

## Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community

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**These guidelines have been developed by a Working Party convened on behalf of the British Society for Antimicrobial Chemotherapy. Their aim is to provide general practitioners and other community- and hospital-based healthcare professionals with pragmatic advice about when to suspect MRSA infection in the community, when and what cultures should be performed and what should be the management options, including the need for hospitalization.**

Keywords: community onset, case scenarios, MRSA infection, diagnosis, management

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## 1. Introduction

This guidance aims to complement existing guidance on prevention and treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and focuses on typical common and less common community-onset infections with an emphasis on community-associated MRSA (CA-MRSA). An important issue covered by these guidelines is the management of serious infection caused by MRSA arising in the community. Although such infections are rare at present, they usually affect young, previously healthy people and may have a rapid and devastating course. Specific guidance is given on the management of staphylococcal pneumonia, although other serious manifestations of these infections are emerging. Serious *S. aureus* infections can be caused by strains that are methicillin-resistant or -susceptible and which may or may not express the pathogenic Panton–Valentine leucocidin (PVL) toxin. The role of the general practitioner (GP) is to recognize that the patient is seriously unwell and needs to be managed in hospital (see Section 6, Appendix 1 and the algorithm in Figure 1).

A summary of the commonest MRSA clinical problems [skin and soft tissue infections (SSTIs); serious and deep seated infections] presenting to GPs and guidance on their treatment is presented in Appendix 1. Practical advice on the isolation of MRSA in the urine is also provided in the Appendix but not covered in the main body of the guidelines because the evidence base for the management of this situation is poor. The recommendations could be implemented, for example, by their integration into new or existing care pathways.

Guidelines on various aspects of the management and control of MRSA are available and are revised regularly.

- This guidance is for the diagnosis and management of MRSA infections that arise in the community. Much of this is relevant to GPs.
- Guidance for the control of MRSA in healthcare facilities is given by Coia *et al.*<sup>1</sup>
- Laboratory diagnosis of MRSA is discussed by Brown *et al.*<sup>2</sup>
- Revision of previous interim guidance on the diagnosis and management of infection due to PVL-producing

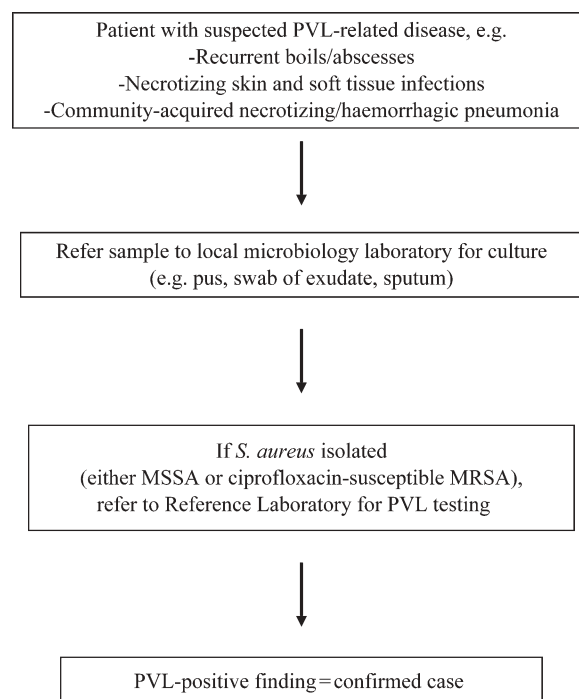


Figure 1. PVL-related disease: microbiology algorithm.

staphylococci is currently undergoing consultation.<sup>3</sup> Whether to decolonize infected patients or screen and decolonize contacts if positive is a key issue that is discussed in the PVL guidance<sup>4</sup> and will not be repeated here. However, the evidence base supporting many of the recommendations related to screening and decolonization is poor and worthy of further investigation.

- Antibiotic treatment of MRSA in general is discussed by Gemmell *et al.*<sup>4</sup> This guidance is currently being revised.

All of these documents can be accessed via the Health Protection Agency (HPA) web site.<sup>5</sup>

## 2. Background and definitions

*S. aureus* is the major bacterial cause of skin, soft tissue and bone infections, and one of the commonest causes of healthcare-associated bacteraemia. About one-quarter of healthy people carry one or more strains asymptotically at any given time and infections are commonly endogenous being caused by the patient's colonizing strain.<sup>6</sup> Antibiotics and surgical drainage are the basis of treatment of staphylococcal infections, but the emergence of multiple resistance to penicillin, methicillin and other agents has compromised therapy. Methicillin resistance was first detected in *S. aureus* in 1961,<sup>7</sup> shortly after the agent was introduced clinically, and over the last four decades, there has been a global epidemic of MRSA.<sup>8,9</sup>

MRSA is usually acquired during exposure to hospitals and other healthcare facilities, and causes a variety of serious healthcare-associated infections. A number of UK and USA guidelines have been produced on the prevention, control,

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diagnosis and treatment of MRSA infections in hospitals and other healthcare facilities.<sup>2,10–12</sup> However, there has been an increase in MRSA infections presenting in the community that has not been properly addressed by existing guidelines.<sup>4</sup>

Many (and in the UK at the present time, most) MRSA infections that appear to have a community onset occur in patients who are found to have had direct or indirect contact with hospitals, care homes or other healthcare facilities.<sup>13,14</sup> These MRSA strains are typical of the local healthcare-associated MRSA (HA-MRSA) and may be carried asymptotically by patients for months after discharge. However, new strains of MRSA have recently emerged that cause infections in community patients who have no previous history of direct or indirect healthcare contact. These strains have been designated CA-MRSA.<sup>15</sup> CA-MRSA strains are genetically and phenotypically distinct from HA-MRSA. They typically resemble some strains of methicillin-susceptible *S. aureus* (MSSA) in being susceptible to a wider range of anti-staphylococcal antibiotics (some are resistant only to  $\beta$ -lactams), and often produce PVL, a toxin that destroys white blood cells and is a staphylococcal virulence factor.<sup>16,17</sup> Differences between CA- and HA-MRSA are summarized in Table 1. PVL-producing strains of CA-MRSA appear to be associated with increased risk of transmission, complications and hospitalization. For example, in one large community outbreak of CA-MRSA, 23% of patients required hospitalization.<sup>18</sup> PVL has a clear role in the pathogenesis of severe necrotizing pneumonia<sup>17,19,20</sup> and is associated with greater pulmonary and bone-related complications. Its role in skin infections is less certain, although PVL is a potent dermatonecrotic toxin.<sup>21</sup>

In the UK, the overall prevalence of *S. aureus* strains that carry the gene for PVL production is believed to be <2%, and these are mainly MSSA.<sup>22</sup> Although the overall prevalence of CA-MRSA is also presently low worldwide (thought to be <0.5% of all MRSA),<sup>23</sup> there is clear evidence that this is

increasing, particularly in the USA, Canada and Australia. In some areas of the USA, a significant proportion of serious *S. aureus* infections presenting in community practice or at accident and emergency departments is now due to CA-MRSA types.<sup>15,24–26</sup> There are also emerging reports of CA-MRSA from Europe, including Scandinavian countries that have, until now, been almost free of HA-MRSA.<sup>27–30</sup> There have been relatively few reports of CA-MRSA from the UK,<sup>31–33</sup> but experience elsewhere suggests that these are likely to increase in the future.

The Department of Health asked the HPA to lead in the production of guidance for PVL-related disease.<sup>3</sup> In 2007, the Specialist Advisory Committee on Antimicrobial Resistance also identified the need to produce some specific guidance around diagnosis and treatment of infections caused by PVL-positive staphylococci. The British Society of Antimicrobial Chemotherapy (BSAC) on the other hand independently wished to consider producing guidance with the broader remit of diagnosis and management of community-onset MRSA including infections acquired in the healthcare setting but which would include PVL-related disease. HPA members with expertise in this area were included in the BSAC Working Party and this guidance recognizes HPA and other related guidance where appropriate. It is hoped that this will raise general awareness about the epidemiology and pathological significance of CA-MRSA. It is hoped that the early implementation of effective diagnosis, management, prevention and control of these new infections will prevent some of the present difficulties with HA-MRSA<sup>34</sup> developing with CA-MRSA.

### 2.1 Definitions

The internationally agreed definitions of HA-MRSA, CA-MRSA and other *S. aureus* strains and their limitations are given below.<sup>35</sup> The definitions were originally based on

**Table 1.** HA-MRSA versus CA-MRSA

Parameter	HA-MRSA	CA-MRSA
Typical patient	elderly, debilitated and/or critically or chronically ill	young, healthy people; students, professional athletes and military service personnel
Infection site	often bacteraemia with no obvious infection focus. Also surgical wounds, open ulcers, IV lines and catheter urines. May cause ventilator associated pneumonia	predilection for skin and soft tissue, producing cellulitis and abscesses. May cause necrotising community acquired pneumonia, septic shock or bone and joint infections
Transmission	within healthcare settings; little spread among household contacts	community-acquired. May spread in families and sports teams
Clinical setting of diagnosis	in an inpatient setting, but increasingly HA-MRSA infections in soft tissue and urine are occurring in primary care	in an outpatient or community setting
Medical history	history of MRSA colonization, infection, recent surgery; admission to a hospital or nursing home, antibiotic use; dialysis, permanent indwelling catheter	no significant medical history or healthcare contact
Virulence of infecting strain	community spread is limited, PVL genes usually absent	community spread occurs easily. PVL genes often present, predisposing to necrotising soft tissue or lung infection
Antibiotic susceptibility	often multiresistant with result that choice of agents often very limited	generally susceptible to more antibiotics than HA-MRSA

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epidemiological features but, for the reasons outlined below, microbiological characteristics are now also important.

