Community-associated methicillin-resistant Staphylococcus aureus infections

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Community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) has been recognized for over a decade, and usually refers to MRSA identified in previously healthy individuals with no recognized MRSA risk factors. Infections range from minor skin and soft tissue infections, through to severe pneumonia and necrotizing fasciitis. This review summarizes the current data on the epidemiology and molecular features of CA-MRSA, in addition to diagnosis and therapeutic measures. We also refer to current national guidelines for the management of these infections. Areas of agreement include the important genotypic and phenotypic differences of community MRSA strains compared with hospital strains. Areas of controversy include the precise epidemiological definition of community-acquired/associated MRSA. Fortunately, true CA-MRSA can be differentiated from hospital MRSA by molecular techniques, as discussed herein. Recent interest has focused on the changing epidemiology of CA-MRSA. Worldwide, CA-MRSA is now seen outside of the initial specific population groups, and in the USA, the successful USA300 community strain is beginning to spread back into hospitals. Reasons why USA300 remains relatively uncommon in Europe are unclear. Topics timely for research include the investigation of the epidemiology of infections and evolutionary genomics.

Keywords: community/MRSA/methicillin resistance/Staphylococcus aureus/skin and soft tissue infections/necrotizing pneumonia, review/staphylococcus chromosomal cassette/genomics

Introduction

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Community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) was first recognized in the mid-1990s.1 The term was originally defined epidemiologically, and referred to strains of MRSA seen in patients presenting with infections in the community or presenting to hospital departments for the first time. Thus patients who had previously been admitted to hospital, or who were receiving prolonged antibiotic treatment, or who were resident in a care-home or healthcare
facility, or had regular contact with hospitals (e.g. dialysis patients)/
healthcare workers were excluded. Indeed, some authors choose to
distinguish between hospital-acquired MRSA, healthcare-associated
MRSA and CA-MRSA, which is often helpful. The US Centre for
Disease Control and Prevention has published criteria to distinguish
CA-MRSA from healthcare-associated MRSA, and tight definitions of
various subgroups of CA-MRSA have been proposed.

The initial reports of CA-MRSA infection tended to come from
specific patient groups, such as military recruits, sports teams and indi-
viduals living in close communities or involved in activities resulting in
skin abrasions. Some of the first countries to report community strains
were Australia, New Zealand, USA, UK, France, Finland and Canada.
However, in 1997, there were reports of four fatal cases in children
from Minnesota and ND, USA, who did not fall into any recognized
risk groups. It also transpired that CA-MRSA strains were somehow
different from hospital strains, not just in terms of the epidemiology
and nature of infection, but also at a molecular level. The distinct
characteristics of CA-MRSA when compared with hospital MRSA, in
terms of clinical presentation, antibiotic susceptibility and molecular
characteristics including the expression of virulence factors such as the
Panton-Valentine leukocidin (PVL) toxin, are summarized in Table 1
and will also be discussed below.

Epidemiology of CA-MRSA

The epidemiology of CA-MRSA is changing. Initial clusters occurred in
sports participants, the military and prisoners, and there were out-
breaks amongst children and adults living in close communities. Other
high-risk groups were identified including men who have sex with
men, the district nurse population, injecting drug users and the
homeless. Of concern, CA-MRSA is now increasingly recognized
outside these patient groups, and the epidemiologic characteristics of
patients with CA-MRSA infections are becoming more similar to
patients with community-associated methicillin-susceptible S. aureus
(MSSA) infections. In addition, several studies have suggested that
CA-MRSA strains may be encroaching on nosocomial settings, and are
causing infections with onset >72 h after admission to hospital.

Of concern, a deterministic mathematical model has predicted that, in
the USA, CA-MRSA will become the dominant MRSA strain in hospi-
tals and healthcare facilities, as a result of the expanding community
reservoir of CA-MRSA and increasing admission to hospital of individ-
uals with CA-MRSA. The model also predicts that increased severity
of CA-MRSA (particularly PVL-positive strains) will lead to increased
length of hospital stay and a larger nosocomial reservoir of CA-MRSA. This will undoubtedly make control of MRSA infections in hospitals an increasing challenge.

