Review

Community-associated meticillin-resistant Staphylococcus aureus: the case for a genotypic definition

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SUMMARY

Background: New distinct strains of community-associated meticillin-resistant Staphylococcus aureus (CA-MRSA) have emerged as a cause of infection in previously healthy individuals in community settings. It is important to identify CA-MRSA for clinical management, epidemiological analysis, infection prevention and control, and regulatory reporting, but definitions and nomenclature of these strains are confused.

Aim: To review attempts to define CA-MRSA and propose a new definition.

Methods: Non-systematic review.

Findings: Epidemiological definitions were useful for differentiating CA-MRSA and healthcare-associated (HA)-MRSA strain types in the past. However, although HA-MRSA strain types are rarely transmitted in the community, CA-MRSA strains have started to be transmitted in healthcare facilities, so epidemiological definitions are breaking down. CA-MRSA are community strains of S. aureus that have acquired the meticillin resistance gene, mecA. They are distinct from HA-MRSA and should be defined genetically. This may be done by combining genotypic typing by multi-locus sequence or spa with analysis of the staphylococcal cassette chromosome mec. Carriage of Panton-Valentine leukocidin or antimicrobial susceptibility profiles can be useful indicators of CA-MRSA but should not be used for their definition.

Conclusion: For full assessment of their epidemiology, MRSA infections should be characterized as: (1) caused by HA- or CA-MRSA strain types; (2) acquired in community or healthcare settings; and (3) onset in the community or healthcare facility.

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Subsequent molecular analysis showed that these infections were being caused by new types of MRSA which appeared to be common community strains of meticillin-susceptible *S. aureus* that had acquired the mobile genetic element, the staphylococcal cassette chromosome mec (SCCmec) that encodes the meticillin resistance gene, mecA.6,7

There is considerable confusion in the literature regarding the definition and nomenclature of these new MRSA types.8,9 For example, they have been termed ‘community-associated’, ‘community-acquired’, ‘community-onset’, ‘community’, ‘true’ and ‘de-novo’ types of MRSA.8–10 The most common term used to describe these strains was initially ‘community-acquired MRSA’,3,4 but this has been widely replaced by ‘community-associated MRSA’ (CA-MRSA), reflecting uncertainty as to whether the MRSA was acquired in hospital or in the community.9,11–13 However, ‘CA-MRSA’ is poorly defined and used in different ways by different authors.8 This review will discuss the limitations of an epidemiological definition of CA-MRSA, and propose practical ways to define CA-MRSA by genotype.

**Definitions of CA-MRSA**

CA-MRSA were traditionally regarded as MRSA strains causing infection in previously healthy young patients without prior healthcare contact, susceptible to most non-β-lactam antimicrobial agents, and carrying Panton-Valentine leukocidin (PVL) genes and SCCmec types IV or V (Table I).2,4,14 However, as the microbiology and epidemiology of CA-MRSA have evolved, traditional definitions has broken down.8

<table>
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<tr>
<th>Clinical features</th>
<th>Microbiological features</th>
<th>Genetic features</th>
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<tbody>
<tr>
<td>Affected patients are less likely to have had healthcare contact11,61</td>
<td>Faster growth rate and competitive advantage with HA-MRSA <em>in vitro</em>67</td>
<td>Usually SCCmec IV or V2–7</td>
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<tr>
<td>Can affect healthy individuals of all ages14,36</td>
<td>Less frequent resistance to non-β-lactam antimicrobial classes4,14</td>
<td>Epidemiological association with PVL carriage4,14</td>
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<tr>
<td>Characterized by primary SSTIs occurring in patients with no initial skin wound, especially abscesses2</td>
<td>Low-level/heterogeneous expression of meticillin resistance69</td>
<td>Distinct and diverse MLST types and clonal complexes2–7</td>
</tr>
<tr>
<td>Can cause life-threatening invasive infections such as bacteraemia and necrotizing pneumonia64</td>
<td>Occasional and fatal in previously healthy paediatric patients and young adults64</td>
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<tr>
<td>Occasionally fatal in previously healthy paediatric patients and young adults64</td>
<td>Apparent association with non-nasal sites of colonization65</td>
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<tr>
<td>Recurrent SSTIs64,25</td>
<td>Transmission within family groups66</td>
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**Epidemiological definitions**