### 2.1.1 MRSA (methicillin-resistant *S. aureus*)

Strains of *S. aureus* that are resistant to the isoxazolyl penicillins such as methicillin, oxacillin and flucloxacillin. MRSA are cross-resistant to all currently licensed  $\beta$ -lactam antibiotics.

### 2.1.2 CA-MRSA (community-associated MRSA)

MRSA strains isolated from patients in an outpatient or community setting (community onset), or within 48 h of hospital admission (hospital onset). Patients also typically have no previous history of MRSA infection or colonization, hospitalization, surgery, dialysis or residence in a long-term care facility within the previous year, and absence of indwelling catheters or percutaneous devices at the time of culture (Table 2).

### 2.1.3 HA-MRSA (healthcare-associated MRSA)

MRSA strains that are transmitted to and circulate between individuals who have had contact with healthcare facilities. These infections can present in the hospital or healthcare setting (hospital or healthcare onset) or in the community (community onset), for example after hospital discharge.

However, the boundaries between HA-MRSA and CA-MRSA are becoming blurred due to the movement of patients and infections between hospitals and the community, and to nosocomial outbreaks of CA-MRSA following admission of colonized or infected patients.<sup>36</sup> In the USA, where CA-MRSA is now common, it is becoming increasingly difficult to distinguish between CA- and HA-MRSA on clinical and epidemiological grounds.<sup>37</sup> Since HA-MRSA and CA-MRSA strains are often genotypically and phenotypically different (Table 1), the microbiological characteristics of the *S. aureus* isolates may help distinguish between HA- and CA-infections.

## 3. Guideline remit

This guideline provides recommendations based on evidence obtained from existing guidance on best practice in the

**Table 2.** Populations at increased risk of community-associated MRSA (adapted from references 20, 32–34 and 38)

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#### Risk groups

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Children <2 years old  
Athletes (mainly contact-sport participants)  
Injection drug users  
Men who have sex with men  
Military personnel  
Inmates of correctional facilities, residential homes or shelters  
Vets, pet owners and pig farmers  
Patients with post-flu-like illness and/or severe pneumonia  
Patients with concurrent SSTI  
History of colonization or recent infection with CA-MRSA  
History of antibiotic consumption in the previous year, particularly quinolones or macrolides

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*principles of diagnosis and management* of MRSA infections in the community. Infection prevention guidance is kept to a minimum as other guidance exists in this area. Our guidance covers:

- (1) Patients whose infections were acquired in the hospital but who present in the community (hospital or healthcare-associated and community-onset MRSA infections). This is the commonest MRSA-related community problem in the UK. GPs may expect to encounter this on a daily basis in patients who are chronically ill, elderly, diabetic with open skin lesions, have had recent surgery or in patients who are regular hospital attendees.
- (2) Infections acquired in the community in patients with no hospital contact or other related risk factors. These may present in the community (community-associated and community-onset, for example the skin infection or pneumonia scenarios) or, rarely, in hospital (community-associated and hospital-onset).

Infections due to hospital or healthcare-associated *S. aureus* strains presenting in hospital (hospital-onset and hospital-acquired) are excluded, since they are already covered in disease-specific guidance (e.g. ventilator-associated pneumonia, endocarditis, surgical site infection). The guidance on antimicrobial treatment and prophylaxis of MRSA infections produced by the Joint Working Party of the BSAC, the Hospital Infection Society and the Infection Control Nurses Association<sup>4</sup> is due to be updated in 2008.

The Working Party recognizes that in the UK, PVL toxin-producing staphylococci are presently uncommon and when they cause infection they are more frequently MSSA. Interim guidance for the diagnosis and management of PVL-associated *S. aureus* infections in the UK has been published by a group convened by the HPA.<sup>3</sup> However, in light of the global emergence of severe infections and outbreaks due to PVL-producing CA-MRSA,<sup>38</sup> infections with PVL-producing MRSA in the UK are likely to increase.

## 4. Guideline development and methodology

The Working Party was convened under the auspices of the BSAC and comprised microbiologists, an infectious disease physician and public health physicians, all of whom had an interest in MRSA infections and had previous experience in guideline development. Advice regarding guideline format and content from a GP and nurse were sought prior to guideline development.

**The Working Party adopted a ‘common clinical scenario’ approach to the diagnosis and recognition of these infections which they hope will be useful for the community practitioner and broader healthcare team.** The evidence base for the guidance in these scenarios has been provided by a systematic appraisal of existing guidelines or consensus documents using the approach developed by the ADAPTE Group.<sup>39</sup> This adaptation process involves six steps: (1) searching for existing guidelines; (2) assessment of guideline quality; (3) assessment of applicability and adaptation of recommendations to target setting; (4) literature update; (5) adaptation of guideline format;



and (6) implementation. We felt that this was more appropriate than a new systematic literature review, since recent guidelines from Canada<sup>40</sup> included a thorough systematic review of much of the relevant CA-MRSA literature. Furthermore, other guidance on community-onset healthcare-acquired MRSA exists but is not presented in the context of 'a community onset' infection.

The levels of evidence and the strength of recommendations were categorized using the Scottish Intercollegiate Guidelines Network (SIGN) evidence statements and grades of recommendations (SIGN Guideline 50—a guideline developers' handbook at [www.sign.ac.uk](http://www.sign.ac.uk)), the details of which are shown in Tables S1 and S2 [Supplementary data available at *JAC* Online (<http://jac.oxfordjournals.org/>)]. On occasion, guideline development groups find that there is an important practical point that they wish to emphasize but for which there is not, nor is there likely to be, any research evidence. This will typically be where some aspect of treatment is regarded as being of such sound clinical practice that nobody is likely to question it. These are marked in the guideline as *Good Practice Points*, and are indicated by the acronym 'GPP'. It must be emphasized that these are not an alternative to evidence-based recommendations and have only been used where there was no alternative means of highlighting the issue.

An English language only literature search was undertaken for existing guidance related to clinical presentation, diagnosis and treatment of CA-MRSA infection with particular reference to SSTIs and pneumonia. We searched Medline and Google/Google Scholar as well as the various guideline databases with the following keywords: 'community-acquired or -onset *S. aureus*', 'Panton-Valentine Leucocidin' and 'methicillin-resistant *S. aureus*'. The following guideline databases were searched in detail: Guideline International Network, National Institute for Health and Clinical Excellence, National Guideline Clearing, SIGN, as well as a recent Canadian guideline.<sup>40</sup> This was deemed sufficiently important to be worthy of more detailed appraisal using the AGREE instrument.<sup>41</sup> The scope and purpose of the Canadian guideline, stakeholder involvement, clarity and presentation were judged to be of good quality, although the guideline provided few support tools for its application. However, the rigour of development was judged moderate to poor because there was no consistent explicit linking of the evidence to the recommendation, no tables of evidence, no supporting evidence for many recommendations, references were often missing and there were no details of how consensus statements were developed for many of the statements. The basis for the Canadian guidelines' recommendations and strength of evidence was less explicit than with the SIGN methodology and more generous in making high-level or strong recommendations based on grade 3 evidence (such as expert opinion, case studies and so on). Other weaknesses include failure to identify the applicability of the guideline to an organization or healthcare system, no appreciation or mention of potential cost implications of the guideline and no criteria for monitoring quality improvement. The guideline group appeared to have editorial independence although there were no conflict of interest statements. We have attempted to address some of these weaknesses in the present guidance.

The other documents looked at included other published reviews of the subject.<sup>15,42</sup> Zetola *et al.*<sup>15</sup> were particularly thorough in defining search strategy and selection criteria, and included papers in Spanish. There were also statements from

governmental and regional expert groups.<sup>43,44</sup> Although none of these documents gave evidence of a systematic process of producing evidence-based recommendations, they provided useful information for some areas of our guidance. Most of our recommendations based on existing guidance, primarily the Canadian guidelines, were SIGN grade D and arose from evidence in non-controlled studies and expert opinion. Only in a few cases did evidence come from the results of case-control or cohort studies, reflecting the evolving nature of the disease. In many areas, our recommendations are simply recommendations for good medical practice and reflect the experience and opinions of the Working Party.

