

Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom

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These evidence-based guidelines are an updated version of those published in 2006. They have been produced after a literature review of the treatment and prophylaxis of methicillin-resistant *Staphylococcus aureus* (MRSA). The guidelines aim to complement those recently published for the antibiotic treatment of common and emerging community-onset MRSA infections in the UK. The guidelines have reviewed and updated, where appropriate, previous recommendations, taking into account any changes in the UK epidemiology of MRSA, ongoing national surveillance data and the value of new antistaphylococcal agents licensed for use in UK practice. Emerging therapies that have not been licensed for UK use are not reviewed, but their future potential role has been mentioned where deemed appropriate. Recommendations are given for the treatment of common infections caused by MRSA, elimination of MRSA from carriage sites and prophylaxis of surgical site infection.

Keywords: update, evidence-based guidelines, methicillin, new antistaphylococcal agents, UK

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Doses of drug, where given, relate to adult and not paediatric dosage.

1. Introduction

Staphylococcus aureus infections are placing an increasing burden upon the UK healthcare economy.¹ Guidelines for the control of methicillin-resistant *S. aureus* (MRSA) infection in the UK have been published previously by a joint Working Party of the British Society for Antimicrobial Chemotherapy

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(BSAC) and the Hospital Infection Society in 1986² and 1990³ and together with the Infection Control Nurses Association (ICNA) in 1998.⁴ In 2006,⁵ revised guidelines concentrating on prophylaxis and treatment of MRSA infections were prepared by the joint Working Party and it is these guidelines that we have updated to take account of new antibiotics and information. This revision does not repeat all the considerations of previous guidelines, but includes revised opinions, new information and a summary of continuing and new recommendations and therefore replaces existing guidelines. More specific guidance related to the diagnosis and treatment of community-onset and -acquired MRSA has also recently been published.⁶ Where it is available, the Working Party has also considered information on unlicensed compounds in Phase 3 clinical trials. In the implementation of any guidelines, an assessment of the economic value or impact of the proposed therapy for a healthcare setting is deemed increasingly important.⁷ In our guidance, we have not reviewed the literature related to this and therefore are not able to give any guidance related to this. We suggest that local policy-makers decide on the resource implications of some of the therapies recommended in this guidance.

For this update of the guidelines, literature searches of the following databases were conducted in August 2007: Medline, EMBASE, Cochrane Library (issue 3, 2007) and Science Citation Index Expanded. For these searches, MeSH and Emtree subject headings relevant to MRSA were used together with free text terms, and a total of 3398 records were retrieved and assessed for their relevance by members of the Working Party. Additional recommendations for references were also made by members of the Working Party.

The recommendations made in these guidelines are followed by the same category classification indicating the level or strength of the evidence supporting the recommendation as in the previous guidance. The category given is taken from the evidence grades of the Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and Prevention.⁸ Each recommendation is categorized on the basis of existing scientific data, theoretical rationale, applicability and economic impact. The categories are:

- IA. Strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiological studies.
- IB. Strongly recommended for implementation and supported by certain experimental, clinical or epidemiological studies and a strong theoretical rationale.
- IC. Required for implementation, as mandated by federal or state regulation or standard or representing an established association standard.
- II. Suggested for implementation and supported by suggestive (non-definitive) clinical or epidemiological studies or a theoretical rationale.
- Unresolved issue. No recommendation is offered. No consensus reached, or insufficient evidence exists regarding efficacy.

The use of alternative agents for patients who are either hypersensitive to, or intolerant of, first-line agents has not been comprehensively addressed since there is usually insufficient evidence or indication of which agent should be used. Nevertheless, the wide choice of agents included in these guidelines gives some

indications of potential appropriate choice, if antimicrobial susceptibility data are taken into account.

There has been a major attempt in recent years in the UK to reduce cases of MRSA bacteraemia by setting targets for hospitals. Some measures have been specifically aimed at bacteraemias and their common causes such as line sepsis and some aimed at general cross-infection measures, but with the exception of 'screen and treat' carriage programmes, no advice touching on therapy has been issued. The success of these measures varies by hospital and this guidance, where referring to empirical therapy, assumes a high prevalence of MRSA. Some hospitals will have a low incidence of new cases of infection with MRSA, active screening programmes in high-risk groups and good information systems for clinicians on past MRSA colonization and infection in patients. Our previous recommendation of a resistance rate of 10% in bacteraemia was deemed by one group to be substantially too low.⁹ However, local case mix data will affect mortality and morbidity rates with MRSA and methicillin-susceptible *S. aureus* (MSSA) and local data are essential to this decision as is a reliable categorization as severe (complicated) or mild and whether of community or hospital onset. Interestingly, resistance rates of 10% to 20% have been used as the threshold justifying changes in the usage of antibiotics for urinary infection with other organisms.^{10,11} Therefore it is up to individual bodies to determine their thresholds depending on local experience.