Epidemiological definitions of CA-MRSA are based on the timing of the first MRSA isolate relative to hospital admission, and were originally developed to determine whether an infection was likely to have been acquired during a hospital stay.15 Typically, these definitions regard MRSA colonization or infection presenting in community settings or at hospital readmission as ‘community-acquired’ or ‘community-associated’, regardless of whether or not the patient has a history of healthcare contact.16–18 MRSA causing such infections may then be misclassified as CA-MRSA. For example, several studies have found that most MRSA bacteraemias diagnosed at hospital admission, and therefore designated by some as community-acquired infections, are caused by nosocomial strains of MRSA (HA-MRSA) from a previous healthcare contact.16,17 Similarly, several reports in the era before the emergence of true or de-novo CA-MRSA described HA-MRSA strains causing infection in community settings as ‘community MRSA’.19,20 The limitations of epidemiological definitions of CA-MRSA are illustrated by a study comparing two different epidemiological definitions of CA-MRSA: one identified 49% of 100 isolates as CA-MRSA, whereas the other only identified 5% as CA-MRSA.21

The US Centers for Disease Control and Prevention (CDC) proposed an epidemiological definition of CA-MRSA that has been widely adopted.22–24 In order to fulfil the current CDC definition of CA-MRSA, MRSA must be identified in the outpatient setting or less than 48 h after hospital admission in an individual with no medical history of MRSA infection or colonization, admission to a healthcare facility, dialysis, surgery or insertion of indwelling devices in the past year.5,23 In the CDC definition, the inclusion of an assessment of previous healthcare contact means that MRSA linked to a hospitalization but presenting in the community or at hospital re-admission are classified correctly as HA-MRSA. Indeed, in a recent study from Oxford, none of the MRSA bacteraemias identified on hospital admission met the CDC definition of CA-MRSA.16

However, as more patients in the community are affected by CA-MRSA, repeat MRSA episodes are increasingly likely to be misclassified as HA-MRSA by epidemiological definitions.25,26 A particular challenge to epidemiological definitions is the transmission of CA-MRSA among the injecting drug user/homeless group.27,28 These patients often have a history of previous hospital admission for other reasons, but their infections may be caused by CA-MRSA strains originally acquired in the community.

Epidemiological definitions are further limited by the emergence of CA-MRSA clones as an increasingly common cause of healthcare-associated infection.9,11–13 Purely epidemiological definitions of CA-MRSA do not consider the genetic background of the MRSA involved and will misclassify CA-MRSA acquired in hospital.

**Need for a genotypic definition**

Millar *et al.* proposed guidelines for developing a definition of CA-MRSA combining epidemiological factors, antimicrobial susceptibility (AMS) pattern, clinical presentation and SCCmec type.8 However, although this is an improvement on the CDC definition, these guidelines are confounded by CA-MRSA acquired in healthcare settings which only meet
some of the proposed criteria for CA-MRSA.8 Also, the guidelines recommend the use of SCCmec typing alone for inferring the MRSA genetic background, but this is not useful for determining the MRSA lineage because isolates with a non-typeable SCCmec cassette may be missed, and SCCmec IV carrying HA-MRSA lineages such as ST22-IV (EMRSA-15) and ST5-IV (USA800/paediatric clone) may be misclassified as CA-MRSA.2,29

CA-MRSA are usually common community types of meticillin-susceptible S. aureus that have acquired mecA de novo.6,7 Therefore, it is proposed that combining a genotyping method [such as multi-locus sequence typing (MLST), spa or pulsed-field gel electrophoresis] with SCCmec analysis to infer the likely origin of the MRSA is the best way to define CA-MRSA strains at the current time. These isolates may be PVL-positive or PVL-negative, have any clinical presentation, have any AMS pattern, and can be classified as either healthcare- or community-associated using epidemiological criteria.

**Practical definition of CA-MRSA**

The introduction of a genotypic method into the definition of CA-MRSA adds extra cost, time and requirement for laboratory equipment, expertise and experience to define these strains. However, the costs of genotyping are decreasing, and the equipment and expertise required, particularly for spa typing, is within the capabilities of most clinical laboratories.30 Furthermore, collaboration with reference centres can be sought to provide genotyping. If this approach becomes more widely accepted and the demands for genotyping increase, it is likely that simpler/automated methods may become commercially available.

Despite these difficulties, the authors believe that future studies of MRSA should use genotypic rather than epidemiological definitions of CA-MRSA. Ideally, all isolates should be genotyped, but in many circumstances, molecular markers or AMS profiles can be used to select representative strains for more detailed genotypic analysis, as discussed below.

