

# Community-acquired methicillin-resistant *Staphylococcus aureus*: an emerging threat

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Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is becoming an important public-health problem. New strains of *S aureus* displaying unique combinations of virulence factors and resistance traits have been associated with high morbidity and mortality in the community. Outbreaks of epidemic furunculosis and cases of severe invasive pulmonary infections in young, otherwise healthy people have been particularly noteworthy. We review the characteristics of these new strains of community-acquired MRSA that have contributed to their pathogenicity and discuss new approaches to the diagnosis and management of suspected and confirmed community-acquired MRSA infections.

## Introduction

The emergence of a community pathogen depends on its ability to survive in different environments and to interact successfully with the host. *Staphylococcus aureus* is one of the most successful and adaptable human pathogens. The remarkable ability of the bacterium to acquire antibiotic-resistance mechanisms and advantageous pathogenic determinants has contributed to its emergence in both nosocomial and community settings. However, because of different selective pressures, several notable differences exist between nosocomial isolates and community-acquired strains.

Methicillin resistance first appeared among nosocomial isolates of *S aureus* in 1961.<sup>1</sup> Since that time, methicillin-resistant *S aureus* (MRSA) has become widespread in hospitals and intensive care units around the world. MRSA is now one of the most common causes of bacterial nosocomial infections, accounting for 40–70% of the *S aureus* infections in intensive care units.<sup>2,3</sup> In the past, acquisition of MRSA colonisation or infection was generally considered to be restricted to the nosocomial setting. However, in the past decade new strains of MRSA have emerged in the community, causing aggressive infections in young, otherwise healthy people.<sup>4–11</sup> Suppurative skin infections (including epidemics of furunculosis, figure 1) and severe necrotising pneumonias are the most well-known clinical syndromes caused by these new strains. The increasing prevalence of community-acquired MRSA in multiple countries and the substantial morbidity and mortality associated with these infections suggest that community-acquired MRSA will continue to develop into a challenging public-health problem.

What makes these new isolates of community-acquired MRSA particularly well equipped to succeed as community-based pathogens? We summarise the available information regarding community-acquired MRSA infections, emphasising the characteristics that have prompted the recent emergence of MRSA in the community setting and the virulence factors associated with its typical clinical presentations.

## Genetic basis of methicillin resistance

Resistance to penicillin is now widespread in *S aureus* and may be conferred by the production of a beta-lactamase coded by the *blaZ* gene. Methicillin resistance results from the production of an altered penicillin binding protein known as PBP2a, which has decreased affinity for most beta-lactam antibiotics.<sup>12–15</sup>

PBP2a is encoded by the gene *mecA*, which is carried on a mobile genetic element known as the staphylococcal cassette chromosome (SCC) *mec*.<sup>12,16</sup> Besides the *mecA* gene itself, the SCC*mec* element contains regulatory genes, an insertion sequence element (IS431*mec*), and a unique cassette of recombinase genes (*ccr*) responsible for the integration and excision of SCC*mec*.<sup>16</sup> Based on the class of *mecA* gene complex and the type of *ccr* gene complex, at least five types of SCC*mec* elements have been identified and are numbered from I to V.<sup>17,18</sup> A second SCC*mec* typing system has also been described<sup>19</sup> that uses a multiplex PCR assay to accurately identify types I–IV. This assay identifies SCC*mec* types based on loci located upstream and downstream of the *mecA* gene, and does not take into account the specific *ccr* gene complex.

Type I SCC*mec* contains the *mecA* gene as the sole resistance determinant, whereas SCC*mec* types II and III contain multiple determinants for resistance to non-beta-lactam antibiotics and are responsible for the multidrug resistance commonly found in nosocomial



Figure 1: Furuncle near the right knee

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MRSA isolates. However, most probably due to their larger size, the horizontal transfer of SCCmec types II and III occurs with less ease compared with type IV<sup>12,20–24</sup> and spread of MRSA strains harbouring these elements mainly occurs as a result of the selective pressure of antibiotic exposure over time (vertical spread).<sup>17</sup>

Several subtypes of type IV SCCmec are now recognised based on the polymorphism of the region upstream of the *ccr* genes, a location known as L-C.<sup>17,21,25</sup> Although the L-C subtyping system has been used before, many groups now sequence larger regions of the SCCmec type IV element as a method of subtyping. Like type I, type IV elements lack other resistance determinants.<sup>21,26</sup> Their smaller size, compared with type II and III elements, may serve as an evolutionary advantage by making them more amenable to horizontal spread among a bacterial population.<sup>26,27</sup> Strains of community-acquired MRSA that have emerged over the past decade have mostly harboured the SCCmec type IV element<sup>18,21,22,26</sup> and they are typically susceptible to multiple antibiotics with non-beta-lactam susceptibility patterns resembling those of methicillin-susceptible *S. aureus* (MSSA) strains prevalent in the community. The genome sequence for only one community-acquired MRSA strain (MW2) is available; the sequence from a closely related strain of community-acquired MSSA (MSSA476)—known to have caused severe invasive disease in an immunocompetent child—has also been published.<sup>28</sup> MSSA476 shares many virulence factors with MW2 and contains a novel SCC element (SCC<sub>476</sub>) remarkably similar to the one described for *Staphylococcus hominis* (SCC<sub>12263</sub>).<sup>29</sup> Although SCC<sub>476</sub> does not carry the *mec* genes, it carries genes that might confer resistance to fusidic acid (*far1*).<sup>28</sup> Like MW2, MSSA476 is sensitive to a great variety of non-beta-lactam antibiotics and both belong to the same sequence type.<sup>30,31</sup> Therefore, most authorities feel that it is the acquisition of the SCCmec IV element by MSSA strains in the community that has given rise to the emerging community-acquired MRSA strains.<sup>25,32</sup>