Recommendation 1: Step-down therapy from an agent that encompasses MRSA to flucloxacillin if the strain proves to be flucloxacillin-susceptible is a safer process than the alternative of escalation therapy, unless the proportion of hospital-acquired and community-acquired MRSA infections is known to be very low as established by local surveillance, which is now well established in the UK. [Category II]

MRSA presenting from the community is sometimes associated with previous silent acquisition in the healthcare environment,^{12,13} or household contacts,¹⁴ and one study suggests that silent acquisition is associated with inpatient care for more than 5 days within the last year.¹⁵ There is also a less common emerging UK problem, more widespread in some parts of the USA and Europe, of truly community-acquired MRSA with Panton-Valentine leucocidin (PVL),¹⁶⁻²⁰ although the spread of these strains in hospitals confuses a previously straightforward epidemiological and therapeutic picture. Once established within hospitals or long-term care centres, any MRSA is difficult to control and its survival is probably promoted by the increasing use of antibiotics,^{21,22} although the Society for Healthcare Epidemiology of America (SHEA) in a careful analysis of potential interventions did not quote any specific example of successful general control by antibiotic policy.²³

Selection of new clones of MRSA may follow changes made in usage in antibiotic prophylaxis and treatment. The time course for evolution and spread of an antibiotic-resistant strain is not well described, but antibiotic use needs to adapt in a timely fashion to both national and sometimes local changes in the prevalence of resistance. Overall, antibiotic use in the UK resembles that in low-MRSA-prevalence countries such as Finland.²⁴ Reversion to the use of first-generation cephalosporins in surgery,²⁵ reduced use of third-generation cephalosporins and clindamycin²⁶ and reduced use of ceftazidime and ciprofloxacin²⁷ have been described as contributing to the reduced prevalence of MRSA in different hospitals. Reduced rates with modified antibiotic policies in healthcare settings smaller than

whole hospitals are described, but are difficult to evaluate.^{28–30} High usage of cephalosporins^{31–34} and fluoroquinolones^{33–41} has apparently been important in selecting for MRSA in some settings, as has use of macrolides, penicillins and to some extent aminoglycosides,⁴² but the evidence was not conclusive. Quinolone use has been associated in one study with prolongation of MRSA carriage. A recent report using the UK GP Research database showed that community-acquired MRSA in the UK was associated with quinolone or macrolide use in the previous year.⁴³ Latest SHEA guidelines lay emphasis on good antibiotic stewardship and specifically that for fluoroquinolone use.⁴⁴ Changes in overall antibiotic usage advocated to reduce *Clostridium difficile* infections would not be expected to have as much effect on MRSA characteristics, but changes in the specific classes of agents used and the widespread use of mupirocin in 'screen-and-treat' programmes require careful monitoring for their effect on MRSA resistance.

Reduced use of an antibiotic has also coincided in the past with elimination of certain clones resistant to the drug and those referred to in previous guidance continue to have current relevance, e.g. the reduced use of tetracyclines in the 1970s was associated with reductions in tetracycline-resistant MRSA in Denmark and Birmingham.^{45,46} However, this has not been proved with respect to modern epidemic strains. In addition, this was not conclusive as additional interventions such as infection control measures may have confounded the association. Antibiotics that achieve high skin concentrations include linezolid, fluoroquinolones, macrolides, tetracyclines and clindamycin. Information on the value of restriction of the use of these compounds, in particular in diminishing MRSA selection, is scanty, but their role in selecting for resistant *Staphylococcus epidermidis* is well recognized especially with quinolones.^{47,48} This may be important for MRSA selection given the extensive use of macrolides, licensing of fluoroquinolones for the treatment of respiratory tract infection and widespread susceptibility to tetracyclines of MRSA currently in the UK. Guidelines for appropriate antibiotic use in chronic obstructive pulmonary disease (COPD) and pneumonia in the UK are overdue for change to take account of wider availability of diagnostic tests for pneumococci and *Legionella* and a greater emphasis on support measures and less on treatment of *Haemophilus influenzae* in COPD.

The appearance of strains of MRSA for which glycopeptide MICs were raised and with clinical resistance to vancomycin and teicoplanin is a cause for concern because the use of more expensive and less familiar new agents could be driven by the emergence of such resistance. The presence of the *vanA* gene in a few MRSA isolates from patients in the USA is troubling, but as yet has not produced a flurry of cases. The source of the *vanA* gene is obscure and some cases suggest transfer from other Gram-positive organisms,^{49,50} but most isolates are resistant by non-transferable mechanisms.⁵¹ Vancomycin-resistant MRSA have not been isolated in the UK and the HPA Reference Service has not confirmed any isolates with stable intermediate resistance—glycopeptide-intermediate *S. aureus* (GISA) (unpublished results, Antibiotic Resistance Monitoring and Reference Library, HPA Centre for Infections). The number of cases of vancomycin-resistant MRSA or GISA internationally remains low, despite alarm at their initial emergence.⁵² However, there is no new, comprehensive or adequate national information or surveillance on the prevalence of heteroresistant GISA strains or on

