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

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These evidence-based guidelines have been produced after a literature review of the treatment and prophylaxis of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The guidelines were further informed by antibiotic susceptibility data on MRSA from the UK. Recommendations are given for the treatment of common infections caused by MRSA, elimination of MRSA from carriage sites and prophylaxis of surgical site infection. There are several antibiotics currently available that are suitable for use in the management of this problem and potentially useful new agents are continuing to emerge.

Keywords: methicillin, MRSA guidelines, evidence-based guidelines, meticillin

Contents

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

1. Introduction

Guidelines for the control of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in the UK have been previously published by a joint Working Party of the British Society for Antimicrobial Chemotherapy, and the Hospital Infection Society in 1986,[1] 1990[2] and together with the Infection Control Nurses Association in 1998.[3] With the licensing of newer antibiotics, including teicoplanin, quinupristin/dalfopristin and linezolid, the Department of Health's Special Advisory Committee on Antimicrobial Resistance (SACAR) asked the three professional bodies to revise the guidelines. Where available, the Working Party also has considered information on unlicensed compounds in Phase 3 clinical trials. Unlike the previous reports, which focused on the prevention and control of MRSA infections, SACAR requested that guidelines should be extended to cover prophylaxis and therapy of MRSA infections and also the laboratory diagnosis and susceptibility testing of MRSA. There is no shortage of agents effective against MRSA in the UK. These guidelines deal with the prophylaxis and therapy of MRSA infections in adults and children in hospital and the community (guidelines for the laboratory

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diagnosis and susceptibility testing of MRSA were published in the December 2005 issue of *JAC* and guidelines for the control and prevention of MRSA in hospitals are due to be published in the *Journal of Hospital Infection*).

Literature searches were conducted from 1998, the date of the last published guidelines, to 2003. The online searches used MEDLINE and EMBASE and were restricted to human studies and publications in English. The subject headings (MeSH headings or Emtree terms) used by MEDLINE or EMBASE indexers respectively have been used resulting in a core of about 1000 abstracts from MEDLINE and about 1600 from EMBASE. Where no satisfactory MeSH or Emtree heading existed textword searching was done. The members of the Working Party supplemented these references from personal reference collections and searches.

The recommendations made in these guidelines are followed by a category classification indicating the level or strength of evidence supporting the recommendation. The category given is taken from the evidence grades of the Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and Prevention.[4] 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 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.

For the past 10 years there has been a major increase in the number of infections caused by MRSA in some countries, especially the UK. To quote from the New Zealand Guidelines: 'In general, inadequate ward or unit staff, or staff training, overcrowding of patients, lack of isolation facilities, frequent relocation of patients and staff, and poor attention to infection control procedures increase the risk of MRSA as well as other nosocomial infections'.[5] MRSA is still largely associated with patients in hospitals and nursing and residential homes although it is now appearing increasingly in a community setting. MRSA presenting from the community is sometimes associated with silent acquisition previously in the healthcare environment,[6,7] or household contacts,[8] and one study suggests that silent acquisition is associated with inpatient care for more than 5 days within the past year.[9] There is also a less common emerging problem of truly community-acquired MRSA with Panton-Valentine leucocidin.[10–13] Once established within hospitals or long-term care centres, MRSA is difficult to control and its survival is probably promoted by the increasing use of antibiotics,[14,15] 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.[16]

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 prevalence of resistance. Overall, antibiotic use in the UK resembles that in low-MRSA-prevalence countries such as Finland.[17] Reversion to the use of first-generation cephalosporins in surgery,[18] reduced use of third-generation cephalosporins and clindamycin,[19] and reduced use of ceftazidime and ciprofloxacin[20] have been described as contributing to reduced prevalence of MRSA in different hospitals. Reduced rates with modified antibiotic policies in healthcare settings smaller than whole hospitals are described but difficult to evaluate.[21–23] High usage of cephalosporins[24–27] and fluoroquinolones[26–34] apparently have been important in selecting for MRSA in some settings, as has use of macrolides, penicillins and to some extent aminoglycosides[27] but the evidence was not conclusive. Quinolone use has been associated in one study with prolongation of MRSA carriage.[35] Latest SHEA guidelines lay emphasis on good antibiotic stewardship and specifically that for fluoroquinolone use.[36]

