as recent hospitalization, presence of an invasive device, history of surgery, haemodialysis or residence in a nursing home [1,2]. Traditionally, an infection is defined as hospital-acquired if it occurs more than 48 h after admission to the hospital, whereas it is community-acquired if it occurs within 48 h of admission. Therefore, the term community-onset MRSA (CO-MRSA) referred to an infection diagnosed in the community or to an infection with an index culture collected in the community, in patients with established risk factors for healthcare-associated MRSA. Thus, until recently, all MRSA infections were associated with a well-defined setting and well-defined risk factors. In the late 1990s, however, the first reports of so-called community-associated MRSA (CA-MRSA) infections appeared from the USA, and were defined as occurring in patients who had no identifiable predisposing risk factors for MRSA [3,4]. Subsequent studies confirmed that CA-MRSA infections occur commonly in otherwise healthy children and young adults.

Genetic and microbiological studies have revealed that CA-MRSA is associated with a novel genetic profile and phenotype that distinguish it from hospital-acquired MRSA (HA-MRSA). Unlike HA-MRSA, CA-MRSA is remarkably fit and able to spread within communities; it is virulent and often susceptible to multiple narrow-spectrum antimicrobial agents. CA-MRSA has emerged very rapidly since it first appeared in the late 1990s, having been reported in virtually every geographic region of the world [5].

CA-MRSA is probably the most important challenge to routine practice in infectious disease management in internal and emergency medicine to have emerged over the last decade.
2. Resistance and epidemiology of *Staphylococcus aureus*

The epidemiology of MRSA and the factors driving resistance bear strong similarities and parallels to those occurring with penicillin-resistant strains of *S. aureus* in the 1940s. The first penicillinase-producing strains were described in 1944 by Kirby et al. [6]. These penicillin-resistant strains were isolated from hospitalized patients [7]. In the same period, community strains remained susceptible to penicillin. Approximately 6 years from the introduction of penicillin, the resistance rate among hospital isolates was 25% and, similar to the present situation, previous treatment with a β-lactam antibiotic was considered a risk factor for promoting resistance [7].

Although penicillinase-producing strains were universally present in hospitals in the early 1950s, community isolates were largely penicillin-susceptible. Penicillin continued to be recommended as an active anti-staphylococcal agent as late as the early 1970s [8]. During this period, no systematic surveillance of antibiotic resistance among *S. aureus* isolates circulating within communities was performed. The first description of resistance among community-acquired *S. aureus* was performed in 1969 by Jessen et al. [9]. This study confirmed the high prevalence of penicillin resistance (85–90%) among hospital isolates of *S. aureus*, but also underlined the unexpectedly high prevalence of penicillin-resistant strains in community isolates (65–70%). Moreover, the community-acquired isolates were often resistant only to penicillin, whereas hospital-acquired strains were resistant to multiple antibacterials. Many studies confirmed these data and showed the worldwide spread of this phenomenon [10–12]. The increase in resistance among community isolates was observed soon after nosocomial rates exceeded 40–50%, and by the 1970s the rates of penicillin resistance among hospital- and community-acquired strains were practically equal (Table 1) [13].

A similar situation is now being observed with meticillin resistance rates. In the past two decades, the prevalence of MRSA strains has rapidly increased in hospitals. National Nosocomial Infections Surveillance (NNIS) data collected by the US Centers for Disease Control (CDC) in the early to mid 1980s suggested that MRSA infections were limited to large, urban medical centres (with more than 200 beds), with a prevalence of 5–10%. By the 1990s, MRSA prevalence rates among both large and small hospitals had increased to 40% and 20%, respectively [14]. More recent data from NNIS indicate that rates have continued to rise, and the prevalence of MRSA isolates from intensive care units was approaching 50% by the end of the 1990s. Between 2001 and 2004, the prevalence of MRSA among patients with skin and soft tissue infections (SSTI) in the emergency department of a Los Angeles hospital increased from 29 to 64% [15].