In the USA, two clones of CA-MRSA (USA300 and USA400) have caused particularly aggressive infections over a wide geographical area.\(^\text{16}\) These both harbour the PVL toxin genes (see below). A study in 2006 found that MRSA was the most commonly identifiable cause of the acute skin and soft tissue infections in adults presenting to university-affiliated emergency departments in the USA, and USA300 accounted for 97% of all MRSA isolates.\(^\text{17}\) The origins and epidemiology of USA300 have been comprehensively reviewed.\(^\text{18}\) These American clones are not yet common in the UK or elsewhere in Europe, reasons for which are unclear.\(^\text{19}\)

### Table 1 Hospital versus community-associated MRSA.

<table>
<thead>
<tr>
<th></th>
<th>Hospital MRSA</th>
<th>Community MRSA</th>
</tr>
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<tbody>
<tr>
<td>Typical patients</td>
<td>Elderly patients, often debilitated Patients with chronic disease, e.g. diabetic skin ulcers</td>
<td>Previously healthy people, often younger Those involved in close contact activities, e.g. sports teams or military service, especially those resulting in skin abrasions</td>
</tr>
<tr>
<td>Clinical infections</td>
<td>Intensive care unit patients Renal patients with indwelling lines Device associated</td>
<td>Tend to be more aggressive skin and soft tissue Necrotizing pneumonia</td>
</tr>
<tr>
<td></td>
<td>Wound infections Respiratory and urinary tracts</td>
<td>Septic shock and bacteraemia in more severe cases</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Indwelling devices, lines, prolonged hospitalization, long-term antibiotics</td>
<td>Close physical contact, poor hygiene, shared sanitary facilities, crowded living conditions (e.g. military recruits, prisons)</td>
</tr>
<tr>
<td>Transmission</td>
<td>Nosocomial Little spread among household contacts</td>
<td>Predominately community acquired Spreads within families and sports teams</td>
</tr>
<tr>
<td>Antibiotic susceptibility</td>
<td>Typical UK clones (EMRSA 15 and 16) resistant to erythromycin, ciprofloxacin, with or without aminoglycosides, clindamycin, tetracycline, rifampicin, fusidic acid.</td>
<td>Generally more susceptible to non-beta-lactam agents, including ciprofloxacin</td>
</tr>
<tr>
<td>Molecular characteristics</td>
<td>(\text{SCCme}c) types I, II or III (except EMRSA-15 in the UK, which has (\text{SCCme}c) type IV)</td>
<td>Mainly (\text{SCCme}c) type IV or V</td>
</tr>
<tr>
<td></td>
<td>PVL less common</td>
<td>PVL more common</td>
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</table>

### Prevalence—how common are these strains?

The prevalence of nasal carriage of \(S.\ aureus\) in the community in the USA has been studied as part of the National Health and Nutrition...
Examination Survey. Nasal swabs were obtained from 9,622 individuals selected to be representative of the general US population for a variety of social and demographic characteristics. Overall, 0.8% (95% CI: 0.4–1.4%) were found to be colonized with MRSA. The carriage rate for any *S. aureus* was 32.4% (95% CI: 30.7–34.1%). Multivariate analysis showed that the carriage of MRSA was associated with age over 60 years and female gender, but was not associated with hospital contact, as defined as an overnight stay in the previous 12 months. The MRSA isolates were subject to further characterization. Two *Staphylococcus* chromosome cassette (SCCmec) types were identified (see below and Fig. 1), with approximately half of the isolates carrying SCCmec type II and half SCCmec type IV. The presence of SCCmec type varied with age of the individual. SCCmec type IV was associated with those in younger age groups, whereas the opposite was true for SCCmec type II. Strains carrying SCCmec type IV were less likely to be multiply antibiotic resistant, but were more likely to carry PVL or enterotoxin B genes. There were also some ethnic differences in carriage rates. These characteristics are typical of those described for CA-MRSA strains. However, the overall prevalence of PVL genes was very low [6 of 75 (8%) MRSA strains and 9 of 372 (2.4%) total *S. aureus* strains tested]. Also, pulsed-field gel electrophoresis (PFGE) showed that only 6 of the 75 (8%) MRSA isolates belonged to the MRSA300 lineage and therefore the carriage of specific clonal types associated with severe infection in reported outbreaks was low. This suggests that, at the time of this survey in 2001–2002, these virulent CA-MRSA strains were restricted to localized groups of younger individuals in specific social settings (sports teams, military recruits, prisons, etc.) and were not widely prevalent in the general population.