The Working Party assessed all the contributions and agreed on the key recommendations before submitting the draft for external peer review. Changes suggested by the external review were incorporated before finalizing its adoption, endorsement and implementation. The BSAC agreed that this guideline would be developed in close collaboration and consultation with a Working Group of the HPA which was revising guidance on PVL-associated staphylococcal infections in England. Other stakeholders are the Royal College of Nursing, the Infection Prevention Society (formerly the Infection Control Nurses Association), the Hospital Infection Society, the British Infection Society, the Royal College of General Practitioners, the Royal College of Physicians, the Royal College of Surgeons, the College of Emergency Medicine, the Royal College of Paediatricians and the UK Pharmacy Association.

## 5. General principles of diagnosis and management

### 5.1 Clinical assessment

When presented with a patient in the community who the clinician thinks may have a staphylococcal infection, the decision-making process related to diagnosis and treatment includes answering the following questions:

- (1) What is the severity of illness?
- (2) Is distinction between MSSA or MRSA infection possible?
- (3) If MRSA is suspected, is it likely to be CA-MRSA or HA-MRSA?
- (4) Should further microbiological assessment/investigation be undertaken and, if so, how?
- (5) Does empirical antibiotic therapy (or definitive therapy if microbiology results are available) need to be started?
- (6) Does adjunct therapy (for example surgical drainage) need to be considered?
- (7) Does the patient need to be admitted to hospital?
- (8) What advice should be given to direct contacts and household members?

This clinical risk-assessment is detailed for each of the 'typical' clinical scenarios below. Many factors in these risk-assessments are similar for all the scenarios, including distinguishing between CA-MRSA and HA-MRSA strains (Table 1) and risk factors for CA-MRSA based on clinical, epidemiological, laboratory and treatment factors (Tables 1 and 2). The predictive value of these risk factors for distinguishing between different strains, healthcare associated as opposed to

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community associated, is poor. Nevertheless, the scenarios presented provide guidance for best practice.

### 5.2 Laboratory investigation

Because of the changing epidemiology of community-onset MRSA and the need to optimize antibiotic therapy, clinical samples should be sent for microbiological testing.

#### 5.2.1 Clinical samples

Appropriate clinical samples (e.g. pus, swabs from lesions, sputa etc.) from suspected cases should be submitted to the local microbiology department for analysis. Accident and emergency staff, GPs and other healthcare practitioners should be alerted to the importance of taking specimens when incising and draining abscesses. Samples should be cultured on non-selective media (e.g. blood agar) for the recovery of potential pathogens, including *S. aureus*.

#### 5.2.2 Testing for PVL

Genes encoding PVL may be carried by both MSSA and MRSA. PVL-positive MSSA display variable antimicrobial susceptibility profiles, whereas the majority of PVL-positive MRSA currently found in the UK are susceptible to ciprofloxacin.<sup>45</sup> *S. aureus* (MSSA or ciprofloxacin-susceptible MRSA) recovered from suspected cases should be referred to the HPA Staphylococcus Reference Laboratory for toxin gene profiling including PVL testing. This is a PCR-based assay that can be completed within a working day. Figure 1 is a suggested algorithm.

#### 5.2.3 Antimicrobial susceptibility testing

This should be performed by the laboratory's routine methods. However, if the organism is erythromycin-resistant by disc testing, inducible clindamycin resistance should be tested for by the D-zone test, which involves placement of erythromycin and clindamycin discs in close proximity on an agar plate inoculated with a standardized suspension of the isolate. Flattening of the clindamycin zone of inhibition in the area between the two discs (resulting in a D-shaped zone of inhibition) indicates the presence of inducible clindamycin resistance in the presence of erythromycin resistance (positive D-zone test).

## 6. Clinical case scenarios

In the following section, three case scenarios are presented. The key questions related to clinical assessment are presented and guidance in the form of **recommendations** (in bold) are provided. Additional guidance is provided on isolation of MRSA in the urine.

### 6.1 Community-associated and community-onset MRSA skin and soft tissue infection

*A 14-year-old school boy with a skin infection is brought by his mother to their GP. He is not systemically unwell but has a red, tender, fluctuant discharging skin lesion over his thigh. There is*

*a moderate amount of surrounding erythema. It has not responded to topical antiseptic cream. He gives a history of three previous 'skin infections' over the last year, treated with several courses of oral antibiotics. The current infection appears to have been precipitated by a 'minor' injury to his thigh during football at school.*

#### 6.1.1 What is the likely clinical diagnosis?

The clinical diagnosis of an SSTI presenting as an abscess is straightforward. Pain, tenderness, erythema and swelling are common in SSTIs and offer around a 93% to 97% sensitivity (95% CI 83–100) in the clinical diagnosis of cellulites.<sup>46</sup> The most likely microbial cause of this is *S. aureus*, although pyogenic streptococci (e.g.  $\beta$ -haemolytic streptococci such as *Streptococcus pyogenes*, and group C or G streptococci) are other possibilities.

#### 6.1.2 When to suspect PVL+ CA-MRSA (currently rare)

**6.1.2.1 Clinical presentation.** The spectrum of disease caused by CA-MRSA appears to be similar to that caused by CA-MSSA. Furuncles (abscesses in hair follicles, or 'boils'), carbuncles (coalesced masses of furuncles with deeper tissue involvement) and other abscesses appear to be the most frequently reported clinical manifestations. They may or may not have accompanying cellulitis. Erythematous papules and nodules, folliculitis and/or impetigo are less common presentations.

One specific presentation appears to be typical of cutaneous CA-MRSA infections. This is the spontaneous appearance of a raised tender red lesion, which may progress to develop a necrotic centre. This may lead to the suspicion of a 'spider bite' where such occurrences are common, e.g. North America or Australia. Most reports of such lesions have come from the USA and have not been as frequently reported from other countries. In the UK, where spider bites are rare, these 'dermatonecrotic' lesions increase the likelihood of a diagnosis of CA-MRSA but are not pathognomic. They can also be found in infections due to PVL-positive MSSA strains.

#### Recommendation 1

- **If 'spider bite' lesions are present, the possibility of CA-MRSA or PVL-positive MSSA infection should be considered and appropriate investigation and management instituted. [D<sup>3</sup>].**

Many other severe cutaneous complications of CA-MRSA have been reported and include extensive cellulitis, necrotizing fasciitis and purpura fulminans.<sup>47</sup> Involvement of adjacent structures, either by direct spread or bacteraemia, such as septic thrombophlebitis, pyomyositis, septic arthritis and osteomyelitis, has all been described.<sup>15,40,42</sup> No particular patterns of clinical presentation have yet emerged to allow differentiation from MSSA infections.

Anecdotal reports suggest that recurrent (two or more in 6 months) furuncles or abscesses, or clusters of infections within a household may indicate PVL-positive CA-MRSA. [D<sup>3</sup>]. However, this pattern can also be seen in PVL-positive MSSA infections.

**Recommendation 2**

- **If there is a history of recurrent abscesses or household clusters of infection, the possibility of CA-MRSA or PVL-positive MSSA infection should be considered and appropriate investigation and management instituted. [D<sup>3</sup>].**

*6.1.2.2 Treatment factors.* In the absence of an undrained abscess or focus of infection, a poor response to existing therapy (which in most cases will be an isoxazole penicillin such as flucloxacillin) increases the likelihood of CA-MRSA infection [D<sup>3</sup>].

**Recommendation 3**

- **If there has been a prior poor response to  $\beta$ -lactam therapy, the possibility of CA-MRSA or PVL-positive MSSA infection should be considered and appropriate investigation and management instituted. [D<sup>3</sup>].**

Exposure to one or more antibiotics in the past year (as opposed to no use) and use of quinolones or macrolides are potential treatment-related risk factors for CA-MRSA infection. [D<sup>2</sup>].

In a large English case-control study, there was a significant relationship between exposure to increasing numbers of antibiotics and diagnosis of CA-MRSA. This paper made no distinction related to the PVL status of these organisms. For exposure to 1, 2–3 or  $\geq 4$  antibiotics in the previous year, the odds ratios (ORs) were, respectively, 1.57 (CI 1.36–1.80), 2.46 (CI 2.15–2.83) and 6.24 (CI 5.43–7.17). Receipt of quinolones [OR 3.37 (CI 2.80–4.09)] and macrolides [OR 2.50 (CI 2.14–2.91)] in the previous year was specific associations.<sup>48</sup> However, it is not clear in this study whether these cases were due to PVL-positive or -negative strains of *S. aureus*. In another large prospective study of adult patients in the USA with SSTIs presenting to the emergency department, results of a multi-regression analyses showed that use of an antibiotic in the past month (as opposed to no use) had a 2.4-fold (95% CI 1.4–4.3) greater risk of infection with CA-MRSA.<sup>24</sup>

**Recommendation 4**

- **If there is a history of exposure to one or more antibiotics in the past year, especially quinolones or macrolides, the possibility of CA-MRSA infection should be considered and appropriate investigation and management instituted. [D<sup>2</sup>].**

*6.1.2.3 Other risk factors.* A recent prospective USA cohort study found that clinical and epidemiological risk factors in persons hospitalized for CA-MRSA infection cannot distinguish reliably between MRSA and MSSA.<sup>37</sup> Indeed, in this study, *post hoc* modelling revealed that in a country where the prevalence of MRSA in the community is <10%, as is presently the case in the UK, patients lacking the three strongest risk factors would only have a 7% post-test probability of MRSA. In another prospective prevalence study of MRSA infections among patients in the emergency department, the presence or absence of these clinical and epidemiological risk factors was not useful in guiding decisions about the use of antibiotic therapy. Most patients without MRSA had at least one of these risk factors,

and almost half of those without any of these factors were found to have MRSA.<sup>24</sup>

CA-MRSA has been linked to the specific risk factors outlined in Table 2. However, the value of these risk factors in differentiating between MRSA and MSSA and predicting successful antimicrobial therapy is uncertain and currently should not be relied upon. [C<sup>2-</sup>]. In UK practice, many of these risk factors are probably not relevant, except for (1) history of travel to an endemic area such as North America and (2) recent colonization or contact with CA-MRSA.