**Molecular markers**

There is no single, stable genetic marker for CA-MRSA strains. PVL has been proposed as a marker of CA-MRSA.8,22,31 There is undoubtedly an epidemiological association between CA-MRSA and the carriage of PVL,8,14 but some globally disseminated CA-MRSA clones do not carry PVL.22,32,33 Many of the reports of CA-MRSA have come from the USA, where USA300 (ST8-IV), which is predominantly PVL-positive,34 is the dominant clone.1,2,12,35 In contrast to the dominance of USA300 in the USA, the common CA-MRSA clones in Europe and elsewhere are heterogeneous, including a mixture of PVL-positive and PVL-negative clones.1,2 Successful PVL-negative CA-MRSA clones include ST1-IV (WA-MRSA-1), which is the most common CA-MRSA clone in Western Australia,33 and was the most common CA-MRSA clone at a London hospital from 2000 to 2006,36 and the ST398-V pig-associated clone in Europe.37 One study reported the co-existence of sibling clones of PVL-positive and PVL-negative USA400 in Canada.32 A study from Ireland found that only two (7%) of 30 isolates that met the CDC definition of CA-MRSA carried PVL. Therefore, although MRSA producing PVL are likely to be CA-MRSA, PVL production should not be used as part of the definition of CA-MRSA.

CA-MRSA usually carry SCCmec types IV or V, whereas HA-MRSA usually carry SCCmec types I–III.7,38 Some researchers have used the carriage of SCCmec IV as a molecular marker for CA-MRSA.39,40 For example, a retrospective study from Chicago used an AMS-based algorithm for the presumptive detection of ‘SCCmec IV phenotype’ isolates, which were used to infer changes in the prevalence of CA-MRSA.39 Since the study was performed in the USA, this approach was valid given the dominance of SCCmec IV USA300 and the fact that SCCmec IV HA-MRSA lineages are rare in the USA.

However, the SCCmec region is variable, and new types and subtypes are emerging constantly, leading to problems with nomenclature.7,38 For example, SCCmec V, which is carried by successful CA-MRSA lineages, was first reported in 2004, a decade after the first emergence of CA-MRSA.41 A particular problem with the use of SCCmec type as a marker for CA-MRSA is the presence of successful hospital lineages carrying SCCmec IV in some parts of the world. For example, unlike most other parts of the world, the most common HA-MRSA clone in the UK, ST22 EMRSA-15, is SCCmec IV.2,29 as is the ST5/USA800 paediatric clone which is disseminated in the USA and South America.2 Furthermore, these SCCmec IV carrying HA-MRSA tend to be relatively susceptible to antimicrobial agents, compounding the likelihood that they will be misclassified as CA-MRSA unless their lineage is determined.29

**AMS-based markers**

The SCCmec I–III cassettes, common in HA-MRSA, carry additional antimicrobial resistance genes that are not present in the smaller SCCmec IV and V cassettes associated with CA-MRSA.8,34 Furthermore, CA-MRSA have emerged without the antimicrobial pressure that selects for multiple antimicrobial resistance in hospitals.42 Consequently, the first CA-MRSA were susceptible to non-β-lactam antimicrobial agents,3,14 and this susceptibility has been used as a screening marker for these strains. For example, ciprofloxacin susceptibility has been used as a phenotypic marker of CA-MRSA in the UK.30,40,41

Several studies have attempted to assess the accuracy of AMS-based algorithms for the presumptive identification of CA-MRSA.43–45 However, even the best AMS-based classification systems only have a sensitivity of 70–80%.43–45 For example, in one UK study, the use of ciprofloxacin susceptibility as a marker missed approximately one-third of CA-MRSA isolates,43 and it is likely that mutational ciprofloxacin resistance will increase in these strains in future.42

AMS profiles tend to vary with lineage, thus algorithms for the presumptive identification of CA-MRSA will need to be developed locally.4,35,43 The resolution of AMS-based algorithms is likely to decrease further over time as CA-MRSA develop broader antimicrobial resistance by continued exposure to antimicrobial selective pressure in hospitals.24,46,47 In addition, a particular problem with using antimicrobial susceptibility as a phenotypic marker of CA-MRSA in the UK is that the most common cause of HA-MRSA, EMRSA-15, is typically susceptible to most non-β-lactam antimicrobials.29 Furthermore, useful algorithms will need to be assessed periodically to reflect changes in resistance patterns.
Addressing variation in the molecular epidemiology of CA-MRSA