Besides intraspecies transfer of resistant determinants, other commensal staphylococcal species may act as a reservoir for antibiotic resistance islands that may be transferred to *S. aureus*. Notably, the SCCmec type IV element was found to be prevalent in isolates of *Staphylococcus epidermidis* from the 1970s, and has been rarely described in *S. aureus* isolates before 1990.<sup>33</sup> Furthermore, three other SCCmec elements that contain genes encoding biosynthetic enzymes for capsular polysaccharides have been identified in MSSA, *S. epidermidis*, and *S. hominis* strains.<sup>27,29,34</sup> These elements share most of the essential characteristics of SCCmec, including regulatory genes and insertion sequences, but lack the *mecA* gene. Interestingly, sequences found within the L-C region of SCCmec type

IV were found to be virtually identical to those found in *S. epidermidis*, suggesting extensive horizontal exchange between staphylococcal species.<sup>34</sup>

### New strains of community-acquired *S. aureus*

Strains of *S. aureus* (including MRSA) are able to colonise the host for very long periods of time before causing infection.<sup>35–38</sup> Because nosocomial colonisation with MRSA usually goes undetected and may lead to infection many months after hospital discharge (when the patient is in the community), it may be difficult to establish the origin of strains causing MRSA infections in the community. This difficulty differentiating nosocomial MRSA from community-acquired MRSA has led to confusion regarding the prevalence of MRSA in the community. Substantial heterogeneity is found among the definitions used by different authors to define community-acquired MRSA.<sup>39</sup> For example, defining a case as being community acquired is usually based on the timing of isolation of MRSA in relation to the time of hospitalisation. As a result, the vast majority of cases attributed to community-acquired MRSA are associated with recent direct or indirect exposure to the health-care setting (eg, hospitalisation, outpatient visit, nursing home admission, antibiotic exposure, chronic illness, or close contact with people with these risk factors), suggesting that these infections are caused by nosocomial strains that have been carried into the community. When risk factors for acquisition of strains related to the health-care environment are not rigorously assessed, the term “community-onset” MRSA is technically more accurate than community-acquired MRSA for isolates causing infections that arise in the community.<sup>39</sup>

Over the past decade, reports of severe community-onset MRSA infections occurring in the absence of clear risk factors for nosocomial acquisition have been associated with isolates that are unusually susceptible to a wide variety of antimicrobials, including clindamycin, macrolides (variable), co-trimoxazole, tetracyclines, and fluoroquinolones,<sup>40</sup> indicating that the epidemiology of MRSA is changing.<sup>4,41</sup> The introduction of molecular typing techniques (panel) into epidemiological investigations confirmed that some isolates from community-onset infections were

#### Panel: Techniques used for molecular typing of MRSA

Pulsed-field gel electrophoresis<sup>42</sup>  
 Multilocus sequence typing<sup>20</sup>  
 Multilocus restriction fragment typing<sup>43</sup>  
 Sequence analysis of the polymorphic repeat region of the staphylococcal protein A gene typing (*spa* typing)<sup>44</sup>  
 High-throughput amplified fragment length polymorphism analysis<sup>45</sup>  
 Genotyping<sup>46</sup>

genotypically distinct from typical nosocomial isolates and demonstrated clonal spread within the community.<sup>22</sup> Other isolates from community-onset infections were clonally related to common nosocomial isolates, suggesting spread of MRSA from the health-care setting. Furthermore, the publication of five complete *S aureus* genomes—nosocomial MRSA strains N315, Mu50, MRSA252,<sup>28,47</sup> community-acquired MRSA strain MW2,<sup>48</sup> and community-acquired MSSA476<sup>28</sup>—plus two others that are publicly available—MSSA COL (<http://www.tigr.org>) and MSSA NCTC 8325 (<http://www.genome.ou.edu/staph>)—have added great insights to the understanding of the factors involved in *S aureus* pathogenesis and emergence in different settings.

Three groups of individuals can be differentiated from a clinical point of view: people with community-onset MRSA infections without health-care-associated risk factors; people with community-onset MRSA and health-care-associated risk factors; and people with nosocomial MRSA infections.