**Recommendation 5**

- **If any of the risk factors outlined in Table 2 are present, especially recent travel to an endemic area such as North America and recent colonization or contact with CA-MRSA, the possibility of CA-MRSA infection should be considered and appropriate investigation and management instituted. [C<sup>2-</sup>].**

*6.1.2.4 Prevalence of CA-MRSA.* The threshold where the prevalence of CA-MRSA in the community becomes an important consideration in determining the choice of initial empirical antibiotic therapy is uncertain. In the UK, the prevalence of CA-MRSA infection is very low or unknown. Although there is evidence of emerging PVL-related infection in certain parts of the country, prevalence of infection or colonization on its own currently cannot be regarded as a reliable indicator of the likelihood of MRSA infection in an individual patient and therefore is not a guide to antibiotic choice. [GPP].

**Recommendation 6**

- **Because the prevalence of CA-MRSA in the UK is presently very low, suspected community staphylococcal infections should not be treated as if they were CA-MRSA in the absence of significant specific risk factors. This is an evolving situation and the local prevalence of CA-MRSA should be monitored and advice modified as necessary.**

*6.1.3 When should specimens be sent for culture?*

**Recommendation 7**

- **Cultures should be taken from septic sites if:**

- (1) **CA-MRSA is suspected because of the risk assessment based on clinical presentation, treatment factors and other risk factors outlined in Tables 1 and 2. [D<sup>3</sup>].**
- (2) **There are recurrent furuncles or abscesses (two or more in 6 months). [D<sup>3</sup>].**
- (3) **There is a history of spread in the family or to others, e.g. sporting contacts (the information may be available from the public health/infection control team). [D<sup>4</sup>].**
- (4) **If there is severe infection (extensive or progressive disease with evidence of systemic sepsis), the patient should be hospitalized and a skin/abscess culture and blood culture should be taken. [GPP].**



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Cultures will determine the prevalence of these infections in a particular setting or community and will allow appropriate rationalization of antibiotic treatment.

### 6.1.4 When should specimens for culture not be taken?

#### Recommendation 8

- **Do not take cultures routinely from patients presenting with minor SSTIs and without a history of previous MRSA. [D<sup>4</sup>].**
- **Do not routinely aspirate material for culture from cellulitis in the absence of discharge or broken skin. [GPP].**

### 6.1.5 Treatment principles

#### Recommendation 9A

- **Do not give systemic antibiotics to patients with minor SSTIs or small abscesses (<5 cm). [D<sup>3</sup>].**
- **Incise and drain small abscesses without cellulitis and do not give antibiotic therapy. [A<sup>1-</sup>].**
- **After incision and drainage start empirical or culture-guided systemic antibiotic therapy for larger abscesses or if there are infections in other family members. [D<sup>3</sup>].**

#### Recommendation 9B

- **Guidance regarding topical antibiotic treatment, decolonization and screening is beyond the remit of this guideline although the group recommend that existing evidence for need and effectiveness is poor. For further information, refer to guidance provided by the HPA.<sup>3</sup>**

A recent randomized controlled trial, in a single centre with large numbers of injecting drug users, compared treatment with cefalexin, which lacks activity against MRSA, with placebo in 166 adult patients who had surgically drained abscesses. Although MRSA was isolated from most patients, more than 85% of patients in both arms were cured without the need for additional therapy at a 1 week follow-up visit, suggesting that most of these infections resolve without antimicrobial therapy.<sup>49</sup> Another prospective study of otherwise healthy children with skin and soft tissue abscesses concluded that incision and drainage of CA-MRSA abscesses with a diameter of less than a 5 cm without antibiotics was adequate.<sup>50</sup> However, these findings should be balanced by reports of recurrence or worsening of infections not treated with systemic antibiotics effective against MRSA.<sup>51</sup>

#### Recommendation 9C

- **In compromised patients or those with severe disease, give systemic antibiotic therapy based on clinical assessment and local susceptibilities of strains while awaiting definitive susceptibility results. [GPP].**
- **Ensure that empirical treatment also provides cover against *S. pyogenes*. [GPP]. Oral flucloxacillin and clindamycin have activity against *S. pyogenes*, whereas tetracycline and trimethoprim often do not.**

### 6.1.6 Empirical antibiotic therapy

There is conflicting evidence that inappropriate empirical therapy for SSTIs at the time of initial clinical presentation leads to an inferior outcome. Four studies<sup>18,24,50,51</sup> compared susceptibility of the pathogen to the prescribed antimicrobial agent with clinical outcome. The patients involved mainly had abscesses. There was no difference in outcomes, suggesting that these infections, even when caused by MRSA, can be cured with drainage only. However, in one recent retrospective analysis of the impact of antimicrobial therapy on outcome for uncomplicated community-onset SSTIs, there was a small but significant (OR 2.80; 95% CI 1.26–6.22;  $P = 0.01$ ) increase in treatment failures (defined as worsening of signs of infection, requiring additional incision and drainage, subsequent hospital admission, microbiological failure or new culture proven lesions during antimicrobial therapy), in those who received initial therapy with agents ineffective *in vitro*.<sup>52</sup> Use of ineffective agents was the only independent predictor of treatment failure in multivariate analysis.

The discrepancy between the results in this study and those of previous reports could be due to a variety of reasons. They include: the larger size of the study population,<sup>52</sup> which may be more likely to detect a true difference in outcome compared with smaller studies; different patient populations, such as adults from one healthcare system compared with children from another; and differences in underlying health status.<sup>53</sup> Furthermore, since most of these patients had non-life-threatening cutaneous infections, it is difficult to extrapolate these data to more severe infections. Additional support for empirical therapy that is active against the isolated pathogen comes from a retrospective chart review of 399 sequential, culture-confirmed community-onset *S. aureus* SSTIs, of which 227 were due to MRSA. Use of an effective agent in empirical therapy was associated with an increased odds ratio [OR 5.91 (95% CI 3.14–11.13)] of clinical resolution when controlled for incision, drainage and HIV status.<sup>54</sup> This study confirmed the effectiveness of trimethoprim/sulfamethoxazole as the empirical therapy in this setting. A further prospective randomized trial of empirical therapy of trimethoprim/sulfamethoxazole or doxycycline for outpatient SSTIs in an area of high MRSA prevalence showed the equivalent effectiveness of either therapy, although the treatment failure rates were 9% in the trimethoprim/sulfamethoxazole arm compared with none in the other.<sup>55</sup>

**Epidemiological profiling of CA-MRSA strains in England and Wales over a 2 year period 2004–05 suggests that all were susceptible to clindamycin, trimethoprim, vancomycin, linezolid and mupirocin.<sup>56</sup>**

CA-MRSA strains that are erythromycin-resistant (by possession of the *erm* gene) and are initially susceptible to clindamycin can potentially develop resistance to clindamycin during therapy. The global reported rates of such inducible resistance vary from 2% to 94%. A double disc diffusion test (D-test) can be used to determine whether clindamycin-susceptible CA-MRSA strains harbour inducible resistance.<sup>57</sup> The local laboratory should perform a D-test.