The SENTRY Antimicrobial Surveillance Program has monitored the aetiology of SSTIs since 1997, and all the data collected from three continents during a 7 year period were reported in the study of Moet et al. [16]. The predominant pathogens were, respectively, *S. aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Enterococcus* spp, *S. aureus* being the most common pathogen in all geographic regions. The incidence of meticillin resistance among *S. aureus* was highest in North America (35.9%), followed by Latin America (29.4%) and Europe (22.8%). However, the MRSA rate varied considerably among European countries, ranging from 0.8 to 50% [16]. Moreover, MRSA rates remained unchanged in Europe, whereas they increased in North and Latin America, as shown in Fig. 1 [16]. Considering the resistance pattern in Europe, a report of the European Antimicrobial Resistance Surveillance System (EARSS) depicted a dramatic situation in 2007, with MRSA accounting for 25–50% of invasive infections in Italy, France, Spain, Portugal, the UK, Ireland, Croatia, Greece, Hungary, Turkey, Bulgaria and Israel [17]. Additionally, a study by Gregory et al. published in 2006, which evaluated the prevalence of MRSA in SSTIs in an emergency department, found that *S. aureus* was isolated from 76% of patients with SSTI and the prevalence of MRSA was 59% (range 15–74%) [18]. Importantly, CA-MRSA was the most prevalent strain [18].

All of these data suggest that meticillin-resistant *S. aureus* is an important pathogen, the prevalence of which is continuously rising worldwide. Reports of infection and colonisation by MRSA provide compelling evidence that MRSA strains, like penicillinase-producing strains almost 30 years ago, have gained a foothold in the community and are emerging as an important outpatient pathogen. Based on the experience with penicillin-resistant strains, the prevalence of MRSA among community isolates may be as high as 25% within the next 5–10 years (Table 1) [14].

![Fig. 1. The percent incidence rate of meticillin-resistant Staphylococcus aureus among pathogens causing skin and soft tissue infections worldwide during the years 1998–2004. Data from the SENTRY Antimicrobial Surveillance Program [16].](image)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year introduced</th>
<th>Years to first report of resistance</th>
<th>Years to 25% resistance rate in hospital</th>
<th>Years to 25% resistance rate in community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1941</td>
<td>1–2</td>
<td>6</td>
<td>15–20</td>
</tr>
<tr>
<td>Meticillin</td>
<td>1961</td>
<td>&lt;1</td>
<td>25–30</td>
<td>40–50 (projected)</td>
</tr>
</tbody>
</table>

Table 1. Emergence of resistance in *Staphylococcus aureus* (adapted from Chambers [14])
3. Community-associated MRSA

In the late 1990s a new strain of MRSA emerged in the community that caused infections in young adults and healthy individuals who had no exposure to healthcare settings and no classical risk factors [19]. Since then, CA-MRSA strains have spread rapidly throughout the world [20] and outbreaks of CA-MRSA have been reported among children, athletes, prisoners, military trainers and men who have sex with men [21–23]. Between 1997 and 1999 four paediatric deaths related to CA-MRSA were described in Minnesota and North Dakota, USA [4].

Since 1998 many studies have been performed to investigate the clinical and microbiological features of CA-MRSA strains. Patients with CA-MRSA are usually younger than those with HA-MRSA (median age 30 vs. 70 years; P < 0.01) and CA-MRSA infections are more likely to involve the skin and soft tissue [24]. CA-MRSA isolates are generally more susceptible to antibiotics than HA-MRSA. While HA-MRSA tends to be multi-resistant, CA-MRSA is usually susceptible to narrow-spectrum non-β-lactams such as fluoroquinolones, clindamycin, trimethoprim–sulfamethoxazole (TMP–SMX) and tetracyclines.

Resistance to meticillin, and in consequence to β-lactam antibiotics, is mediated by the mecA gene, which codes for the penicillin-binding protein 2A. The mecA gene is located on a genetic island called the staphylococcal cassette chromosome mec (SCCmec), differences in which are used to categorise MRSA. HA-MRSA strains carry SCCmec types I–III, whereas CA-MRSA strains carry SCCmec IV and the more recently isolated SCCmec V. Another distinguishing genetic feature of CA-MRSA is that a high percentage of strains carry the gene for Panton-Valentine leukocidin (PVL), an exotoxin that is lethal to leukocytes. PVL is able to cause tissue necrosis and destruction of leukocytes by forming pores in the cellular membrane. The PVL locus is considered to be a stable genetic marker of CA-MRSA strains that explains the high frequency of primary skin lesions and the occurrence of necrotizing pneumonia and necrotizing fasciitis [25–29]. The clinical and genetic differences between CA-MRSA and HA-MRSA are outlined in Tables 2 and 3.