the 'creep' upwards in vancomycin MICs and the impact of such changes on the comparative outcome of treatment. European information on such strains remains patchy.^{53,54} No new information is available on methods for detection of such strains, and no routine changes have been made to laboratory practice and BSAC susceptibility testing guidance. There is no new information since their description in 2002 on the spread of teicoplanin-resistant MRSA including EMRSA-17.^{55,56} Vancomycin treatment failures occur with strains apparently susceptible *in vitro*.^{57–59} Infections with susceptible strains having MICs ≥ 1 mg are said to be more likely to fail on vancomycin therapy than those with susceptible strains having MICs < 1 mg/L. This is associated with Group 2 polymorphism at the accessory gene regulator.^{60,61} It is important to note that in the original report, treatment failure was not associated with changed 30 day mortality, but this may reflect changed treatment after vancomycin failure. This poor response has been confirmed in a study in renal unit *S. aureus* bacteraemia where previous vancomycin use was a risk factor for raised vancomycin MICs,⁶² but this subject has not been prospectively studied. There is evidence that even high-dose vancomycin treatment does not improve the prognosis in renal patients, which may suggest that poor outcome is related to other biological factors.⁶³ This might suggest that other treatment should be used for MRSA infections where the vancomycin MICs for the infecting strains are between 1 and 4 mg/L and therefore that vancomycin MICs should always be measured for MRSA treated with this drug. However, routine substitution of other agents may not necessarily be the appropriate response. A recently reported study of bacteraemia and endocarditis indicated that daptomycin resistance⁶⁴ was more likely to emerge at the trial dosage with strains with heteroGISA phenotypes. The absence of improved response with high-plateau vancomycin levels of 20–25 mg/L suggests that increasing the dose of the drug and accepting that higher serum levels are needed for treatment are not necessarily appropriate responses to the heterogeneous vancomycin-intermediate *Staphylococcus aureus* (heteroVISA) or the raised MIC resistance phenomenon.⁶⁵ Examination of data stratified on vancomycin trough levels and area under the curve did not differentiate between survivors and non-survivors in one study of healthcare-acquired pneumonia due to MRSA⁶⁶ and did not demonstrate that higher serum levels are needed for therapy. Alternative higher dosing schedules have not been specifically trialled for improved efficacy in heteroGISA MRSA infections and there are reports of increased renal impairment associated with vancomycin levels in excess of 15 mg/L, although it is not clear which is cause and which is effect.⁶⁷ Mortality associated with MRSA bacteraemia has been found to be significantly higher when vancomycin was empirically used to treat strains with a high vancomycin MIC (> 1 mg/L).⁶⁸ A reduction in the CLSI vancomycin breakpoint to 2 mg/L has not been copied in the BSAC guidance and the breakpoint remains at 4 mg/L. Meanwhile, the rationale for the CLSI decision to change vancomycin breakpoints to 2 mg/L as indicating susceptibility has been reviewed and noted to include 14 cases of treatment failure where the vancomycin MIC was 4 mg/L.⁶⁹

Mortality rates with MRSA are higher than with MSSA in most studies and this appeared to be attributable mortality in a meta-analysis,⁷⁰ but the difficulty of interpretation is that MRSA infection is usually acquired in hospital, when other cofactors of illness that require a hospital stay are present and so mortality

may not be due to the antibiotic resistance *per se*.^{70–77} Recent studies confirm this effect of co-morbidity (Charlson score) and previous hospitalization on outcome.^{78,79} UK information on outcomes in MRSA and MSSA bacteraemia using record linkage has also been published.⁷⁹ We referred in previous guidance to two studies showing that a relatively short period of up to 48 h delay in switching from β -lactam antibiotics to appropriate therapy for non-severe methicillin-resistant infections does not affect outcome.^{80,81} Previous guidance of a step-down approach to severe *S. aureus* infection was accepted,⁸² but there is little audit information that vancomycin use empirically or in MSSA infection is being reliably implemented in the UK. The use of initial anti-MRSA treatment may become less relevant in institutions that have achieved excellent control of serious MRSA infection and it will become increasingly important to ensure that step-down is actually being followed.

For MSSA, we reiterate our advice that flucloxacillin is a preferable agent and is available orally when this is the preferred route of administration. Flucloxacillin is safer and has a higher cure rate than glycopeptides for susceptible strains in patients with bacteraemia and infection in respiratory primary sites.^{72,83} Other factors including acute physiological score have been shown to be important in predicting mortality in bacteraemia overall,^{81,84} although agents such as linezolid may be required to adequately treat infections due to PVL-positive strains.⁶ This would have to be through a hospital microbiologist after detection of PVL. Good control of diabetes mellitus, drainage of abscesses and particularly removal of sources such as intravenous lines⁸⁵ are important in improving outcome. The reasons for use of β -lactams are overall patient safety, convenience and cost, rather than survival, but the higher relapse rate in patients with MSSA infections treated with vancomycin means that β -lactams are preferable agents if the infecting strain is susceptible.^{86–88} It is notable that such studies contain a preponderance of patients with renal impairment. The use of flucloxacillin or cloxacillin in these patients, when appropriate, is particularly emphasized. Nevertheless, overall 30 day mortality rates in patients treated with glycopeptides, or β -lactams for MSSA bacteraemia, were similar in two studies.^{73,84} There are few data comparing cloxacillin or flucloxacillin with nafcillin or other penicillinase-resistant penicillins, but little reason to expect differences in efficacy.