MRSA infections in individuals without typical health-care-associated risk factors have mostly been associated with staphylococcal strains bearing the SCC*mec* type IV element and the Panton-Valentine leukocidin (PVL) genes. These strains are more frequently susceptible to a variety of non-beta-lactam antibiotics, although macrolide resistance is variable.<sup>40,49,50</sup> The highly virulent strain MW2 that resulted in severe infections among healthy children and young adults in the USA is, to date, the only community-onset MRSA strain from people without typical MRSA risk factors that has been completely sequenced.<sup>4,48</sup> A study within the USA showed that MW2 and other community-onset MRSA strains belonged to just two of the eight pulsed-field types known at that time—USA300 and USA400.<sup>42</sup> Within the USA400 pulsed-field type (including MW2), multilocus sequence typing (MLST) revealed an ST 1 profile, and strains were of the staphylococcal protein A gene (*spa*) type motif UJJJFE. MLST of USA300 isolates showed they had an ST 8 profile and shared a common *spa* type motif (MBQBLO).<sup>42</sup>

Although most of the *S aureus* strains found in nosocomial and community settings belong to few clonal populations,<sup>31</sup> from a clinical and therapeutic perspective it is important to recognise that some strains of MRSA causing community-onset infections in people with health-care-associated risk factors may be typical nosocomial MRSA strains, or they may represent community-acquired MRSA strains, each presenting different resistance patterns and a different array of virulence factors.<sup>51–53</sup> Nosocomial MRSA carrying a type II SCC*mec* element are more likely to be resistant to macrolides, clindamycin, and fluoroquinolones.<sup>40</sup> Community-acquired MRSA strains carrying a type IV SCC*mec* element are more

frequently susceptible to these non-beta-lactam antibiotic classes. Community-acquired MRSA strains are genetically diverse—some have a genetic background similar to “archaic” or “historic” MRSA,<sup>23,49</sup> but most harbour the SCC*mec* type IV element (associated with remaining susceptibility to many non-beta-lactam antibiotics), and some may also carry the PVL genes.<sup>18,23,24,49,53–55</sup>

Nosocomial MRSA strains are typically resistant to a wide range of antibiotics. Although the N315 and Mu50 strains are closely related to MW2 and MSSA476, they harbour several differences among their accessory genes. Notably, nosocomial MRSA strains have multiple mobile and non-mobile genetic elements that confer resistance to multiple antibiotics, allowing them to succeed under heavy selective pressure.

Both health-care-associated community-onset MRSA and non-health-care-associated community-onset MRSA are highly virulent strains, capable of clonal dissemination, and have the ability to cause epidemics of furunculosis and other skin and soft-tissue infections.<sup>56,57</sup> Nevertheless, non-health-care-associated MRSA strains are now responsible for the majority of community-onset MRSA infections in some areas of the USA.<sup>24,58–60</sup> Furthermore, despite their designation as community-onset MRSA strains, these strains are no longer restricted to that setting, since community-onset MRSA strains have now been found in association with nosocomial infections.<sup>61,62</sup> Irrespective of the characteristics of the population or the setting, community-onset MRSA carrying the SCC*mec* type IV element poses a real threat and will likely continue to emerge as a major public-health concern.

### Prevalence of MRSA in the community

Because of different definitions of community-acquired infections used in the literature, and the limited number of population-based studies that include molecular typing techniques, the reported prevalence of MRSA in the community varies widely. However, regardless of the definition, prevalence of MRSA in the community seems to be increasing. In a meta-analysis, Salgado and colleagues<sup>39</sup> summarised many studies reporting the prevalence of community-onset MRSA both with and without health-care-associated risk factors in the community. The authors divided the reports into two groups: studies of the prevalence of community-onset MRSA infection among hospitalised patients, and studies of the prevalence of MRSA colonisation in the community.

In the first group of studies, patients were identified by routine clinical specimens and cases were defined based on the timing of isolation of MRSA in relation to the time of admission. The pooled data from 27 retrospective studies (5932 patients) and from five prospective studies (636 patients) showed prevalences

of community-onset infection among hospitalised patients with MRSA isolates of 30.2% and 37.3%, respectively. Of note, approximately 85% of community-onset MRSA patients in both the retrospective and prospective groups reported at least one health-care-associated risk factor.<sup>39</sup>

In the second group, ten studies reporting the prevalence of MRSA in the community with surveillance cultures were analysed. The pooled data (8350 patients) showed a prevalence of 1.3% for MRSA colonisation (2.1% after stratification based on methodological differences).<sup>39</sup> Again, most people colonised with MRSA had health-care-associated risk factors. After excluding those patients, the prevalence of MRSA colonisation was only 0.2%. Leman and colleagues have found a similar prevalence in selected populations.<sup>63</sup> Patients with intravenous drug abuse or HIV infection have a higher prevalence of MRSA infection and colonisation.<sup>61,64–66</sup>

### Clinical presentation and virulence factors

*S aureus* has the capacity to produce a wide array of virulence factors, some of which are responsible for

specific clinical syndromes (table 1). Community-acquired MRSA isolates have been associated with many of the same clinical presentations known to occur with traditional *S aureus* infection. However, outbreaks of epidemic furunculosis and severe invasive paediatric infections caused by community-acquired MRSA have been particularly noteworthy.<sup>55</sup>

The ability of new community-acquired MRSA strains to colonise hosts in the community and cause clinical syndromes is mediated by unique combinations of traditional and newly described virulence factors. Analysis of the genome of MW2 demonstrated 19 unique genes encoding virulence factors that were not found on other *S aureus* genomes that had been sequenced to date.<sup>48</sup> A better understanding of MRSA virulence factors and how they mediate disease may ultimately lead to new therapeutic interventions.