No clear risk factors have been linked to CA-MRSA [22,30]. Outbreaks have been reported among members of cultural minorities [31], persons who have close contact, especially if there is skin trauma (e.g. athletes) [32], and people living in closed communities (e.g. maternity wards, military establishments, day-care facilities and prisons) [15,33]. MRSA is normally transmitted from person to person by hand or other skin contact, sharing contaminated items (e.g. razors, athletic equipment, soap or towels) or via contaminated surfaces.

CA-MRSA infections can present as simple lesions (pimples or boils) and may mistakenly be identified as spider bites [24,34]. However, cases of fatal necrotizing pneumonia have also been described linked to CA-MRSA [35]. CA-MRSA strains are usually considered to be more virulent than HA-MRSA, leading to an important problem in terms of morbidity and mortality if they reach the hospital population. The circulation of CA-MRSA strains in hospitals has been already described and several reports suggest that CA-MRSA may be replacing HA-MRSA strains, with potentially catastrophic consequences [36–38]. A recent mathematical model developed by D’Agata et al. suggested that the prevalence of CA-MRSA would continue to increase over time and would surpass that of HA-MRSA [39]. However, this phenomenon requires that a large number of patients with CA-MRSA be admitted to hospital for them to act as a reservoir of this pathogen and provide a continuous source of transmission [39]. If this were to happen, CA-MRSA could become dominant among hospital S. aureus strains by competitive exclusion, or near exclusion, of traditional HA-MRSA strains. The replacement of the traditional HA-MRSA strains by CA-MRSA is further supported by the unique bacterial characteristics of CA-MRSA, including a rapid growth rate, which provide it with a competitive advantage over HA-MRSA [40].

4. Treatment

The resistance of a S. aureus strain to meticillin means that no β-lactam antibiotics are effective in treating infections caused by that strain. As first-generation cephalosporins and anti-staphylococcal penicillins have long been the first-choice agents for treating SSTIs, it is not surprising that ineffective empiric antibiotic therapy of these infections has been documented in numerous recent studies. TMP–SMX and doxycycline are commonly recommended for treating CA-MRSA SSTIs in adults; however, it should be recognised that large outcome studies documenting their safety and efficacy in this condition are lacking. Although clindamycin is a good choice for many types of CA-MRSA infection, the possibility of inducible resistance to clindamycin must be recognised. Isolates initially reported as susceptible to

Table 2. Differences between CA-MRSA and HA-MRSA, particularly when age and site of infection are considered (adapted from Naimi et al. [24])

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>23</td>
<td>68</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Skin</td>
<td>98</td>
<td>343</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>8</td>
<td>205</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Blood</td>
<td>5</td>
<td>83</td>
<td>NS</td>
</tr>
<tr>
<td>Urine</td>
<td>1</td>
<td>185</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>110</td>
<td>NS</td>
</tr>
</tbody>
</table>

CA-MRSA, community-acquired meticillin-resistant Staphylococcus aureus; HA-MRSA, hospital-acquired meticillin-resistant Staphylococcus aureus; NS, non-significant.

Table 3. Clinical and genetic differences between CA-MRSA and HA-MRSA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HA-MRSA</th>
<th>CA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare onset of infection</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mean age at infection</td>
<td>Older</td>
<td>Younger</td>
</tr>
<tr>
<td>Prevalence of SSTIs among other infections</td>
<td>35%</td>
<td>75%</td>
</tr>
<tr>
<td>Antibiotic resistance</td>
<td>Many agents</td>
<td>Some agents</td>
</tr>
<tr>
<td>Resistance gene</td>
<td>SCCmec Types I, II, III</td>
<td>SCCmec Type IV, V</td>
</tr>
<tr>
<td>Main strain type</td>
<td>USA100 and 200</td>
<td>USA300 and 400</td>
</tr>
<tr>
<td>PVL producer</td>
<td>Rare (5%)</td>
<td>Frequent (almost 100%)</td>
</tr>
</tbody>
</table>

CA-MRSA, community-acquired meticillin-resistant Staphylococcus aureus; HA-MRSA, hospital-acquired meticillin-resistant Staphylococcus aureus; SSTI, skin and soft tissue infection; SCCmec, staphylococcal cassette chromosome mec; PVL, Panton-Valentine leukocidin.
clindamycin (but resistant to erythromycin) may develop clindamycin resistance within days of starting treatment. Inducible resistance is a fairly uncommon problem; however, treatment failures attributable to this mechanism have been reported [41].