In severe infections with features of toxic shock or necrotizing fasciitis, there is a theoretical case for using two or three agents such as linezolid combined with clindamycin and rifampicin. This is based on *in vitro* synergy<sup>58</sup> and the ability of linezolid and clindamycin to inhibit toxin production.<sup>58,59</sup> [GPP]. A D-test should be performed if clindamycin is used. Existing



MRSA treatment guidance does not recommend three agents but rather linezolid with rifampicin as initial therapy.<sup>4</sup>

### Recommendation 10

- Because of the absence of evidence of rising prevalence of CA-MRSA in the UK and the lack of unequivocal evidence that inappropriate antimicrobial therapy alters outcome, there is no need to change existing empirical therapy recommendations (below) for non-severe presumed *S. aureus* infections. [C<sup>3</sup>].
- In the UK, the recommended community treatment for suspected MSSA infections is oral flucloxacillin 500–1000 mg 6 hourly (or oral clindamycin 300–450 mg 6 hourly in penicillin allergic patients); 5–7 days of treatment is normally sufficient.
- If the patient is known to be MRSA-positive OR lesion cultures yield MRSA alone, then community treatment should be either oral doxycycline (contra-indicated in children <12 years) 100 mg 12 hourly, or fusidic acid 500 mg 8 hourly, or trimethoprim 200 mg 12 hourly, each combined with rifampicin 300 mg 12 hourly (see Appendix). Fusidic acid and rifampicin should NOT be used as monotherapy because of the danger of resistance emergence. All these agents can be used in penicillin allergic patients.
- Trimethoprim (combined with sulfamethoxazole) or doxycycline without rifampicin is also effective for ambulatory therapy of MRSA SSTIs.<sup>51</sup> [A1<sup>+</sup>]. Oral linezolid 600 mg twice daily is an alternative option for use ‘under expert guidance’, but because of its high cost it should be reserved for patients who are not able to take or tolerate the above regimens. Linezolid may not be readily available in primary care pharmacies.
- If Group A streptococcal (GAS) infection is suspected, oral therapy should include an agent active against this organism (β-lactam or clindamycin).
- For severe infections with known or suspected CA-MRSA, start treatment in hospital with parenteral vancomycin, teicoplanin, daptomycin (but not for pneumonia) or linezolid. Tigecycline may also offer broader polymicrobial cover if required. There is no evidence that one agent is superior to another. [GPP].
- In severe infections with features of toxic shock or necrotizing fasciitis, there is a theoretical case for using two or three agents such as linezolid combined with clindamycin and rifampicin.

More detailed guidance in this area is available.<sup>4</sup> A good example of a care pathway for SSTIs has recently been published from Washington, USA (<http://www.metrokc.gov/health/providers/epidemiology/MRSA-guidelines.pdf>).

### 6.2 Community-associated and community-onset pneumonia suspected to be due to PVL-producing MRSA (this would apply to PVL-producing MSSA also)

A 37-year-old mother of two young children is admitted to hospital very unwell with a 48 h history of pleuritic chest pain, cough with frank haemoptysis and increasing shortness of

breath. Nobody else in the family has been unwell. She was previously healthy, but had a flu-like illness 5 days prior to her rapid deterioration. She had been given amoxicillin the previous day by her GP. She is admitted to hospital with the working diagnosis of community-acquired pneumonia (CAP). Her temperature is 39.5°C, respiratory rate is 40/min, white cell count is  $3.7 \times 10^9/L$  and C-reactive protein (CRP) 360 mg/L. Chest X-ray reveals some increased shadowing in both lungs, with fluffy opacities.

#### 6.2.1 What is the likely clinical diagnosis?

This clinical diagnosis is of a community-acquired lower respiratory tract infection, with the unusual feature of severe haemoptysis. Severe CAP with haemoptysis following a flu-like illness could also indicate primary influenza pneumonia, although the absence of family members with flu-like symptoms is against this. The most likely microbial cause of the pneumonia is bacterial and *S. aureus* should be considered as a potential pathogen because of the combination of high CRP and low white cell count in a young patient with haemoptysis. *Streptococcus pneumoniae* and *S. pyogenes* may also present with a similar picture. The fact that she has worsened on amoxicillin therapy also supports a diagnosis of staphylococcal rather than streptococcal pneumonia. Pulmonary embolus is unlikely because the features of sepsis predominate, but this should be excluded if in doubt.

#### 6.2.2 When to suspect CA-MRSA

6.2.2.1 *Clinical presentation.* There is nothing in this history to suggest infection with CA-MRSA rather than with CA-MSSA. There are features, however, consistent with PVL-associated staphylococcal disease, including haemoptysis, high respiratory rate and a low white cell count (leucopenia) in the presence of a high CRP and systemic sepsis in a previously healthy individual.<sup>20,60</sup> The presence of blood in sputum should alert the clinician to the possibility of PVL production. Assessing the severity of pneumonia in children or young adults should not include age-dependent scoring systems such as CURB-65 as the score will be misleadingly low.

### Recommendation 11

- Consider a diagnosis of lower respiratory tract infection caused by PVL-producing *S. aureus* in rapidly progressive pneumonia evolving into acute respiratory distress syndrome. A fever of >39°C, respiratory rate of >40 breaths per minute, a tachycardia of >140 beats per minute with haemoptysis and hypotension make the diagnosis likely. The presence of significant haemoptysis and hypotension usually confirms the diagnosis. [C<sup>2+</sup>].

Additional questions should be asked to elicit whether any family members have a history of skin sepsis, any contact with healthcare facilities or are known MRSA carriers.

### Recommendation 12

- Although relatively few patients developing necrotizing pneumonia due to CA-MRSA have a previous history of skin sepsis themselves,<sup>60–64</sup> consider the possibility of CA-MRSA infection if there is a history of recurrent (two or more in 6 months) furuncles or abscesses in

## Review

family members or clustering of infections within the household. [D<sup>3</sup>].

6.2.2.2 *Treatment factors.* Use of any antibiotic in the past month (versus no use) has been identified as a potential treatment-related risk factor for CA-MRSA SSTI. [D<sup>2</sup>]. However, there are no such data for CA-MRSA pneumonia.

### Recommendation 13

**Until further evidence is available, do not discount the possibility of CA-MRSA infection in severe pneumonia on the basis of a lack of history of recent antibiotic therapy.**

6.2.2.3 *Other risk factors.*

### Recommendation 14

- **If any of the risk factors outlined in Table 2 are present, especially (in the UK) recent travel to an endemic area such as North America and recent colonization or contact with CA-MRSA, the possibility of CA-MRSA infection should be considered and appropriate investigation and management instituted. [C<sup>2-</sup>].**

6.2.2.4 *Prevalence of CA-MRSA.* The threshold where the prevalence of CA-MRSA in the community becomes an important consideration in determining the choice of empirical antibiotic therapy is uncertain. In the UK, the prevalence of this infection is very low or unknown. Therefore, local variations in prevalence currently have very little influence on the likelihood of an individual patient having CA-MRSA infection.

### Recommendation 15

- **Consider the possibility of CA-MRSA infection in severe community pneumonia regardless of the local prevalence of CA-MRSA. [GPP].**

### Clinical Practice Point

*In this patient, the absence of previous recurrent infections does not lessen the probability that the infection is due to PVL-producing *S. aureus*. Previous exposure to antibiotics has been recognized as a potential risk factor for HA-MRSA but is not yet identified clearly as a risk for CA-MRSA.<sup>65</sup>*

6.2.3 *When should specimens be sent for culture?*

### Recommendation 16

- **Gram's stain and culture should be performed immediately on admission. The Gram stain result may point to the identity of the likely infecting organism. Relative paucity of neutrophils in the Gram stain in a patient with advanced pneumonia, severe haemoptysis and a low white count is supportive of PVL-associated staphylococcal pneumonia. [GPP].**
- **The 2004 update of the British Thoracic Society (BTS) guidelines recommends taking blood cultures from patients with severe CAP preferably before antibiotic therapy is commenced in patients with a severity**

**CURB-65 score of three or above. However, if a diagnosis of CAP has been definitely confirmed, and a patient has no severity indicators or co-morbid disease, then blood cultures may be omitted. [A<sup>-</sup>].<sup>66</sup>**

Taking cultures will help to estimate the prevalence of CA-MRSA and rationalize antibiotic treatment. Fewer than 25% of patients with CA-MRSA pneumonia have had positive blood cultures.<sup>64,67-76</sup>

6.2.4 *Radiological investigation*

Multilobular alveolar infiltrates are still usual in pneumonia due to PVL-producing staphylococci. Compared with pneumonia due to HA-MRSA, they are more likely to cavitate and produce effusions.<sup>61</sup> However, more commonly, acute PVL-related infections produce initially few, if any, chest X-ray changes, leading clinicians to misdiagnose infections as simple exacerbations of bronchitis or asthma.<sup>77,78</sup> Radiological changes develop rapidly, with single or multiple opacities <3 cm diameter being suggestive of staphylococcal infection. Cavitation may appear on serial X-rays and may be detected earlier with ultrasound. However, computed tomography (CT) scanning or magnetic resonance imaging allows the best evaluation of the ongoing pathology, particularly with cystic changes.<sup>74,79</sup> The classical multilobular infiltrates and diffuse multilobar opacities followed by cavity formation may develop after only a few days and are best confirmed with CT.<sup>80,81</sup> Overall, the incidence of complicated pneumonia caused by PVL-producing *S. aureus* is far higher than with non-PVL-producing strains.