The most well-known community-acquired MRSA virulence factor is PVL, which elicits tissue necrosis and may contribute substantially to the clinical findings of epidemic furunculosis and severe necrotising pneumonia in young, otherwise healthy individuals. Given that community-acquired MRSA strains have spread into the hospital, the ability to differentiate between what is a typical nosocomial MRSA strain versus an emerging community-acquired MRSA strain is becoming difficult. Therefore, since *S aureus* strains carrying the PVL genes cause similar clinical syndromes, irrespective of where the infection is acquired or even the particular antimicrobial susceptibilities of the strain, in the future it might be appropriate to use the term “PVL syndrome” when describing a patient’s presentation.

Several studies suggest that community-acquired MRSA strains harbouring the smaller SCCmec type IV element grow faster and achieve higher infection burdens than nosocomial MRSA strains.<sup>84,85</sup> This property has been attributed to the extra metabolic burden that multiresistant bacteria have secondary to the synthesis of extra proteins during replication,<sup>86</sup> and may provide a selective advantage to community-acquired MRSA. Despite these studies it should be noted that community-acquired MRSA would likely compete mostly with MSSA strains in the outpatient setting.

### Skin infections

Skin infections caused by *S aureus* are generally believed to follow colonisation of the skin or nares of the host. To colonise the host, the organism must compete successfully with other commensal bacteria. Community-acquired MRSA strains that have become established in the community setting might have virulence determinants that confer a competitive advantage. A novel gene cluster, known as *bsa* (bacteriocin of *S aureus*), described in the MW2 and MSSA476 genomes, may confer such an advantage.

Virulence factor	Characteristic	Clinical syndrome	References
<b>Resistance determinants</b>			
SCCmec type IV	Resistance to methicillin		21,22,48
SCC <sub>476</sub>	Resistance to fusidic acid		28
<b>Adherence</b>			
Collagen-adhesin protein (CNA)	Greater adherence to host tissues	EF, NP, arthritis, osteomyelitis	4,67–71
<b>Colonisation</b>			
Bacteriocin of SA ( <i>bsa</i> )	Intraspecies and interspecies competition	EF	4,28,48,72
Unknown	Greater tolerance to salt	EF	67
<b>Superantigens</b>			
Enterotoxins	Activation of T cells	EF, NP, TSS-like illness	
Staphylococcal enterotoxin A ( <i>sea</i> , <i>sak</i> )			28,73,74
Staphylococcal enterotoxin B			4,48,75
Staphylococcal enterotoxin C ( <i>sec4</i> )			4,48
Staphylococcal enterotoxin G ( <i>seg2</i> )			28,48,76
Staphylococcal enterotoxin H	Extremely potent superantigen		48,73,76,77
Staphylococcal enterotoxin K ( <i>sek2</i> )			28,48
Staphylococcal enterotoxin L ( <i>sel2</i> )			48
Staphylococcal enterotoxin O' ( <i>seo'</i> )			48,73
<b>Exotoxins</b>			
Staphylococcal exotoxin T ( <i>set16–26</i> )	Possible defence against immunity		28,48
<b>Pore-forming toxins</b>			
PVL (LukSPV+LukFPV)	Necrosis, oedema	EF, NP	48,77,78
LukE+LukD	Destruction of intestinal microvilli	Postantibiotic diarrhoea	77,79,80
LukEv+LukDv	Necrosis	EF	79
α-Haemolysin	Necrosis, vascular leakage, shock	EF, NP	67,81
<b>Exfoliative toxins</b>			
Exfoliative toxin A			82,83
Exfoliative toxin B			

EF=epidemic furunculosis, NP=necrotising pneumonia, SA=Staphylococcus aureus, TSS=toxic shock syndrome

Table 1: Virulence factors of community-acquired Staphylococcus aureus

Bacteriocins are naturally synthesised antibiotics found in several Gram-positive bacteria,<sup>87</sup> which have a relatively narrow killing spectrum and are toxic only to bacteria closely related to the producing strain.<sup>72,87,88</sup> Similar molecules found in other bacteria serve as anti-competitive factors enabling the invasion of a strain into an established microbial community. Additional roles have been proposed for bacteriocins, such as quorum sensing and intercellular communication.<sup>72,89</sup>

Adherence of *S aureus* to host tissues is an important step for both colonisation and pathogenesis. Studies have not shown an advantage of epidemic MRSA types 1 and 16 over MSSA strain Cowan I or other MSSA clinical isolates in attaching to epithelial cells in vitro.<sup>90,91</sup> However, one study suggests certain strains of community-acquired MRSA (eg, WSPP1 strain 98M7611) may be better able to adhere to epithelial cells than other MRSA strains (eg, epidemic MRSA16).<sup>67</sup>

Another virulence factor found in the MW2 genome, as well as MSSA and nosocomial MRSA, is the collagen-adhesin protein (CNA), encoded by the *cna* gene. CNA is a microbial surface component that recognises adhesive matrix molecules not expressed by the majority of *S aureus* strains.<sup>68</sup> CNA has been implicated in the pathogenesis of septic arthritis and osteomyelitis<sup>69,70</sup> and might be important in the development of infected thrombi in endocarditis and in adherence to lung epithelium in pneumonia.<sup>71,92,93</sup> However, at present, the role of CNA in disease is speculative and remains to be elucidated.