Practical guidelines for the treatment of CA-MRSA SSTIs have been published [42]. Nevertheless, the recommendations remain vague, reflecting a lack of quality prospective data. Four antibiotics are currently approved by the US Food and Drug Administration for the treatment of complicated SSTIs caused by MRSA: vancomycin, linezolid, daptomycin and tigecycline [43]. All the agents effective against CA-MRSA are listed in Table 4.

The choice of antibiotic and the route of administration should be governed by the severity of the infection. For adult and adolescent outpatients following abscess incision and drainage, where the only issue is possible surrounding cellulitis, TMP-SMX or doxycycline are good choices. Linezolid is another option for outpatient oral therapy. Seven days of therapy is usually adequate for abscesses that have been drained, although 10–14 days of treatment are generally recommended for cellulitis.

Patients with severe or complicated SSTIs requiring hospitalization should receive intravenous antibiotic therapy. Vancomycin was for many years the first-line therapy for MRSA infections because of its relative safety, its low incidence of acquired resistance and, until recently, the lack of approved alternatives for the treatment of MRSA. However, vancomycin is being increasingly linked to clinical failures, possibly caused by under-dosing, poor tissue penetration, loss of accessory gene regulator function in the organism, slow bactericidal effect and, not least, an increase in vancomycin minimum inhibitory concentrations (MICs) [44].

A newer agent with activity against Gram-positive organisms, linezolid, is the second most studied antibiotic for MRSA infections. Linezolid is approved for severe SSTIs in adults and offers a good first choice for empiric therapy in communities with a high rate of inducible clindamycin resistance among CA-MRSA. Linezolid has a 100% bioavailable oral formulation and has been associated with a shorter length of stay and a shorter duration of intravenous treatment than vancomycin [45].

Daptomycin, a cyclic lipopeptide, is a potent bactericidal agent that has no cross-resistance with other glycopeptides. Although it is available in intravenous form only, daptomycin may be administered as an outpatient regime thanks to its once daily or alternate daily dosing.

Tigecycline, approved in 2005, is the first agent of the glycyclcline class. It is effective against numerous pathogens, including resistant Gram-positive and Gram-negative bacteria. In skin structure infections caused by MRSA, cure rates were similar for tigecycline and vancomycin (86.4% vs. 86.9% in microbiologically evaluable populations and 78.6% vs. 87.0% in microbiologically modified intent-to-treat populations, respectively) [46].

5. Conclusions

Prompt and appropriate treatment of complicated SSTIs caused by MRSA increases the chances of a successful outcome. The choice of antimicrobial agent for empirical treatment of an SSI should be guided by a number of considerations, including the site and type of infection and the risk factors for HA-MRSA or CA-MRSA infection.

CA-MRSA infections are susceptible to more antibiotics than HA-MRSA infections, which are commonly multi-drug resistant. Most CA-MRSA strains remain susceptible to ciprofloxacin, clindamycin, gentamicin and TMP-SMX, although resistance to clindamycin can emerge during treatment and there are no robust data from large trials on their efficacy. Among the currently available agents, vancomycin has been the gold standard, but increasing clinical failures have been reported, possibly due to poor tissue penetration and increasing MIC values. Alternative agents active against CA-MRSA include linezolid, daptomycin and tigecycline, all of which have been well studied and are approved for the treatment of SSTIs.

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References


Table 4. Treatment options for meticillin-resistant Staphylococcus aureus available in the European Union in January 2009

<table>
<thead>
<tr>
<th>Antibacterial</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>Oral / IV</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Oral / IV</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Oral / IV</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Oral</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Oral / IV</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>IV</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>IV / IM</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>IV</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>IV</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>IV</td>
</tr>
</tbody>
</table>

IV, intravenous; IM, intramuscular.