### Recommendation 17

- **Consider the possibility of PVL-producing CA-MRSA pneumonia if there are suggestive chest radiological features such as multilobular alveolar infiltrates, cavitation and pleural effusions. [D<sup>3</sup>].**

6.2.5 *Treatment principles*

Owing to the small numbers of cases reported, there is not yet clear evidence that early appropriate antibiotic therapy will improve outcomes in PVL-producing staphylococcal pneumonia. However, with an expected mortality approaching 75%,<sup>60,82</sup> and in line with data from other types of CAP, hospital-acquired pneumonia, ventilator-associated pneumonia and severe sepsis, early intensive care support and appropriate antimicrobial therapy are essential.

### Recommendation 18

- **Refer patients with suspected CA-MRSA pneumonia to intensive care as soon as possible. Basic principles of resuscitation should be followed and ventilatory support implemented when clinically necessary. [GPP].**
- **Pending antibiotic susceptibility results implement empirical antibiotic therapy that covers CA-MRSA as soon as possible. [GPP].**

6.2.6 *Empirical antibiotic therapy*

According to the BTS guidance,<sup>66</sup> patients with severe CAP should receive antibiotics (co-amoxiclav or cefuroxime or

cefotaxime plus a macrolide) within 2 h of hospital admission. [C]. Many current hospital antibiotic policies recommend avoiding cephalosporin use because of the association between these antibiotics and *Clostridium difficile* colitis. The Working Party recommends that the CURB-65 severity scoring tool for CAP should not be applied to young people or children who initially may appear to only have a mild respiratory illness. [GPP].

Unsuspected MRSA caused fatal pneumonia in four Minnesotan children who were initially treated empirically with cephalosporins.<sup>61</sup> Conventional doses of vancomycin may produce inadequate lung concentrations for MRSA infection and, despite high trough serum levels, breakthrough continuous bacteraemia has been reported days into glycopeptide therapy.<sup>79,82</sup>

Antimicrobials effective against MRSA that also decrease exotoxin production, such as clindamycin and linezolid, are theoretically desirable. Clindamycin decreases production of toxic shock syndrome toxin 1 by 95% in stationary-phase cultures<sup>83</sup> and stops the normal peak of  $\alpha$ -toxin production during the late exponential phase of growth.<sup>59</sup> Clindamycin and linezolid both markedly suppress PVL production as staphylococci approach stationary phase and there may be no PVL detectable 12 h after starting treatment.<sup>59</sup> Flucloxacillin is bactericidal, but the low subinhibitory concentrations achievable *in vivo* in necrotic tissue may further augment PVL toxin and  $\alpha$ -haemolysin production.<sup>59</sup> Subinhibitory concentrations of clindamycin, linezolid and fusidic acid all induce a concentration-dependent decrease of PVL concentration, whereas with low concentrations of oxacillin, the concentration of PVL increases up to 3-fold.<sup>84</sup>

Various combinations of vancomycin, clindamycin, linezolid, rifampicin and co-trimoxazole have been used in differing doses and combinations in PVL pneumonia cases, with varying degrees of success.<sup>20,79,82–85</sup> Linezolid treatment successes have been reported by several authors.<sup>79–81,86–88</sup> Three of four patients with necrotizing pneumonia clinically failing vancomycin therapy responded to a change to linezolid and rifampicin.<sup>79</sup> Decreased vancomycin susceptibility discouraged the use of vancomycin in two cases.<sup>63,81</sup> A PVL-positive USA300 MRSA strain for which the vancomycin MIC was 2–4 mg/L responded to a combination of linezolid, teicoplanin and rifampicin, although the infected patient was hospitalized for 6 weeks.<sup>81</sup>

Predicting the susceptibility of staphylococci is becoming increasingly difficult and depends largely on the geographical location and clonality of the circulating strains. Most isolates of strain USA300 are resistant only to  $\beta$ -lactams and macrolides, but recently mupirocin, tetracycline, clindamycin and fluoroquinolone resistances have been reported.<sup>89</sup> Twelve of 123 isolates examined contained *tetK* and *ermC* genes, but remained susceptible to doxycycline and minocycline. *S. aureus* isolates resistant to erythromycin but sensitive to clindamycin must be 'D-tested' to exclude inducible clindamycin resistance. Combining clindamycin with linezolid is synergistic *in vitro*.<sup>58</sup> In the UK, pneumonia due to clindamycin-resistant CA-MRSA has not been reported so far and the majority of CA-MRSA are PVL-negative (Angela Kearns, Laboratory of Healthcare-Associated Infection, HPA, personal communication).

Although there is as yet no unequivocal clinical evidence to support the combination of linezolid (intravenous, 600 mg 12 hourly) plus clindamycin (intravenous, 1.2–1.8 g 6 hourly), because of the life-threatening nature of this disease, the

Working Party recommends that consideration be given to using this combination for initial therapy.<sup>90</sup> The combination can be started empirically in a patient with the clinical features listed above AND Gram-positive cocci in clusters in respiratory secretions. Some experts suggest adding rifampicin 600 mg twice daily, based on synergistic activity and intracellular clearance of staphylococci.<sup>91</sup> The potential role of tigecycline (a glycylcycline) or tetracyclines in severe necrotizing PVL-associated pneumonia is as yet unclear and daptomycin is not indicated as it is inactivated by lung surfactant.<sup>92</sup>

### Recommendation 19

- **The CURB-65 severity scoring tool for CAP should not be applied to young people or children who initially may appear to only have a mild respiratory illness. [GPP].**
- **If a risk assessment suggests the possibility of CA-MRSA, then empirical therapy for CAP should include cover for CA-MRSA. Consider adding linezolid 600 mg 12 hourly and high dose clindamycin 1.2–1.8 g 6 hourly. If the organism is isolated, check that it is susceptible to clindamycin and the D-test is negative. [GPP]. Some authors have also suggested the routine addition of rifampicin 600 mg twice daily if PVL-positive staphylococcal pneumonia is suspected.<sup>3,90</sup> [GPP]. The roles of ceftobiprole (a cephalosporin with anti-MRSA properties) and tigecycline in this setting have yet to be determined.**