Community-acquired MRSA strains from New Zealand were found to have a higher tolerance to salt compared with nosocomial strains. This high salt tolerance might also help in its ability to survive as skin flora.<sup>67</sup>

Furunculosis is the most frequently reported presentation of community-acquired MRSA infection (figure 1).<sup>41,57,94,95</sup> The syndrome is characterised by the development of primary necrotic lesions of the skin and soft tissues caused by direct invasion and tissue destruction. Crusted lesions and plaques that progress to abscesses (70–100% of cases) or cellulitis (50–70% of cases) are the most common lesions. Less commonly impetigo, nodules, and pustules are also part of the clinical picture.<sup>94–96</sup> Although the infection usually remains localised to the skin and soft tissues, bacteraemia, septic shock, toxic shock-like syndrome, and other systemic complications have been reported.<sup>41,57,96</sup>

One of the most striking characteristics of the strains causing epidemic furunculosis is their ability to cause necrosis and to form abscesses.<sup>41,63,96</sup> Although usually found in only 2% of all *S aureus* clinical isolates, the PVL genes have been found in virtually all isolates of community-acquired MRSA causing epidemic furunculosis worldwide,<sup>77</sup> suggesting a key role in its pathogenesis.<sup>78,97</sup> PVL genes are also found in MSSA

strains and, since they may be horizontally transmitted via phages, it is likely they originated from community-acquired MSSA strains.<sup>98</sup> The PVL genes encode a bicomponent leukotoxin, that, together with  $\delta$ -haemolysin and  $\alpha$ -haemolysin, constitute the pore-forming staphylococcal toxins.<sup>78</sup> The leukotoxins are produced as two non-associated secreted proteins, referred as S and F. To date, six different leukotoxin class S proteins (LukSPV, LukE, LukM, HlgA, HlgC, and LukSI) and five leukotoxin class F proteins (LukFPV, LukD, LukF'PV, HlgB, and LukFI) are known.<sup>78</sup> In the case of PVL, LukSPV and LukFPV bind sequentially, creating hexamers of S/F proteins with a 1/1 molar ratio.<sup>99</sup> PVL contact with human neutrophils, monocytes, macrophages, and erythrocytes results in pore formation and cell lysis through osmotic rupture. Binding of PVL also causes the activation of the target cell by the rapid opening of membrane calcium channels.<sup>100</sup> For neutrophils, this activation triggers the exocytosis of granules and production of interleukins and other inflammatory mediators.<sup>101,102</sup> This activation generates a cascade of local vasodilation, chemotaxis, and additional neutrophil infiltration, with subsequent secretion of degradative enzymes and generation of superoxide ions, promoting necrosis of the tissue. Injection of purified PVL into the skin of rabbits produces necrotic lesions similar to the ones found in epidemic furunculosis, proving its dermonecrotic properties.<sup>103</sup> A variant of LukE+LukD (LukEv-LukDv) that is structurally close to PVL has been described from a clinical strain of *S aureus* carrying  $\delta$ -haemolysin genes but not the PVL genes.<sup>79</sup> This variant shares many of the characteristics of the PVL toxin and might have a role in pathogenesis.<sup>79</sup>

Other pore-forming toxins are produced in greater amounts by community-acquired MRSA strains.<sup>67</sup>  $\alpha$ -Haemolysin acts on a wide variety of cells (erythrocytes, leucocytes, platelets, fibroblasts, etc). Like PVL,  $\alpha$ -haemolysin is also dermonecrotic.<sup>81</sup>  $\beta$ -Haemolysin is a sphingomyelinase active against a great variety of cells (erythrocytes, leucocytes, platelets, fibroblasts). The role of  $\beta$ -haemolysin in disease is not clearly understood; however, the high level of expression in several strains indicates that  $\beta$ -haemolysin production may confer a selective advantage.<sup>81</sup>

Several cases of impetigo, bullous impetigo, and scalded skin syndrome have been described, adding a new clinical presentation to community-acquired MRSA infection.<sup>82,104</sup> These clinical syndromes are caused by an unexpected clonal group of MRSA producing exfoliative toxins A and B (*eta* and *etb*).<sup>105</sup> These strains also carry the SCCmec IVa element and the PVL genes.<sup>82,106</sup>

### Necrotising pneumonia

Necrotising pneumonia is another clinical presentation strongly associated with *S aureus* strains