Reduced use of an antibiotic has also coincided in the past with elimination of certain clones resistant to the drug, e.g. the reduced use of tetracyclines in the 1970s was associated with reductions in tetracycline-resistant MRSA in Denmark and Birmingham.[37,38] However, this was not conclusive as additional interventions such as infection control measures may have confounded the association. Antibiotics that achieve high skin concentrations include fluoroquinolones, macrolides, tetracyclines and lincosamines. 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.[39,40] This may be important for MRSA selection given the extensive use of macrolides, and increasingly fluoroquinolones, in the treatment of respiratory tract infection, and widespread susceptibility to tetracyclines of MRSA currently in the UK.

The appearance of strains of MRSA with raised MICs and 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 some cases suggests transfer from other Gram-positive organisms[41,42] but most isolates are resistant by non-transferable mechanisms.[43] The number of cases of vancomycin-resistant and intermediate-resistant *S. aureus* in the UK and internationally remain low despite the alarm at their initial emergence.[44] However, MRSA strains with a low frequency of bacteria with higher MICs of glycopeptides (hetero-GISA; where GISA stands for glycopeptide intermediate-resistant *S. aureus*) are likely to be more common in the UK as judged by surveys in France and Belgium.[45,46] Although individual treatment failures with such strains have been described, their reliable detection is difficult, and systematic studies of whether such hetero-resistance is associated with treatment failure have not been

carried out.[47] Such strains are likely to have higher vancomycin MICs.[48] MRSA strains with reduced teicoplanin susceptibility have been described in the UK and one clone has been sufficiently defined and prevalent to be designated as EMRSA-17.[49] Teicoplanin-resistant strains have also been reported from France.[50] Vancomycin treatment failures occur with strains apparently susceptible *in vitro*.[51–53] Infections with susceptible strains with MICs ≥ 1 mg/L are said to be more likely to fail on vancomycin therapy (success rates of 7/42) than those susceptible strains with MICs < 1 mg/L (success rates of 10/21). This is associated with group II polymorphism at the accessory gene regulator.[48,54] This needs confirmation. It might suggest that other treatment should be used for MRSA infections with MICs between 1 and 4 mg/L and therefore that vancomycin MICs should always be measured for MRSA treated with this drug. It might also suggest that alternative means of diagnosing this polymorphism would be useful in routine clinical practice. It is noteworthy that the genetic marker described was also associated with possession of the hetero-GISA phenotype. It is important to note that in this study treatment failure was not associated with changed 30 day mortality but this may reflect changed treatment after vancomycin failure. The absence of improved response with high plateau vancomycin levels of 20–25 mg/L does not support the alternative response to the hetero-VISA (where VISA stands for vancomycin-intermediate *S. aureus*) resistance phenomenon of increasing the dose of the drug[55] and accepting that higher serum levels are needed for therapy. However, such alternative higher dosing schedules have not been specifically assessed for improved efficacy in hetero-VISA MRSA infections.

Most published guidelines focus on infection control measures rather than the appropriate use of antibiotics either in long-term care or acute facilities.[56–59] Previous guidelines from this Working Party[1–3] have short sections only on chemotherapy. The present guidelines are specifically directed at aspects of antimicrobial chemotherapy that relate to *S. aureus.*

Mortality rates with MRSA are higher than methicillin-susceptible *S. aureus* (MSSA) in most studies and this appears to be attributable mortality in a meta-analysis,[60] 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.[60–67] There is evidence from two studies that the relatively short period of up to 48 h delay in switching from β-lactam antibiotics to appropriate therapy for methicillin-resistant strains, does not affect outcome.[68,69]