**Fig. 1** Comparison of the SCCmec typical of hospital and CA-MRSA. The legend helps explain why SCCmecII (A) encodes resistance to multiple antibiotics, whereas SCCmecIV encodes resistance to methicillin alone. Adapted from *Nat Rev Microbiol* 2009; 7:629–412. Orf X (open reading frame): SCCmec cassettes integrate into the integration site sequence (ISS), which is located at the 3’ end of orfX ccr: The Cassette chromosome recombinase (ccr) gene complex is composed of one or two site-specific recombinase genes, (responsible for the mobility of SCCmec), and surrounding orfs of unknown function. Tn554: This transposon is present in SCCmecI but not SCCmecIV, and encodes resistance to the MLSβ (macrolide-lincosamide-streptogramin) antibiotics and spectinomycin. mec: This encodes methicillin resistance, and is full length in SCCmecII but truncated in SCCmecIV. IS431: insertion sequence 431 harbour an integrated plasmid pUb110 in SCCmecI, which encodes a tobramycin resistance gene. This plasmid is not present in SCCmecIV.
We are not aware of similar data for the general community population in the UK, although there are MRSA prevalence data for specific groups of, mainly elderly, people. A retrospective case–control study performed using the UK General Practice Research Database between 2000 and 2004 assessed the community acquisition of MRSA in a population who had no hospital admission in the previous 2 years.\textsuperscript{21} The average incidence of MRSA acquisition was 15.2 cases per 100 000 population per year, which over the period of the study gives a similar prevalence (0.7\%) to that seen in the USA. However, individuals <18 years were excluded from the study and therefore there is no information from an age group of particular interest in this setting. Also, cases were identified retrospectively from clinical coding information and therefore no MRSA isolates were available for laboratory characterization. Current estimates of prevalence of CA-MRSA in the UK general population lie between <0.1 and 1.5\%.\textsuperscript{22,23}

**Clinical presentation**

*Staphylococcus aureus* normally causes a spectrum of infections ranging from common, mild skin and soft tissue infections to severe haematogenous infection with multi-organ involvement. Outbreak reports of CA-MRSA infection in specific groups have suggested that these strains are more aggressive than has been seen previously with *S. aureus* outside hospital. Severe skin and soft tissue infections (perhaps starting with a ‘spider bite’ lesion), large and/or recurrent abscesses, necrotizing pneumonia or bone and joint infections have been typical. The presence of PVL and other toxin production is an important element to this, although it should be recognized that these toxins are not restricted to MRSA and are seen in MSSA too. However, these outbreak reports may not necessarily be representative of the spectrum of CA-MRSA infection seen more generally.

The prevalence, natural history and clinical impact of CA-MRSA colonization were assessed in a population of 812 US Army soldiers.\textsuperscript{24} Nasal swabs were taken on recruitment and 8–10 weeks later and the soldiers were observed prospectively for evidence of infection. CA-MRSA was defined as a strain with an antibiotic susceptibility profile and molecular PFGE profile different from the prevailing hospital MRSA strains in an individual with no contact with hospital or other risk factor for colonization with a hospital MRSA strain. At the time of recruitment, the CA-MRSA colonization rate was 3%. A further 28\% of soldiers were colonized with MSSA. Nine of the 24 (38\%) with CA-MRSA colonization developed skin and soft tissue infection, compared with only 8 of 229 (3\%) with MSSA and 12 of
559 (2%) soldiers not colonized with either. Eight of the 9 soldiers with CA-MRSA infection had a PVL-positive CA-MRSA strain.