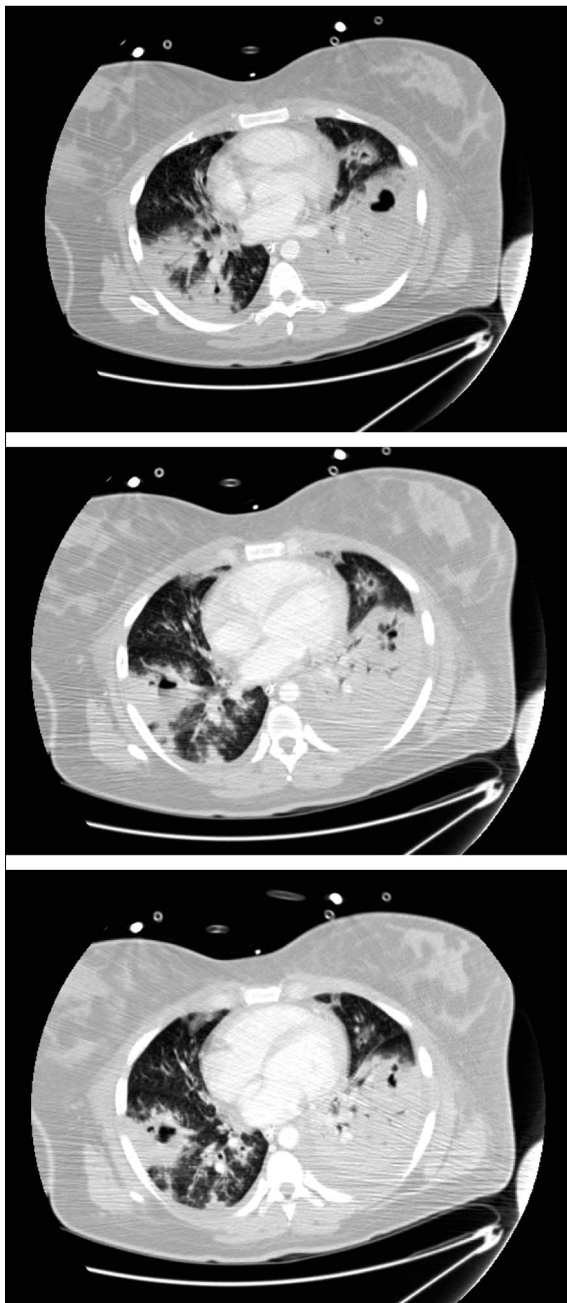


Figure 2: Necrotising pneumonia secondary to MRSA carrying PVL genes<sup>10</sup>

producing PVL (figure 2). Originally described in children and young, healthy adults, it has also been described in older adults.<sup>41,107–109</sup> The syndrome is characterised by high fever, haemoptysis, hypotension, leucopenia, and multilobular alveolar infiltrates that, unlike nosocomial MRSA pneumonias, usually progress into abscesses.<sup>10,41,108,109</sup> Diffuse alveolar haemorrhage has been described and may be life-threatening.<sup>107</sup> Positive blood cultures and rapid progression to septic shock and acute respiratory

distress syndrome are the rule.<sup>41,109</sup> The mortality is extremely high, and autopsies usually show diffuse bilateral necrotic haemorrhagic pneumonia. Necrotic lesions of the tracheal mucosa and alveolar septa, with numerous clusters of Gram-positive cocci are usually seen in histopathological studies.

Preceding influenza or influenza-like prodromes are commonly described with necrotising pneumonia. Although not unique for community-acquired MRSA, the relation between influenza and staphylococcal pneumonia has long been recognised. The expression of multiple distinct surface proteins that mediate the binding of *S aureus* to uninfected cells and those infected with influenza A, a substantially reduced ability to clear the bacteria, and an inability to mount an adequate immune reaction have been proposed to have a role in this relation.<sup>110–112</sup> CNA has also been associated with *S aureus* adherence to human endothelium<sup>70</sup> and may have a role in colonisation or invasion of the airways.<sup>92</sup>

As with epidemic furunculosis, almost all of the cases of necrotising pneumonia have been associated with *S aureus* strains carrying the PVL genes—the properties described above are likely responsible for the necrotic manifestations in the lung. The production of interleukins and other inflammatory mediators<sup>101,102</sup> are likely responsible for the local vasodilation and progression to acute respiratory distress syndrome. The associated leucopenia may also be related to the action of PVL.<sup>42,109</sup> In animal models, the intravascular injection of PVL results in accumulation of the toxin in the bone marrow and subsequent neutropenia.<sup>78</sup>

Although it has a key role in the pathogenesis of necrotising pneumonia, PVL is not likely to be the only pathogenic determinant responsible for this syndrome.  $\alpha$ -Haemolysin is expressed at higher concentrations by some community-acquired MRSA strains.<sup>67</sup> This toxin is also dermonecrotic and, when injected intravenously, causes vascular leakage in perfused rabbit lungs.<sup>113</sup> Endothelial cells are sensitive to  $\alpha$ -haemolysin and the toxin might have a role in the onset of pulmonary oedema and septic shock.<sup>114,115</sup>

### Other presentations

Rapid development of septic shock has characterised the course of most reported cases of necrotising pneumonia and some cases of skin or soft tissue infection. The high mortality, frequent failure to improve with antibiotics, and similarities with Gram-negative sepsis suggest a key role of staphylococcal toxins in its pathogenesis. Because of its strong epidemiological linkage, PVL has been suggested as a possible mediator of shock. However, despite the multiple systemic manifestations associated with the intravenous administration of PVL in animal models, it has not proven to be lethal even when applied at high doses.<sup>116</sup>

Although most patients presenting with shock do not fit the established definition of toxic shock syndrome,<sup>117</sup> most do fit with the proposed “toxic shock syndrome-like illness”.<sup>118</sup> The *tst* gene that encodes toxic shock syndrome toxin 1 (TSST1), the toxin associated with most typical toxic shock syndrome cases, is absent in the majority of community-acquired MRSA isolates, but other toxins capable of producing toxic shock syndrome-like illness have been identified.<sup>83</sup> The importance of these toxins in the pathogenesis of community-acquired MRSA infections was first suggested in the initial report of four children who died of fulminant MRSA infection in Minnesota and North Dakota, USA. Isolates from each of the four patients produced staphylococcal enterotoxins B and C (SEB and SEC) as well as PVL.<sup>4</sup> Pulsed-field gel electrophoresis analysis of MRSA isolates from a native American community demonstrated strains highly related to one another and indistinguishable from strains reported in other areas of USA.<sup>58,119</sup> The majority of those strains produced either SEB, SEC, or both, unlike nosocomial strains used as controls.<sup>22</sup> SEB and SEC have been implicated as causes of non-menstrual severe toxic shock syndrome<sup>120–123</sup> and, together with TSST1, account for nearly all cases of staphylococcal toxic shock syndrome.<sup>120</sup>