Genotypic definitions of CA-MRSA will need to reflect differences in the molecular epidemiology of community and healthcare-associated MRSA, and variations in the molecular techniques adopted between countries and laboratories. A genotypic definition is easier to derive in the USA and Latin America, where predominant HA-MRSA lineages are not SCCmec IV and USA300 is so prominent among CA-MRSA. Similarly, genotypic definitions are straightforward where there is a predominant CA-MRSA clone; for example, PVL-positive ST30-IV (“SWP”) in Uruguay, PVL-positive ST5-IV clone in Argentina, PVL-positive ST22-IV and ST772-V in India, PVL-positive ST80-IV in North Africa, and PVL-positive ST59-VII in Taiwan. However, developing a genotypic definition is more difficult in Europe and Australia where CA-MRSA are currently characterized by genotypic heterogeneity. The global molecular epidemiology of CA-MRSA is poorly described, so it is difficult to judge how easy it would be to derive a workable genotypic definition in many parts of the world.

The present authors recently developed a genotypic definition of CA-MRSA at their London teaching hospital, which currently has a low but apparently increasing prevalence of CA-MRSA, and the predominant HA-MRSA clone is ST22-IV EMRSA-15. CA-MRSA were defined as isolates that were SCCmec IV or V that did not have a spa type in the same clonal cluster as EMRSA-15 (using Based Upon Repeat Pattern clustering). Isolates with non-typeable SCCmec regions were defined as CA-MRSA because they were considered to be unlikely to represent epidemic hospital lineages, and all other isolates were classified as HA-MRSA. In common with previous reports (Table 1), isolates defined as CA-MRSA were more likely to be associated with younger patients, abscess formation and PVL production; classified as community acquired by epidemiological criteria; and resistant to fewer classes of antimicrobial agents than isolates defined as HA-MRSA. Until the emergence of CA-MRSA as a cause of healthcare-associated infection, both genotypic and epidemiological definitions would have identified a broadly similar set of isolates. This is now not the case, as illustrated by the fact that 70% of these CA-MRSA isolates were classified as HA-MRSA by epidemiological criteria. This highlights the limitations of epidemiological classifications if used for presumptive identification of CA-MRSA types, and thus supports the use of a genotypic definition. Although the authors suspect that many of these patients, such as intravenous drug users, probably had community acquisition followed by repeated hospital contacts, genuine nosocomial transmission of CA-MRSA strains appears to be occurring with increasing frequency in other parts of the world.

Acquisition and onset of clinical infection

Although it is essential to have clear definitions to distinguish between HA- and CA-MRSA strain types, the time and place of onset of colonization and/or infection are also important for epidemiological analysis, and infection prevention and control. Thus, CA-MRSA can be acquired in either community (common) or healthcare (uncommon but increasing) settings. HA-MRSA strains are nearly always acquired during healthcare contact, but with both strain types, the onset of infection may be in either the community or in hospital. Where the information is available, MRSA infections should therefore be characterized as: (1) caused by HA- or CA-MRSA strain type; (2) acquired in community or healthcare settings; and (3) onset in the community or healthcare facility. These data are important for epidemiological analysis, risk assessment, regulatory reporting, and the development of appropriate infection prevention and control in the community, healthcare facility and community/hospital interface.

Recommendations and conclusion

At the current time, MRSA strains involved in outbreaks should either be typed by individual hospital laboratories or referred to reference laboratories in order to determine whether they are CA-MRSA or HA-MRSA strain types, because a wider group of patients and staff may be at risk and novel control strategies may be required for CA-MRSA. Novel strategies may include hospital staff screening, increased follow-up of cases with hospital and community onset to reduce household transmission, enhanced infection prevention and control measures in community settings, and a focus on preventing transmission of MRSA from livestock to humans in affected areas. Periodic investigation of AMS patterns among MRSA infections, perhaps combined with typing of local sets of isolates, would also be useful to ensure that empiric therapy is appropriate, given that the emergence of CA-MRSA in some parts of the world has forced a change of empiric therapy of staphylococcal skin infections to cover MRSA. Reference laboratories should continue to type representative sets of isolates periodically to ensure that MRSA trends and emerging strain types are monitored adequately.

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Conflict of interest statements

JAO is employed part-time by Bioquell UK Ltd. GLF declares no potential conflict of interest.

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