From a study using a combination of population-based surveillance in Atlanta and Baltimore and laboratory-based surveillance in Minnesota, 1647 cases of CA-MRSA infection were identified. Again, cases were ascribed to the community if there were no established risk factors for hospital acquisition. The incidence of CA-MRSA infection was highest in children <2 years. Abscesses, cellulitis or other skin and soft tissue infections were most common (77% infections), whereas 6% infections were invasive (bacteraemia, meningitis, or bone and joint infection). Pneumonia was present in 2%. As an indicator of severity, 22% of the patients required hospital admission as a direct result of the infection.

The distribution of CA-MRSA infection is different from that seen with typical hospital MRSA strains. Naimi et al. (2003) compared the epidemiology of 131 CA-MRSA infections with 937 healthcare associated MRSA infections. The CA-MRSA infections occurred in a significantly younger age group (median 23 years versus 68 years) and were more likely to affect skin and soft tissue compared with hospital MRSA infections. They were less likely to affect the chest or urinary tract.

However, this situation is rapidly becoming more complex. Infection with hospital strains of MRSA occurring in patients in the community has been recognized for some time. Many of these patients have risk factors for these infections, which often include recent contact with hospital or other healthcare services. Hence, the designation of these as ‘healthcare-associated’ infections. Now, community strains of MRSA are appearing in hospitals. As part of ongoing surveillance of invasive MRSA infections in 9 US states, 100 MRSA isolates from both community and hospital settings were characterized using PFGE. Hospital-acquired MRSA strains were predominately USA100, but 28% were USA300, previously considered the archetypal community strain in the USA. As noted above, several nosocomial outbreaks of CA-MRSA have now been described worldwide and CA-MRSA strains are now an important cause of MRSA bacteramia in some US hospitals.

Molecular typing of MRSA

Of the multiple techniques that exist for molecular typing of S. aureus, the commonly used ones are toxin gene profiling, antimicrobial resistance typing, accessory gene regulator (agr) typing, PFGE, multilocus sequence typing (MLST), multilocus restriction fragment typing,
staphylococcal protein A gene typing (spa typing), amplified fragment length polymorphism analysis and genotyping (e.g. of the SCCmec element). MLST has proved particularly useful in elucidating the evolutionary origin of clones, and has demonstrated considerable global variation in predominant genetic background types among CA-MRSA strains. For example, most cases in the USA belong to clonal complex 8 (CC8), and are designated sequence type 8 (USA300:ST8) and ST1 (USA400:ST1). In Europe ST80 strains predominate whereas in Australia ST93 strains are common. Some continent-specific clones described in the early 2000s, such as clone ST8, have now spread all over the world. There are also specific clones circulating in certain populations, e.g. clone ST1-SCCmec type IV (see below), which has a broad range of bacteriophage and usually harbours genes for enterotoxins A and H (sea; seh) but does not encode the PVL toxin, is circulating amongst the IDU population in England and Wales. This is truly a dynamic process, with new clones constantly emerging (e.g. ST377) on new genetic backgrounds. For a more detailed description of the molecular epidemiology of the epidemic waves of CA-MRSA, see the review by Chambers and DeLeo.