Genes encoding staphylococcal enterotoxins A and H (SEA and SEH) were also found in all the isolates obtained from another cluster of four paediatric patients with severe pneumonia and sepsis caused by community-acquired MRSA or MSSA.<sup>73</sup> SEH is one of the unique genes present in the MW2 genome and has been found in most community-acquired MRSA isolates reported in the USA.<sup>77</sup> SEH is a potent superantigen that causes toxic shock syndrome-like illness in rabbits.<sup>74–76,124</sup> The toxin is produced in large amounts by isolates carrying the respective gene<sup>125</sup> and

its activity may be enhanced by low concentrations of endotoxin. SEA also shares many biochemical and biological properties with TSST1 and has been associated with toxic shock syndrome-like illness in rabbits.<sup>74,75,126</sup>

Additional enterotoxins have been reported in community-acquired MRSA isolates. Although the role of the unique toxin gene sequence fragment *seo*—a truncated copy of staphylococcal enterotoxin O described in strain MW2<sup>48</sup>—is still unknown, it might have a pathogenic role.<sup>73</sup> Similarly, a staphylococcal enterotoxin-like toxin gene known as *set* was described in MW2; clustering of *set* on pathogenicity islands suggests a role in virulence.<sup>75</sup>

Better understanding of the role of these toxins in the pathogenesis of community-acquired MRSA infections may have therapeutic relevance. Studies have suggested that the use of intravenous immunoglobulin is beneficial as an adjunctive therapy in severe toxin-mediated shock.<sup>125</sup> However, higher doses of intravenous immunoglobulin may be required to neutralise staphylococcal superantigens compared with streptococcal superantigens.<sup>126</sup> Neutralisation of PVL and other toxins by intravenous immunoglobulin has also been demonstrated in vitro. Although the role of intravenous immunoglobulin in the treatment of severe community-acquired MRSA infections remains to be defined, intravenous immunoglobulin could be considered as an adjunctive treatment for people presenting with severe necrotising pneumonia or toxic shock syndrome-like illness. Higher doses of intravenous immunoglobulin than those used for streptococcal shock might be necessary.

Multiple other clinical presentations are also caused by community-acquired MRSA. Osteomyelitis and mediastinitis are known complications of bacteraemia, pneumonia, and soft tissue infections. Postantibiotic

	Severe infections		Non-severe infections	
	First-line agents	Second-line agents	First-line agents	Second-line agents
Patient with health-care-associated risk factors*	Vancomycin	Linezolid Quinupristin/dalfopristin Daptomycin†	Empiric penicillinase-resistant penicillin‡§ First-generation cephalosporin§¶ Vancomycin**	Linezolid Co-trimoxazole Clindamycin Tetracycline††
Patient without health-care-associated risk factors*	Vancomycin	Linezolid Quinupristin/dalfopristin Daptomycin†  Penicillinase-resistant penicillin‡§ PLUS one of the following: Trimethoprim/sulfamethoxazole Clindamycin Tetracycline††	Penicillinase-resistant penicillin‡§ First-generation cephalosporin§¶	Co-trimoxazole Clindamycin  Tetracycline††

\*Recent hospitalisation (1–24 months), recent outpatient visit (12 months), recent nursing home admission (12 months), recent antibiotic exposure (1–12 months), haemodialysis, chronic illness, intravenous drug use, or close contact with persons with risk factors. †Daptomycin should be avoided in the treatment of MRSA pneumonia. ‡Oxacillin, nafcillin, dicloxacillin. §Avoid beta-lactam in areas with high prevalence of community-acquired MRSA. ¶Cefazolin, cefalexin. \*\*Vancomycin should be discouraged as empirical treatment of furuncles and non-severe skin and soft tissue infections. ††Minocycline (preferred) or doxycycline.

**Table 2: Suggested initial empiric therapy for patients with suspected staphylococcal infections**

diarrhoea has also been associated with other pore-forming toxins different from PVL.<sup>77,80,99</sup> The leukocidin LukE+LukD, produced by 30–100% of clinical isolates, causes destruction of epithelial microvilli and diarrhoea when given to rabbits<sup>78</sup> and has been implicated in this clinical presentation. Although less frequent, cases of infective endocarditis, urinary tract infections, and enterocolitis have also been described in association with pore-forming toxins.

### Management of community-acquired MRSA infections and antibiotic selection

The emergence of MRSA in the community heralds a need for new approaches to the management of both suspected and confirmed staphylococcal infections, particularly regarding the selection of empirical antibiotic therapy (table 2). For now, the selection of initial antibiotic regimens can be guided by the prevalence of MRSA in a given community, the presence or absence of health-care-associated risk factors, and the severity and type of clinical presentation.