The prevalence level for resistance at which flucloxacillin or other staphylococcal penicillinase-stable penicillins, in a patient group, become no longer the drug of choice is debatable; our previous recommendation of a 10% resistance rate was thought to be too low. The precise level is controversial and would depend on relative mortalities in MSSA and MRSA infection, the severity of the infection and their accurate categorization as hospital- or community-acquired.

2. Prevalence of antibiotic resistance in MRSA in the UK

The Working Party has reviewed recent data on the prevalence of antibiotic resistance within MRSA infection in the UK. There remains a relative lack of data, and good quality systematic surveillance is needed. In the previous guidelines, we included data from bacteraemia surveillance from 2001 to 2003. Data from this ongoing surveillance project in 23 laboratories in the UK

and Ireland are now available from 2001 to 2006 and indicate resistance to ciprofloxacin in 96% of isolates, erythromycin in 82%, trimethoprim in 20%, fusidic acid in 9.3%, tetracycline in 3.1% and rifampicin in 2.2%.⁸⁹

Mupirocin testing has only recently been added to the above panel: *mupA* was detected in five MRSA isolates in 2006 (Dr Russell Hope, Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency, personal communication), giving a resistance rate of ~5% based on a small sample. We do, however, appreciate that other resistance mechanisms exist.

Local resistance data should be taken into account when assessing antimicrobial resistance and must be periodically updated.

3. Use of glycopeptides

In the UK, vancomycin has been widely used for parenteral treatment. Clear guidelines on the overall use of glycopeptides are required in hospital. The national guidelines for the judicious use of glycopeptides in Belgium provide a useful basis for discussion.⁹⁰

Recommendation 2: We continue to endorse the specific areas of the Belgian recommendations on the use of glycopeptides for severe MRSA infection, except in the circumstances below where we recommend early use of other agents active against MRSA:

- (i) Surgical prophylaxis where the local epidemiology of antibiotic resistance in staphylococci also influences choice of agents. [Category II]
- (ii) Neutropenic sepsis if there is line infection and the patient has previously had cultures positive for MRSA.

4. Skin and soft tissue infections (SSTIs)

4.1 Impetigo and boils

Impetigo and boils are usually community-acquired. The prevalence of community-acquired MRSA infections in the UK is not systematically surveyed. Incidence data from the General Practice Research Database for the period 2000–04 estimated an average incidence of adult MRSA infection or colonization of 15.2 per 100 000.⁴³ The definition of community-acquired was a patient with no hospitalization within the past 2 years and no previous diagnosis of MRSA.

The use of topical agents for the treatment of impetigo has been reviewed.⁹¹ Fusidic acid and mupirocin are of similar efficacy. The studies did not focus on MRSA. The conclusion was that topical mupirocin is the treatment of choice in systemically well children with impetigo,⁹² but this is unconfirmed microbiologically. Of the new agents used for impetigo, retapamulin was non-inferior to fusidic acid with reduced efficacy in patients with MRSA infections.⁹³ There are no published data on the efficacy of hydrogen peroxide gel against MRSA.

Recommendation 3: Impetigo caused by MRSA should be treated with topical mupirocin or fusidic acid, where the isolate is susceptible. [Category II]

There is evidence for small boils that antibiotics are unnecessary and that drainage of lesions <5 cm diameter is adequate.⁹⁴

Recommendation 4: Antibiotic therapy is not generally required after incision and drainage of small abscesses without surrounding cellulitis.

4.2 Ulcers and sores

MRSA colonization is more common than infection. Occasionally, colonized ulcers may require systemic therapy as part of eradication therapy. Treatment is also required if there is evidence of cellulitis, contiguous osteomyelitis (discussed subsequently) or bacteraemia. Special consideration should be made for foot ulcers in diabetics as colonization may rapidly progress to infection.

4.3 Cellulitis/surgical site infections

An open-label prospective comparative study in the USA demonstrated the efficacy of doxycycline or co-trimoxazole in outpatient or community SSTIs with MRSA and demonstrated equivalence between the agents.⁹⁵ However, the number of evaluable patients was small, and there has been no new information on these older antibiotics. An open-label randomized multicentre international study comparing linezolid with vancomycin reported marginally improved clinical and microbiological outcomes with linezolid in a subset of patients with proven MRSA SSTIs.⁹⁶ A follow-up study designed to seek superiority [Ligand Epitope Antigen Presentation System (LEAPS)] presented at the Eighteenth European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, 2008,⁹⁷ did not confirm superiority in the intent-to-treat population. Clindamycin could also be considered if the isolated organism is susceptible.