Genetics of CA-MRSA

Methicillin resistance arises due to acquisition of the mecA gene encoding the altered penicillin-binding protein PBP2', which has reduced affinity for beta-lactam antibiotics. On the chromosome, mecA is situated within the Staphylococcal chromosome cassette (SCCmec). This mobile genetic element also contains regulatory genes, the insertion sequence IS431mec and cassette chromosome recombinase (ccr) genes, which carry out integration and excision of SCCmec (Fig. 1). Most strains of community MRSA harbour SCCmec types IV, V or VII, while most hospital MRSA harbours SCCmec types II and III, although one major exception is the dominant UK hospital-associated clone EMRSA-15, which harbours SCCmec type IV. SCCmec type IV is smaller than the other types, partly because it contains fewer antibiotic resistant determinants. The small size may enable horizontal transfer of SCCmec IV among a bacterial population. Subtyping of SCCmec is based on sequencing the region upstream of the ccr genes, known as L-C, and the epidemic USA300 and USA400 clones harbor SCCmec subtype IVa.

Whole genome sequencing of two isolates of CA-MRSA is available: MW2 (which caused fatal sepsis and septic arthritis in a 16-month-old girl in the USA in 1998), and FPR3757 (a multidrug resistant USA 300 strain) (www.genomesonline.org). Comparative
genomics with strains of MSSA and hospital-acquired MRSA has enabled exploration of possible mechanisms of evolution, and identified regions affecting virulence and drug resistance. For example, the MW2 chromosome contains a number of additional virulence genes compared with MSSA, mainly within horizontally acquired genomic islands. Comparison with community strain MSSA476, which caused severe invasive disease in an immunocompetent child in the UK,\(^{32}\) points towards the acquisition of SCC\(_{mec}\) IV by MSSA strains in the community as the main event in the emergence of community MRSA.\(^{33}\)

**PVL toxin and other virulence factors**

There are strong epidemiological associations between PVL and highly transmissible, virulent, strains of CA-MRSA and other \textit{S. aureus} and this is particularly true for cases of necrotizing pneumonia presenting from the community. However, overall, less than 2\% of all \textit{S. aureus} (MRSA and MSSA) submitted to the HPA reference laboratory harbour the genes encoding for PVL (http://www.hpa.org.uk). There has been some debate recently concerning its significance as a virulence factor in skin and soft tissue infections, and various alternative pathogenicity factors (e.g. arginine catabolism mobile element (ACME), \(\alpha\)-toxin, regulation of gene expression, newly described cytolytic peptides) have been proposed.

**Diagnosis**

In addition to clinical presentation and lack of traditional risk factors, an antibiogram demonstrating susceptibility to ciprofloxacin sparks initial suspicion of CA-MRSA in diagnostic laboratories. However, ciprofloxacin susceptibility cannot be used as a definitive marker, as work by the HPA staphylococcal reference unit has demonstrated that the sensitivity and specificity of this finding as a maker of CA-MRSA was 97 and 84\%, respectively (http://www.hpa.org.uk). The clinical and molecular epidemiology of PVL-encoding ciprofloxacin-susceptible MRSA in England and Wales has been recently summarized.\(^{34}\) Of interest, specific lineages of CA-MRSA (sequence types ST8 and ST80) can be ciprofloxacin resistant, and ST5 lineages tend to be ciprofloxacin susceptible, whether hospital or community acquired.

As could be predicted from the evolving molecular epidemiology of CA-MRSA, these strains have also been able to acquire a variety of antibiotic resistance determinants. CA-MRSA has been considered
generally to be more susceptible to various classes of antibiotic, apart from the beta-lactam agents, whereas hospital MRSA strains are often multiply resistant. This situation is rapidly becoming more varied. For example, a clone of USA300 has been described in the male homosexual population in San Francisco, which is characterized by carriage of a conjugative plasmid conferring multiple antibiotic resistance designated as pUSA03.\textsuperscript{7} Ellington \textit{et al.}\textsuperscript{35} have also recently described polyclonal multiple antibiotic resistance in strains of PVL-producing MRSA referred to the HPA staphylococcal reference unit, including the emergence in the UK of ST772, which often had links to India or Bangladesh (designated the Bengal Bay strain).