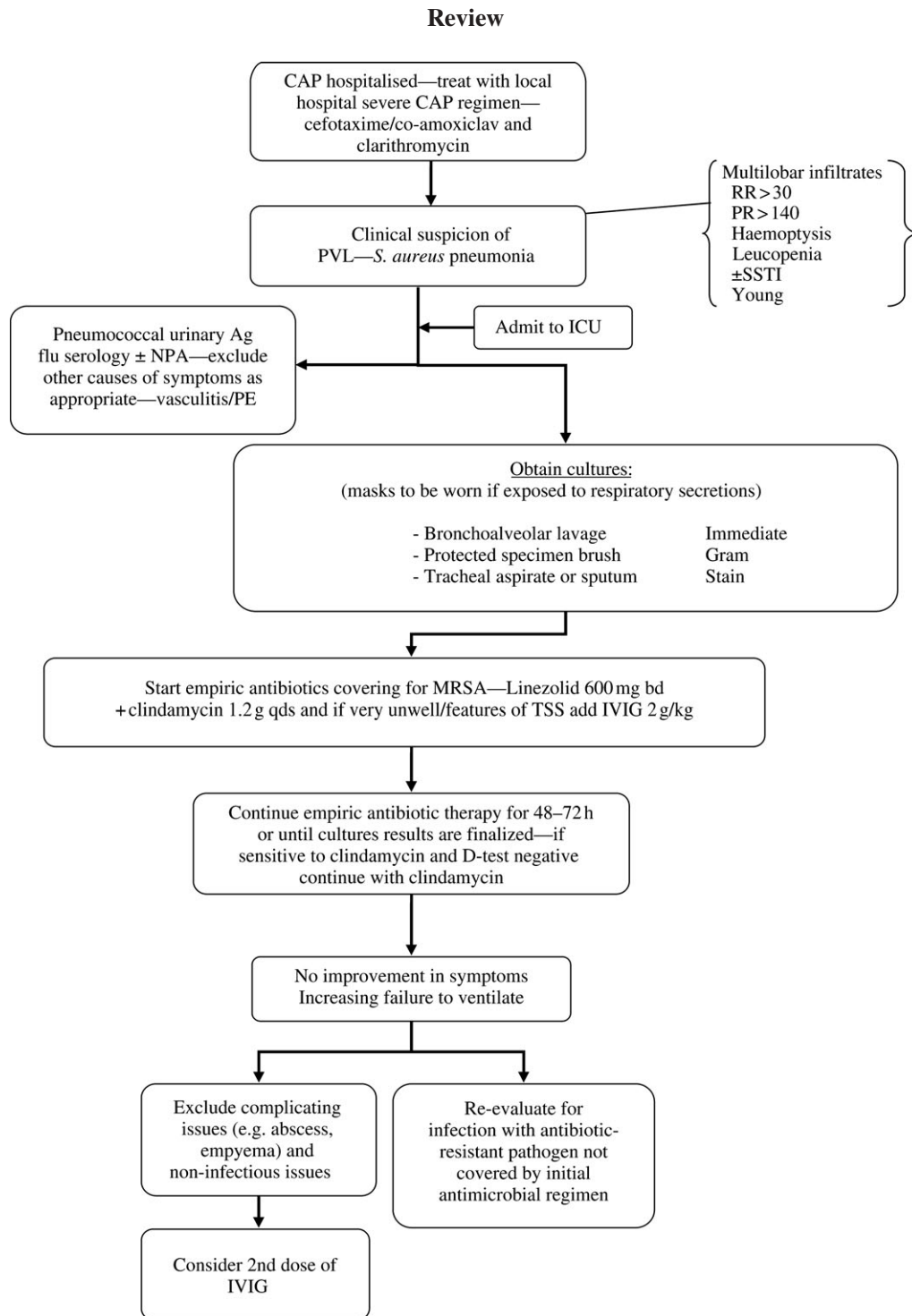
### 6.2.7 Adjunctive therapy options

**6.2.7.1 Immunoglobulin therapy (IVIG).** IVIG neutralizes the cytopathic effect and pore-formation of PVL *in vitro*, the inhibition being concentration dependent.<sup>93</sup> No randomized controlled trials have been performed to assess the role of immunoglobulin therapy in this setting. It has been used in several patients with PVL-associated pneumonia.<sup>63,77,86,94</sup> The optimal dosage of IVIG is uncertain; 2 g/kg is recommended for streptococcal toxic syndrome,<sup>95</sup> repeated at 48 h if there is still evidence of sepsis or failure to respond. The combination of linezolid and IVIG was effective in a boy with septic arthritis and pneumonia, who was discharged from intensive care to the general ward on day 5.<sup>86</sup>

### Recommendation 20

- **Although most supporting evidence is anecdotal, the use of immunoglobulin (IVIG) should be considered in severe sepsis and necrotizing pneumonia known or suspected to be due to *S. aureus*. IVIG should be given at a dose of 2 g/kg, repeating the dose if improvement is not satisfactory. [GPP].**

**6.2.7.2 Other adjunctive therapy.** Anecdotal reports of the usage of granulocyte colony-stimulating factor<sup>96</sup> and extra-corporeal membrane oxygenation<sup>64,94,97</sup> suggest that they are largely unsuccessful. Although of theoretical benefit in very early sepsis, once active haemorrhage has occurred, activated protein C should not be used. It therefore has no role in PVL-associated pneumonia.



**Figure 2.** Management of patient with suspected staphylococcal pneumonia in the healthcare setting. IVIG, intravenous immunoglobulin.

**Recommendation 21**

- **Based on current available evidence and experience, the Working Party cannot provide guidance on the value of the above adjunct therapies.**

Figure 2 provides an algorithm that may help clinicians implement the recommendations related to suspected staphylococcal pneumonia.

**6.3 Healthcare-associated community-onset MRSA skin and soft tissue infection**

Although we have chosen the example below, another very common scenario is a recently discharged hospitalized patient who presents with an ‘infected leg ulcer’ from which MRSA is isolated. The generic guidance and decision-making process provided here should also apply to this scenario.

*The district nurse requests a GP to do a home visit on a 73-year-old man. She has been attending the patient regularly*



over the last 3 weeks to dress a pressure sore that had developed over the sacrum. The man had recently been in hospital for a revision of his left hip prosthesis. The procedure was complicated by an episode of healthcare-acquired pneumonia and rehabilitation had been slow. He had spent 4 weeks in hospital before discharge and during this time he had developed a 6 cm irregular pressure sore over the sacrum. In the 2 days before the attendance of the GP, the lesion had become slightly larger with an increase in foul-smelling exudate. On the day of the visit, there was now a spreading area of redness (erythema) around the site. Although there was now some pain at the lesion, there were no other systemic signs of infection.

### 6.3.1 What is the likely clinical diagnosis?

The pressure ulcer in this case would be defined as Grade 3 as it involves full-thickness skin loss with damage or necrosis of the subcutaneous tissues, extending down to, but not penetrating through, the underlying fascia.<sup>98</sup> All such ulcers are colonized with a mixture of organisms. A chronic non-healing ulcer may reflect underlying osteomyelitis. The diagnosis of active infection involving a pressure ulcer must therefore depend upon clinical assessment rather than microbiology culture results. The European Wound Management Association has defined the criteria for recognizing early wound infection and implementing an escalating therapeutic strategy.<sup>99</sup> The overt signs of local infection (Stage 3 involvement) include the discharge of pus with swelling, pain, erythema and local warmth. On examination, the surrounding tissues may appear unhealthy and deteriorating. The principal pathogens associated with active wound infections of pressure ulcers are *S. aureus*, *Streptococcus* species, anaerobes and *Pseudomonas aeruginosa*.<sup>100</sup> The likely diagnosis here is therefore of a locally infected pressure ulcer where *S. aureus* is one of the most frequently associated pathogens.

### 6.3.2 When to suspect HA-MRSA

**6.3.2.1 Clinical presentation.** There are no specific clinical appearances or relationships that reliably identify a SSTI lesion as being infected with *S. aureus* or any particular type of *S. aureus*.<sup>44,53</sup> Three types of *S. aureus* are recognized as causing disease in community settings, namely MSSA, CA-MRSA and HA-MRSA. The spectrum of disease caused is similar, with SSTI being the commonest related condition. However, CA-MRSA is more strongly associated with SSTI than HA-MRSA and is more likely to occur in younger patients.<sup>101</sup> Although the appearances of SSTI with these types of pathogen are very similar, CA-MRSA is more often associated with red, raised lesions with a central area of necrosis (see case scenario 1).

#### Recommendation 22

- **There are no clinical characteristics that allow differentiation between different strains of MRSA infection. [GPP].**

**6.3.2.2 Risk factors.** The risk factors associated with HA-MRSA are well defined and include:<sup>44,102,103</sup> advanced age; underlying co-morbidities and severity of illness; inter-institutional transfer of the patient, especially from a nursing home or residence in a long-term care facility; prolonged hospitalization (including a

history of frequent hospital admissions or admission to hospital within the last 6 months); surgery or admission to an intensive care unit within the last 6 months; exposure to invasive devices of all types, especially central venous catheters; previous MRSA colonization/infection or exposure to an MRSA-colonized patient; the presence of extensive wounds and/or burns; and exposure to antimicrobial drugs, especially cephalosporins, fluoroquinolones and macrolides.<sup>47</sup>

The ability of these risk factors to predict the likelihood of HA-MRSA is uncertain. In recently hospitalized (<24 h) patients with staphylococcal bacteraemia, one case-controlled study identified previous MRSA infection or colonization as the strongest predictor of HA-MRSA. In this model, previous MRSA infection or colonization, presence of a central venous catheter, documentation of a skin ulcer or cellulitis at hospital admission were all independently associated with HA-MRSA bacteraemia. The model identified 75% of the cases correctly with a sensitivity of 76% and specificity of 73%.<sup>14</sup> In another cohort study of inpatients with *S. aureus* bacteraemia, infection with HA-MRSA was associated with prior antibiotic exposure (within 60 days of the bacteraemic episode) [OR 9.2 (95% CI 4.8–17.9)]; presence of decubitus ulcers [OR 2.5 (95% CI 1.2–4.9)], hospital onset [OR 3.0 (95% CI 1.9–4.9)] and history of hospitalization within 6 months of episode of infection [OR 2.5 (95% CI 1.5–3.8)]. In this model, the clinicians first had to identify the bacteraemia as community or hospital onset, then, depending on the risk factors of either prior antibiotic exposure and/or decubitus ulcer, an estimate of the risk of MRSA could be made. Thus, if the infection was community onset, the patient had recent antibiotic exposure and had a decubitus ulcer, the likelihood of MRSA is 91%. This model is limited to a specific cohort of patients from one site, needs broader validation and is applicable only to hospitalized patients with staphylococcal bacteraemia. However, these principles may prove helpful in assessing patients in the community.

#### Recommendation 23

- **When managing a patient with a community-onset SSTI, the possible involvement of HA-MRSA should be considered and the appropriate risk assessment done. Recent hospitalization, previous MRSA infection or colonization, previous antibiotic exposure and the presence of a decubitus ulcer or wound should alert clinicians to the possibility of HA-MRSA. [D<sup>3</sup>].**

### 6.3.3 When should specimens be sent for culture?

The early diagnosis and treatment of infection in patients with a Stage 3 infected pressure ulcer reduces the risk of complications and leads to improved patient outcomes. Knowing the identity and antimicrobial susceptibility of organisms infecting pressure ulcers is of help when an antimicrobial treatment has failed, when the presence of a resistant pathogen is suspected or when a patient requires screening for a specific organism.<sup>99</sup> Because the presence of MRSA will alter the choice of antimicrobial therapy, it is sensible to culture for MRSA when there is a significant risk and infection is sufficiently severe to warrant systemic therapy. If systemic therapy is not indicated, then there is little benefit from taking a sample except for infection control purposes.

### Recommendation 24

- In an episode of SSTI involving an infected pressure sore or another type of wound infection, a culture should be taken if the condition warrants systemic antimicrobial treatment or for infection control purposes. [GPP].