Recommendation 5—non-hospitalized patients:

- (i) Depending on susceptibility tests, doxycycline or clindamycin is recommended (including a D test for clindamycin resistance on erythromycin-resistant strains) unless the infections are considered severe and/or carry a high risk of bacteraemia or endocarditis. [Category IB]
- (ii) With strains of MRSA resistant to doxycycline or clindamycin, glycopeptides or linezolid should be used. Co-trimoxazole could be considered, bearing in mind the hazards of sulphonamide allergy.
- (iii) Outpatient parenteral therapy with glycopeptides or daptomycin offers a cost-effective option in moderately severe infections where continuing intravenous therapy is deemed necessary. [Category IB]⁹⁸

The possible superiority of linezolid in patients with proven complicated MRSA infection and in SSTIs, along with its availability as an oral agent with a high bioavailability, may also facilitate early hospital discharge and provides another cost-effective alternative where appropriate.

There are a number of new agents licensed for SSTIs. Since our last recommendation, two agents (daptomycin and tigecycline) have been licensed for the treatment of SSTI and studies published and analysed.^{99,100} Clinical trials with other new, as yet unlicensed agents such as ceftibiprole, ceftaroline, telavancin, oritavancin and dalbavancin have also been reported. All of these studies have been powered for equivalence with variable endpoints.

For suspected infections due to *S. aureus* or MRSA producing PVL, either linezolid or clindamycin should be considered since both have been shown to modify the expression of PVL *in vitro*.¹⁰¹

Recommendation 6: We presently cannot make any recommendations on the use of these new licensed agents based on their efficacy alone and relatively early 'real world' clinical experience. However, we note that all of these agents have the limitations and advantages of parenteral therapy, and should be regarded as alternatives in clinical situations in which other agents are deemed inappropriate or failing. Such factors include the type and severity of infection, ease of administration, β -lactam hypersensitivity, clinical failure or poor response, resistance, poor tolerability, significant co-morbidities such as renal disease, duration of therapy and cost-effectiveness. Parenteral therapy may or may not be needed depending on severity and the likelihood of poor compliance with an oral regimen. Since the last guidelines were published, a separate set of guidelines devoted to community-onset MRSA have been published.⁶ Although we accept that there may be some differences in recommendations, these differences can be explained by the difference in emphasis between community treatment of minor infection and more serious or invasive infections in a hospital setting.

Recommendation 7—hospitalized patients:

- (i) Glycopeptides, linezolid or daptomycin should be considered for use in hospitalized patients with severe SSTIs and/or where the risk of bacteraemia is high. [Category IA]

Linezolid may provide marginally greater effectiveness compared with glycopeptides in this patient population. [Category IB]

If the infection is deemed polymicrobial (e.g. diabetic foot infections) and where MRSA is considered to be an important pathogen, monotherapy with tigecycline may be considered as an alternative. [Category IB]

- (ii) We are unable to make any recommendations on the use of combined therapy because of the lack of clinical trials and the risk of additive toxicity. We no longer recommend the use of rifampicin plus fusidic acid to treat SSTIs, because of adverse effects¹⁰² and the availability of newer, less-toxic agents.
- (iii) For clinical treatment failure with glycopeptide monotherapy, we are unable to make a clear recommendation between adding a second antistaphylococcal agent (such as doxycycline, rifampicin or fusidate) to the glycopeptide and switching to monotherapy with either linezolid or daptomycin. A meta-analysis has suggested that linezolid may be superior to glycopeptides for Gram-positive infections in SSTIs and bacteraemia.¹⁰³

We recommend that clindamycin be considered for use in the treatment of MRSA susceptible to erythromycin because the emergence of clindamycin resistance requires two mutations and its bioavailability is superior. In determining clindamycin susceptibility in erythromycin-resistant strains, a D test should always be performed rather than using a clindamycin disc alone. Patients should be warned of the risk of *C. difficile* and the necessity to cease treatment and seek medical attention if they develop diarrhoea. Vigilance for

clindamycin-associated *C. difficile* diarrhoea should be maintained if its use is encouraged as it is not clear whether a change in the likelihood of *C. difficile* being associated with this antibiotic has occurred.

4.4 Intravenous infusion sites

Recommendation 8: Having reviewed the evidence since our last published guidelines, we see no reason to change our recommendation that intravenous antibiotics are used in cases of severe intravenous site infections associated with severe induration, cellulitis or bacteraemia and in such cases a glycopeptide or linezolid should be prescribed. Mild infections may respond well to oral agents. [Category IB]

5. Urinary tract infections (UTIs)

Oral agents usually appropriate for the treatment of MRSA UTIs include nitrofurantoin and, if susceptibility in *in vitro* tests is confirmed, tetracycline or trimethoprim. The higher resistance rate reported for trimethoprim in laboratory surveillance has been maintained (21% versus 3% for tetracyclines). In complicated situations, especially involving surgical sepsis, new agents offer an alternative to glycopeptides. Daptomycin is a potential unlicensed agent for the treatment of UTI caused by MRSA. Studies of *in vitro* activity of daptomycin against Gram-positive pathogens causing complicated UTIs have shown all the strains, including MRSA, to be susceptible with MICs up to 2 mg/L,¹⁰⁴ and daptomycin used to treat complicated UTI due to Gram-positive bacteria had bacteriological eradication rates of 83% and clinical success rates of 93%.¹⁰⁵ However, both BSAC and EUCAST post a clinical breakpoint of 1 mg/L for daptomycin, and strains for which daptomycin MICs are 2 mg/L should be classed as resistant. Most excretion of daptomycin is via the kidney with 80% urine recovery of the total dose, two-thirds as intact drug.¹⁰⁶