**Management/treatment**

UK guidelines for the management of MRSA infections presenting in the community have been published recently by the British Society for Antimicrobial Chemotherapy (BSAC).\textsuperscript{36} These complement recent guidance for management of PVL-associated \textit{S. aureus} infection from the Health Protection Agency (http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1218699411960) and BSAC guidelines for the prophylaxis and treatment of MRSA.\textsuperscript{37} A comprehensive review of the guidelines is outside the scope of this article, but a number of key principles are stated. Although CA-MRSA reports often stress the severity of infection in some individuals, most infections are mild skin and soft tissues infections and can be managed in the community in the same way as infections due to other \textit{S. aureus} strains. Mild infection and small abscesses (<5 cm) may not require systemic antibiotic therapy, but incision and drainage of abscesses is important. At present, CA-MRSA is uncommon in the UK, but it is important that clinicians are aware of factors that would make it more likely (Box 1). In such cases, appropriate samples should be taken for culture and for susceptibility testing to guide antimicrobial therapy. Where this is required, options for oral empirical treatment in the community include doxycycline (not in children), rifampicin, fusidic acid and trimethoprim (either alone or as co-trimoxazole). Rifampicin and fusidic acid cannot be given alone, but combinations of rifampicin with one of the other agents have been recommended.\textsuperscript{36} If susceptibility is confirmed, erythromycin, clarithromycin or clindamycin would be alternative options. It should be noted that tetracyclines and trimethoprim are not optimal choices for empirical treatment of Group A streptococcal infection and that cover for this organism should be considered initially (Table 2).
Box 1 Factors increasing likelihood of CA-MRSA, rather than hospital MRSA.

The presence of a ‘spider bite’-like red, painful papule with a black necrotic centre in a geographical location where spider bites are uncommon.
Severe skin and soft tissue infection (carbuncles, furuncles, other abscesses) in a young person.
Recurrent skin and soft tissue infection or clusters of infection in households or social groups.
Poor response to treatment with a beta-lactam antibiotic.
History of exposure to multiple courses of antibiotic in the recent past, especially quinolones or macrolides.
Severe pneumonia in a young person accompanied by haemoptysis and hypotension.
Recent travel to the USA or other area where CA-MRSA strains are more common.

Table 2 Antibiotic options for treatment of CA-MRSA.

<table>
<thead>
<tr>
<th>Oral</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical therapy</td>
<td></td>
</tr>
<tr>
<td>Doxycycline (not in children)</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Rifampicin*</td>
<td>Teicoplanin</td>
</tr>
<tr>
<td>Fusidic acid*</td>
<td>Daptomycin (not for pneumonia)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Definitive therapy, i.e. susceptibility is confirmed</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Combinations of above antibiotics with another agent, such as rifampicin, should be considered in critically ill patient.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
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*Rifampicin and fusidic acid cannot be given alone, but combinations of rifampicin with one of the other agents have been recommended.36

In the hospital setting, where intravenous therapy is required, vancomycin, teicoplanin, daptomycin (not for pneumonia) or linezolid are options. For severely ill patients, particularly those with necrotizing pneumonia, combinations of antibiotics have been proposed, usually including rifampicin. In addition, linezolid and high-dose clindamycin have proposed as a combination, because they suppress the production of PVL and other toxins. Clearly, in severe infections there are limited trial data to support the use of one regimen over another and recommendations are largely based on expert advice. In addition, the use
of adjunctive therapy, such as intravenous immunoglobulin, has been successful in some case reports, but its contribution is currently uncertain.

Summary

CA-MRSA has appeared, diversified and spread throughout different population groups in a relatively short period. This illustrates the dynamic and highly adaptable nature of the organism, and suggests that the epidemiology and molecular nature of this infection is likely to continue to evolve. While it remains relatively uncommon in the UK as compared with the USA, clinicians should be alert to potential risk factors of infection with community rather than hospital MRSA, as this can have significant prognostic and treatment implications.

References