#### 6.3.4 Treatment principles

The principles of antibiotic therapy are as outlined in scenario 1 and in the Appendix.

- Give appropriate systemic antibiotic treatment guided by laboratory susceptibility results.
- Use appropriate topical antimicrobial and dressing care.
- Implement appropriate surgical adjunctive management.
- Consider the possibility of underlying complications such as osteomyelitis.

#### 6.3.5 Empirical antibiotic therapy

In the majority of such patients, MRSA will have been isolated from a recent microbiological specimen at the time of the consultation and appropriate MRSA treatment can be started. This therapy should be guided by susceptibility results.

### Recommendation 25

- In cases where empirical therapy is required and there are significant risk factors for HA-MRSA, the Working Group recommends starting one of the regimens identified in the Appendix after taking appropriate microbiological specimens. This therapy should be rationalized in light of microbiological culture results. [GPP].
- For severe or more progressive SSTIs, there is as yet no conclusive evidence that empirical therapy covering MRSA leads to improved outcome. However, in severe infections, where a risk assessment suggests the likelihood of HA-MRSA, high-dose empirical therapy against MRSA should be used. [GPP].
- Patients with severe infections should be admitted to hospital where skin and blood cultures should be taken, collections drained, tissues debrided as necessary and parenteral antibiotic therapy started. Appropriate infection control measures should be instigated and urgent consultation made with a local infection specialist. [GPP].
- For severe infections where HA-MRSA might be involved, the Working Party recommends starting the treatment recommended in the Appendix. [GPP]. Wound care should be carried out in the community under strict aseptic technique. Hand hygiene is necessary before and after direct patient contact.
- For further information relating to isolation, screening and decolonization, refer to the guidelines for the control and prevention of MRSA in healthcare facilities.<sup>2</sup>

HA-MRSA carriage constitutes a greater risk for the development of *S. aureus* infection than MSSA carriage.<sup>103</sup> The risk

over an 18 month period of MRSA infection among adult patients harbouring MRSA has been shown to be ~29%,<sup>104</sup> with 28% of them complicated by bacteraemia and 56% by pneumonia, soft tissue infection, osteomyelitis or septic arthritis. On subsequent admission to hospital, MRSA carriage is associated with an increased risk of sepsis. One study showed that 19% of the patients who were MRSA culture positive from an admission nasal sample subsequently developed infection with MRSA during their hospital stay, compared with 1.5% of cases colonized with MSSA and 2.0% of uncolonized patients.<sup>105</sup> Hence, MRSA colonization at admission significantly increased the risk of subsequent *S. aureus* infection compared with MSSA colonization. There are also data to show that morbidity and mortality are increased with MRSA when compared with MSSA infections, even when controlling for co-morbidities and other risk factors.<sup>106,107</sup> This may be related to the increased risk of initial therapy not covering MRSA. A significant increase in mortality has been found to be associated with MRSA when compared with MSSA bacteraemia [OR 1.93; 95% CI 1.54–2.42;  $P < 0.001$ ].<sup>106</sup> MRSA infection may also carry an increase in morbidity related to additional days of treatment required resulting in increased hospital stay.<sup>107,108</sup> No strong relationships have been identified with other morbidity outcomes.<sup>109</sup>

Thus, HA-MRSA carriage is associated with an increased risk of infection and morbidity and mortality. However, no such data are available for CA-MRSA. To date, there are no data to support the use of agents to eliminate *S. aureus* colonization in relation to community MSSA or CA-MRSA SSTIs.

### Recommendation 26

- Standard infection control advice should be given to patients with SSTIs due to HA-MRSA. This should include the importance of dressings management, hand decontamination and the avoidance of transfer of infection by, for example, sharing razors, contact sports etc.

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## Transparency declarations

D. N. declares that during the preparation of this document, he was not in the employment of any pharmaceutical firm with interest in the content of the guidelines although he did accept appointments to the advisory boards of Pfizer, Wyeth, Johnson & Johnson and Novartis, and has spoken at symposia supported by them.

M. D. has received honoraria for consultation and speaking symposia from Bayer, Novartis, Arpida and Pfizer.

B. D. C. accepted appointments to the advisory boards of GlaxoSmithKline, Wyeth and Merck Sharp and Dohme, and has spoken at symposia supported by 3M.

G. F. has accepted appointments to the advisory boards of Pfizer, Wyeth and Novartis, and has spoken at symposia supported by them.

R. G. M. has received speaker honoraria from AstraZeneca and Wyeth.

M. M. and D. L. have nothing to declare relevant to this publication.

### Comment on editorial process

This Working Party Report was put out for consultation on 11 October 2007 (consultation period closed on 8 November 2007) and amended in light of the comments prior to its submission to the journal. This consultation exercise replaced the journal's peer review process.

### Supplementary data

Tables S1 and S2 show the SIGN system used to grade the evidence and recommendations and are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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### Appendix. Summary of treatment recommendations for MRSA infections in the community

Before treating, clinicians may wish to seek advice of a local microbiologist.

#### A. Patients with SSTIs

- Follow local guidelines for treating SSTIs, for example flucloxacillin or clindamycin for minor SSTI without systemic upset. If the patient is febrile, appears unwell or is toxic with SSTI, consider assessment in hospital.
- Swab the lesion if purulent exudate is present.
- If MRSA is suspected because of previous colonization/isolation, or surgical/healthcare-related, it is very important to collect a microbiology sample.
- If MRSA is isolated or strongly suspected, treat with:
  - Rifampicin\* (300 mg po twice daily) PLUS sodium fusidate (500 mg thrice daily) OR doxycycline (100 mg po twice daily) (doxycycline not recommended for paediatric use) for 5–7 days.
  - Rifampicin (300 mg po twice daily) PLUS trimethoprim (200 mg po twice daily) for 5–7 days.
  - Linezolid<sup>†</sup> (600 mg po twice daily) following discussion with Consultant Microbiologist or Infectious Disease physician.

\*When rifampicin is used please consider drug interactions, e.g. warfarin, methadone, hormone contraceptives, theophylline etc.

<sup>†</sup>Linezolid is an expensive alternative and may not be readily available at community pharmacies.

*Note:* if GAS infection is suspected, oral therapy should include an active agent against this organism ( $\beta$ -lactam or clindamycin). Tetracyclines and trimethoprim, although active against MRSA, are not recommended for suspected GAS infections.

#### B. Serious and deep-seated MRSA infections

The Working Party recommends that suspected serious and deep-seated MRSA infections are assessed and treated in hospital. This includes suspected bacteraemia and staphylococcal pneumonia as in Scenario 2. Refer to MRSA treatment guidelines for more detail.<sup>4</sup>

**B1.** For MRSA pneumonia (+/– PVL), treat with:

- Linezolid (600 mg intravenous 12 hourly) PLUS clindamycin (1.2–1.8 g intravenous 8 hourly) +/- rifampicin (600 mg intravenous 12 hourly).

**B2.** For other deep-seated MRSA infections, such as bacteraemia, osteomyelitis, abscesses, endocarditis, and including those infections caused by PVL-producing CA-MRSA, treat with:

- **First-line:** Either teicoplanin (400–800 mg intravenous every 24 h (following loading) or vancomycin (1 g intravenous 12 hourly) PLUS one of the following: gentamicin (5–7 g/kg intravenous once daily), rifampicin (300 mg po twice daily) or sodium fusidate (500 mg po thrice daily).
- **Second-line:** Linezolid (600 mg intravenous/po 12 hourly)
- **Alternative:** Daptomycin (4 mg/kg intravenous once daily). Licensed for SSTIs, and for bacteraemia and right-sided endocarditis due to *S. aureus*.
- **Alternative:** Tigecycline (100 mg loading dose followed by 50 mg intravenous twice daily). Licensed for complicated SSTIs.

*Notes:*

- Assessment in hospital likely to be required.
- Bone and joint infections may require a prolonged course of treatment.
- Monitor serum vancomycin/teicoplanin and gentamicin concentrations (for example adjust doses to achieve trough concentrations for teicoplanin of 10–20 mg/L and for vancomycin of 10–15 mg/L).

#### C. MRSA in urine

The Working Party believes that while this area is not covered in a clinical scenario in the text, it is often a frequently encountered clinical problem. The Working Party felt that recommendations are warranted to provide guidance for practice in the community.

## Review

- Antibiotics are unlikely to clear MRSA in the presence of a urinary catheter. There is no good evidence that catheter changes need to be covered with appropriate antibiotic prophylaxis to prevent catheter-related urinary tract infections.<sup>110</sup>
- A significant MRSA urinary tract infection with systemic symptoms and the presence of white cells in the urine is

likely to require systemic antibiotic treatment. [GPP]. The Working Party recommends that in patients with normal renal function (children excluded), doxycycline (100 mg twice daily) or tetracycline (250–500 mg 6 hourly) should be used. Trimethoprim (200 mg 12 hourly) or nitrofurantoin (50–100 mg four times a day for 5–7 days) could be alternatives.<sup>4</sup>