Tigecycline may not achieve adequate concentration in urine to treat complicated UTI. Only 8% to 11% of the drug is excreted in urine as unchanged drug over 48 h.¹⁰⁷ There are no published studies of its efficacy in treating UTI due to MRSA. Approximately 65% of the total clearance of linezolid is non-renal and of the drug excreted in urine, only 30% is as the parent drug (summary of Product Characteristics, Pfizer, February 2007). There are no published data regarding the use of linezolid in UTI. Similarly, quinupristin–dalfopristin is only partially excreted in urine,¹⁰⁸ with no published data of its use for UTIs.

Recommendation 9: For simple UTIs, an oral agent (nitrofurantoin, trimethoprim, co-trimoxazole or tetracycline) should be considered according to *in vitro* susceptibility. [Category II]

For complicated UTIs, glycopeptides or daptomycin should be considered. [Category II]

6. Bone and joint infections

The management of bone and joint surgery is complicated and must involve a multidisciplinary approach. Choice of antibiotics in these circumstances will depend on the surgical management plan.

Of the newer agents, daptomycin has been demonstrated to be effective in a limited number of cases¹⁰⁹ and in animal models.¹¹⁰ It is well released from polymethylmethacrylate cement incorporation.¹¹¹ There are also animal data for tigecycline,^{112,113} which suggest that it is effective alone or in combination with rifampicin.

There are two published studies on the prolonged use of linezolid (sometimes where it is just one antibiotic among others), in patients with prosthetic joint infections and chronic osteomyelitis, including some patients with MRSA. In one series,¹¹⁴ 21 out of 66 patients developed reversible anaemia requiring transfusion in 16 cases after a median time of 7.3 weeks treatment (range 4–12 weeks) and 6 developed peripheral neuropathy, of whom 4 remained symptomatic after 24 months. In the other series,¹¹⁵ 5 out of 51 developed thrombocytopenia and 5 out of 51 developed anaemia and a further patient developed irreversible peripheral neuropathy after 24 months of linezolid therapy. The manufacturers recommend that courses of therapy should not exceed 4 weeks. However, these infections are difficult to treat even with the necessary surgery and initial reports of short-term successes including these¹¹⁶ are important. Should it be clinically relevant to provide treatment for longer, it is important to monitor liver function and coagulation.

The Working Party considers that oral linezolid has a place in the follow-on treatment of bone and joint infections with MRSA after appropriate surgery, although this is not a licensed indication for the drug, but with weekly monitoring of full blood count and platelets for signs of bone marrow suppression. With short duration therapy, neuropathy should not be a problem. Further large-scale formal studies in patients fully categorized as having prosthetic joint infection with or without retained metalwork are required before firm recommendations on extended linezolid use can be made.

Recommendation 10: The treatment of MRSA bone and joint infection should be based on a multidisciplinary approach. More trials on the efficacy of new agents are underway and welcomed. Until these can be assessed, our previous recommendation to use parenteral glycopeptides with or without adjunctive agents such as rifampicin or sodium fusidate as initial parenteral therapy still stands. Unwanted effects, the patient's desire to be out of hospital, the extent of debridement and removal of metalwork will affect the duration of treatment and use of oral follow-on agents. There is no evidence that any single agent or combination is superior. [Category II]

7. Bacteraemia and endocarditis

There is a single controlled comparative study evaluating daptomycin for the treatment of staphylococcal bacteraemia and endocarditis, which demonstrated equivalence with the comparator, which was vancomycin or an antistaphylococcal penicillin with low-dose gentamicin.⁶⁴ However, in this study, the failure rate for both arms was surprisingly high and probably reflected the protocol definitions requiring late follow-up blood culture before the patient could be deemed a success as distinct from improved. The emergence of daptomycin-resistant strains was documented in 5% of treated cases, but toxicity was minimal compared with the comparator arms where vancomycin use or use of isoxazoyl

penicillin with gentamicin was associated with nephrotoxicity. Outcomes for left-sided endocarditis treated with daptomycin were disappointing in this trial, but open studies in endocarditis reported from a data registry have not confirmed the poor outcomes in left-sided endocarditis.¹¹⁷ Preliminary experience with 23 cases of MRSA endocarditis has been reported with limited successes.¹¹⁸ Many cases have received rifampicin and/or gentamicin in combinations.