Vancomycin should be considered as empirical therapy for people with severe and life-threatening infections while cultures are pending in areas where community-acquired MRSA has been documented. Empirical therapy with vancomycin should also be considered for serious infections in patients with a history of MRSA colonisation, intravenous drug use, and health-care-associated risk factors.

In geographic locations with a low prevalence of community-acquired MRSA, individuals with less severe infections and people without health-care-associated risk factors may be treated with a penicillinase-resistant penicillin (eg, oxacillin or nafcillin) or a first-generation cephalosporin (eg, cefazolin) while cultures are pending.

Community-acquired MRSA isolates from people without health-care-associated risk factors are usually susceptible to a variety of non-beta-lactam antibiotics.<sup>40</sup> Clindamycin, co-trimoxazole, linezolid, and minocycline should be given serious consideration as alternative treatments for skin and soft tissue infections and for selected patients with necrotising pneumonias. Daptomycin also has activity against *S aureus* strains; however, it was found inferior to comparators in a large unpublished community-acquired pneumonia trial, presumably because of poor penetration into alveolar secretions.<sup>127</sup> There are contraindications for the use of co-trimoxazole in children less than 8 weeks old and tetracyclines in children under 8 years of age, thus these agents should be avoided in paediatric community-acquired MRSA infections in the respective age groups. In addition, to our knowledge there is little experience with daptomycin in individuals under 18 years of age.

Given that community-onset MRSA from patients with health-care-associated risk factors have higher

### Search strategy and selection criteria

In preparation for this review we searched PubMed (from 1966) with combinations of the following keywords: "Staphylococcus", "Staphylococcus aureus", "methicillin-resistance", "community-acquired infections", "virulence", "toxins", "leukocidin", "Panton-Valentine", "colonisation", "adherence", "hemolysin", "superantigen" and "toxic-shock". Recent reviews on related topics were also checked. English bibliographies of all articles collected were checked for additional references. English and Spanish papers were evaluated in an attempt to perform an in depth review.

rates of resistance,<sup>40</sup> clinicians may consider avoiding clindamycin, co-trimoxazole, and tetracyclines until the results of susceptibility testing are available. Clinicians should be aware that inducible resistance to clindamycin may not be apparent from the results of routine susceptibility testing.<sup>128–130</sup> Siberry and colleagues<sup>129</sup> demonstrated inducible resistance to clindamycin that could be clinically important in 56% of isolates that were resistant to erythromycin but susceptible to clindamycin on the basis of initial testing. Isolates with this resistance phenotype should be tested to exclude inducible clindamycin resistance before this antibiotic is used for pathogen-directed therapy. Rifampicin is another option when isolates prove to be susceptible, but it should not be used alone due to the rapid selection of resistant organisms.

The emergence of MRSA infections in the community places renewed emphasis on the importance of non-antibiotic management of localised infections. Although sometimes neglected, appropriate drainage is the definitive management of many skin and soft tissue infections and is always an important adjunct to antibiotic therapy in deeper, closed-space infections. Cutaneous abscesses typically resolve with proper drainage and/or debridement alone, and collections left without drainage in the setting of antibiotic treatment promote the emergence of resistance.<sup>131</sup>

Because of the therapeutic implications, every effort should be made to obtain appropriate clinical specimens for culture and susceptibility testing, particularly in areas with high MRSA prevalence and/or in people with health-care-associated risk factors, severe infections, or treatment failure. For people with mild or chronic infections, withholding antibiotics until adequate specimens are obtained and/or drainage is performed will further improve the culture yield.

Renewed emphasis on the prevention of MRSA infections is also necessary. Control of MRSA in the health-care setting remains an important means of limiting its spread in the community. High-risk populations (eg, people with a history of intravenous

drug use, residents of long-term care facilities, patients on dialysis or residing in intensive care units) can be considered for nasal surveillance cultures for MRSA on admission.<sup>132,133</sup> Patients with recognised MRSA colonisation or infections should be isolated and contact precautions implemented.

The eradication of MRSA colonisation is controversial. Topical mupirocin applied to the nares or systemic co-trimoxazole have been used with different rates of success.<sup>134,135</sup> Because of the rapid development of resistance that occurs almost invariably with time, treatment of MRSA colonisation is currently not recommended for most populations.<sup>130</sup> However, given the high morbidity and mortality associated with staphylococcal strains carrying the PVL genes, screening and decolonisation with mupirocin of selected people (eg, individuals with recurrent skin abscesses despite antimicrobial treatment) and their contacts (if nasal cultures are positive) may be appropriate.

## Conclusions

New strains of MRSA have evolved in the community, with unique combinations of virulence factors and resistance traits that confer distinct advantages for colonisation and pathogenesis. Clinicians must be aware of the wide and, in some cases, unique spectrum of disease caused by community-acquired MRSA. Continued emergence of MRSA in the community is a public-health problem that warrants increased vigilance in the diagnosis and management of suspected and confirmed staphylococcal infections.

### Conflicts of interest

ELN has received research grants and honoraria from Abbott and Pfizer. WRB has received research grants from Abbott, Aventis, Bayer, Merck, and Pfizer, and has received honoraria from Abbott, Aventis, Bayer, Merck, Ortho-McNeil, Oscient, Roche, and Pfizer. NZ and JSF have no conflicts of interest.

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