Recommendation 11: A minimum duration of 14 days of treatment with glycopeptides or linezolid for uncomplicated bacteraemia. Longer treatment will be required in patients with, or at higher risk of, endocarditis, and transoesophageal echocardiographic assessment is important. The manufacturer's recommendation of a 4 week limit on linezolid treatment and adverse effects previously referred to may limit use of this agent (discussed earlier). Daptomycin could be considered as an alternative to glycopeptides. [Category II]

8. Respiratory tract infections

Our analysis of the lack of convincing evidence for the superiority of linezolid over glycopeptides in MRSA hospital-acquired pneumonia and *Acinetobacter* ventilator-associated pneumonia has not changed since the last guidelines. Although we accept that there is evidence of equivalence in trials, the appearance of a novel plasmid-mediated linezolid resistance mechanism in MRSA,¹¹⁹ plus descriptions of an outbreak of linezolid-resistant *S. epidermidis* in an intensive care unit (ICU) with heavy usage¹²⁰ and of linezolid- and vancomycin-resistant enterococci in a hospital, including the ICU,^{121–123} all need to be taken into account. As such, heavy usage of either agent may be unwise. The use of antibiotics for MRSA in patients with bronchiectasis, bronchitis or COPD and the significance of these isolates have not been supported by clinical trials, although there are anecdotal reports that they are significant. Making a recommendation for treatment is difficult. Sputum penetration of glycopeptides is likely to be poor. Tigecycline is not currently licensed for respiratory tract infections, and there are as yet no data for tigecycline or anti-MRSA cephalosporins demonstrating superiority or even equivalence. Of the new agents, daptomycin is inactivated by lung surfactant and therefore not recommended in the management of respiratory tract infection.¹²⁴

Recommendation 12: The treatment of infections in patients with bronchiectasis or chronic suppurative lung disease without pneumonia, where MRSA is deemed significant, is unresolved. [Category Unresolved issue]

Linezolid may be used as it offers better lung tissue penetration. [Category IC]

It is recognized that PVL-positive strains of MRSA can cause severe necrotizing pneumonia in the community. In these circumstances, there is some *in vitro* evidence that staphylococcal toxin production can be suppressed by either clindamycin or linezolid. As recommended in the recent published guidelines on community-onset and -acquired MRSA, we recommend that either linezolid, or if erythromycin-susceptible, clindamycin, should be included in therapy.⁶

We recommend that particular care be taken to improve the certainty of diagnosis of lower respiratory tract infection as distinct from colonization.

Recommendation 13: Glycopeptides or linezolid for pneumonic infections where MRSA is the aetiological agent. [Category IA]

9. Eye and CNS infections

The limited published data suggest that linezolid may be considered for the treatment of patients with meningeal or cerebral infections.¹²⁵ Animal data suggest that daptomycin may have some advantages over vancomycin owing to its superior bactericidal activity, but there are no dosing recommendations or human data to support this.¹²⁶ The evidence of good penetration into the eye and the relative toxicity of acidic vancomycin in delicate tissues mean that comparative assessment of linezolid in Gram-positive eye infections in animals is overdue to permit formulation of appropriate human trials in deep eye infections.

Recommendation 14: There is insufficient evidence to make a specific recommendation in deep eye and CNS infection. [Category Unresolved issue] Gentamicin, sodium fusidate or chloramphenicol may be used for superficial eye infections if the strain is susceptible. [Category IB]

10. Elimination of carriage

We have not encountered new studies that bear on this topic, which was extensively discussed in previous guidelines. There continues to be very limited data available regarding the use of oral vancomycin as prophylaxis or as part of clearance regimens for MRSA. A study of 35 patients showed that a short course of oral vancomycin plus intranasal mupirocin eradicated MRSA in 69% of 24 patients and staff after one course.¹²⁷ However, 11 required further treatment and 80% of 28 patients and staff reported side effects; consequently, there is insufficient evidence to recommend this regimen.

For treatment and clearance of mupirocin-susceptible MRSA in patients with carriage or possible infection of soft tissue lesions, we recommend that mupirocin should be used with a systemically active agent to improve clearance rates beyond those achieved with nasal or topical mupirocin alone. For mupirocin-resistant strains, there are no trials to assess efficacy. A range of agents has been used topically, but the emergence of resistance to topical antibiotics is well documented.¹²⁸ With mupirocin-resistant MRSA in soft tissues and other potentially infected sites, and given the high rates of both unwanted effects necessitating treatment withdrawal of rifampicin and sodium fusidate in combination⁹⁸ and of clearance failure and neomycin resistance with chlorhexidine and neomycin cream alone, we believe similar treatment principles of using a systemically active agent with a nasal cream containing an antibiotic that is active against the strain should also be applied.

An association between usage of mupirocin and resistance rate has been demonstrated.¹²⁹ Wider use of screening and consequent decontamination have been recommended in the UK. An active local and national programme for monitoring high- and low-level resistance using a validated method is therefore essential not only in bacteraemia but also other infections as the prevalence of particular types of MRSA may change under selective pressure.

Table 1. Recommendations for therapy

Agent	Use as monotherapy?	Key indications	Unwanted effects	Comments
Aminoglycosides	no	use in prophylaxis	ototoxicity especially in renal impairment; nephrotoxicity, especially when used with vancomycin	
Chloramphenicol	yes	CNS infections	rare cause of marrow aplasia	
Clindamycin	yes	skin and soft tissue infections; bone and joint infections	<i>C. difficile</i> colitis and antibiotic-associated diarrhoea	evidence of efficacy as sole agent against strains with macrolide resistance, but risk of emergence of resistance
Co-trimoxazole	yes	skin and soft tissue infections; eradication therapy in combination	Stevens–Johnson syndrome and marrow hypoplasia associated with sulphonamide usage	trimethoprim alone may be preferred
Daptomycin	Yes	bacteraemia; skin and soft tissue infections	skeletal muscle necrosis; monitor creatine kinase	inactivated by surfactant and not to be used in respiratory infections; adjust dose in severe renal impairment
Fusidic acid	no, except when used topically	skin and soft tissue infections; elimination of carriage; adjunct for bone infections	jaundice on parenteral therapy; highly protein bound	resistance—an emerging problem with topical and systemic use; hepatic excretion
Linezolid	yes	pneumonia; serious soft tissue infections; bacteraemia; GISA and glycopeptide-resistant <i>S. aureus</i> (GRSA) infection	5% to 10% incidence of marrow suppression; caution in pre-existing liver insufficiency; peripheral neuropathy; cortical blindness, interactions with anaesthetic agents and monoamine oxidase inhibitors	no information on combination therapy with antimicrobials against MRSA; limited data in severe renal impairment; recommended maximum duration of therapy of 28 days limits use in bone and joint infection; availability of oral agent attractive
Mupirocin	yes (nasal carriage as sole site)	impetigo; use in eradication therapy	minor	high-level resistance is a problem
Quinupristin/dalfopristin	yes	reserve drug; GISA and GRSA infections	flu-like syndrome with joint pains; thrombocytopenia; P450 cytochrome oxidase-related drug interactions	central line administration required; no oral formulation
Rifampicin	never	bone and joint infections; use in skin and soft tissue infections; eradication therapy; adjunct treatment in management of prosthetic infections such as joints and intravascular catheters	possible jaundice with fusidic acid; hepatic enzyme changes; drug interactions and hepatic enzyme induction	emergence of resistance during therapy a hazard; active against organisms in biofilms
Teicoplanin	yes	serious soft tissue infections; bacteraemia (but loading doses essential and adequate levels unpredictable)	high protein binding	not orally absorbed; dose adjustment required in renal impairment; poorly predictable blood levels mean monitoring essential in serious infection
Tetracyclines	yes	skin and soft tissue infections; urinary tract infections; eradication of carriage	avoid in renal impairment or use doxycycline	emergence of resistance

Tigecycline	yes	skin and soft tissue	nausea	dearth of data in MRSA infection
Trimethoprim	yes	urinary tract infection; other use in combination therapy		
Vancomycin	yes	bacteraemia; serious soft tissue infections; bone infection	renal toxicity associated with concurrent aminoglycoside use	dose adjustment required in renal impairment; not orally absorbed; poorly predictable blood levels mean monitoring essential in serious infection

11. Clearance of enteric carriage

There are studies that examine the use of enteral vancomycin to prevent MRSA infection in ICU.^{130,131} Lower airway infection and oropharyngeal carriage were reduced in the treatment groups compared with controls. In addition, enteral vancomycin has been used to control an MRSA outbreak in ICU.¹³² Despite multiple trials on its use, we remain concerned regarding the potential selection for resistant Gram-positive organisms including enterococci and staphylococci and do not support its regular use.

Recommendation 15: We do not recommend the use of oral vancomycin as prophylaxis or part of clearance regimens for MRSA. In soft tissue lesions, clearance of MRSA should include a systemically active oral or parenteral agent as well as an active nasal cream such as mupirocin. With increased use of mupirocin, mupirocin resistance may become a problem and resistance should be carefully monitored at a local level. [Category Unresolved issue]

12. Surgical site infection prophylaxis

Recommendation 16: We see no reason to change our recommendation that patients who require surgery and have a history of MRSA colonization or infection without documented eradication or are at a high risk of MRSA colonization receive glycopeptide prophylaxis alone or in combination with other antibiotics active against other potential pathogens. The use of glycopeptides may also be considered if there is an appreciable risk that patients' MRSA carriage may have recurred or they come from facilities with a high prevalence of MRSA.

We recommend that the use of aminoglycosides be reassessed for prophylaxis of staphylococcal infections in patients not expected to have MRSA colonization. [Category II]

13. Conclusions

The specialized features of antibiotics used in the treatment of MRSA infections are shown in Table 1.

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F. K. G. has been engaged as a paid speaker for Novartis; P. R. C. has received honoraria or funding from various pharmaceutical companies for lecturing, conference attendance and consultancy; D. N. has been paid honoraria, consultancy or speaker

fees from Wyeth, Pfizer, Johnson & Johnson, Bayer and Astellas who are manufacturers of various antibiotics; R. E. W. has undertaken consultancy for and received support to attend clinical meetings from Pfizer UK, Janssen-Cilag and Wyeth. He has authored a commissioned article for Novartis. As part of a balanced portfolio, he is a stockholder in Johnson & Johnson. All other authors have none to declare.

Comment on editorial process

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