For MSSA, flucloxacillin or cloxacillin are preferable agents and they are available orally for when this is the preferred route of administration. These drugs are safer and have higher cure rates than glycopeptides for susceptible strains in patients with bacteraemia and infection in respiratory primary sites.[62,70] Other factors including acute physiological score have been shown to be important in predicting mortality in bacteraemia overall.[69,71] Good control of diabetes mellitus, drainage of abscesses and particularly removal of sources such as intravenous (iv) lines,[72] are important in predicting 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.[73–75] Nevertheless, overall 30 day mortality rates in patients treated with glycopeptides, or β-lactams for MSSA staphylococcal bacteraemia, were similar in two studies.[63,71] There are few data comparing cloxacillin or flucloxacillin to nafcillin or other penicillinase-resistant penicillins, and little reason to expect differences in efficacy.

Flucloxacillin or cloxacillin are still important agents for treatment of staphylococcal infection in patients in the community but not in environments with a high prevalence of MRSA, e.g. some areas of hospitals. Flucloxacillin is the drug of choice for definitive treatment of MSSA in the UK and is also preferred for empirical therapy except in situations where MRSA is highly prevalent.

The prevalence level at which flucloxacillin or other penicillinase-stable penicillins, in a patient group, becomes no longer the drug of choice is debatable, but 10% resistance has been used as a guide for avoiding the use of empirical gentamicin in Gram-negative infection[76] and we would recommend the same threshold is used when contemplating treatment of staphylococcal infections with isoxazolylpenicillins or cephalosporins. This threshold may be adjusted depending on the apparent severity of infection. Step-down therapy to flucloxacillin from glycopeptides and linezolid should be used where possible when antibiotic susceptibilities of the *S. aureus* strain are known. [Category II]

The remainder of this document addresses treatment of MRSA infection.

2. Prevalence of antibiotic resistance in MRSA in the UK

The Working Party has sought information on the prevalence of antibiotic resistance within MRSA infection in the UK in order to gauge the extent of the threat posed by infection with this organism both within the hospital and the community.

These lines of enquiry include surveillance surveys of blood culture isolates included in the European Antimicrobial Resistance Surveillance System (EARSS) programme, and the incidence of MRSA in bacteraemia (from separate studies in England and Wales, and Scotland).[77] Information on antibiotic resistance rates in MRSA bacteraemia in the UK is available for 2001–03 including systematic information on multiple resistance and regional variation.[78] This bacteraemia surveillance reports ciprofloxacin resistance in 77% of strains, erythromycin in 67%, trimethoprim in 35%, gentamicin in 12%, tetracycline in 4%, sodium fusidate in 2% and rifampicin in 1%. To supplement this information, a questionnaire was sent to hospitals throughout the UK in 2004. It sought information on the number and prescribing patterns of MRSA infection in hospitalized patients over a 7 day period. Details were received from 309 patients with MRSA infection, at all anatomical sites, from 45 diagnostic microbiology laboratories across the UK, a sample of some 15%. Some results are shown in the Appendix. The significant findings were:

- MRSA was predominantly a problem in older patients (82% were aged 60 years or over)
- 92% and 72% of strains were respectively resistant to fluoroquinolones and macrolides (compared with 77.5% and 67.5% in BSAC bacteraemia surveillance)
- Most isolates were susceptible to tetracyclines, fusidic acid, rifampicin and gentamicin
- 12% of tested strains were mupirocin-resistant

- Approximately 50% of treatment regimens used included a glycopeptide alone or with other agents (see Table A2 in the Appendix). The current prevalence in the UK of strains susceptible to other agents may have permitted this diversity of use

The rates of resistance to tetracyclines, macrolides and rifampicin in both a prospective bacteraemia surveillance and our survey appear to be lower than indicated by previously published data for UK strains from strains reported from a wider selection of bacteraemic patients.[79]

In the UK most MRSA from bacteraemias belong to two clones: EMRSA-15 (ST22-MRSA-IV, in new nomenclature) and EMRSA-16 (ST36-MRSA-IV). In 2001, 95% of MRSA reported from 26 hospitals to the EARSS causing bacteraemias, belonged to either EMRSA-15 (60%) or EMRSA-16 (35%).[77] Both clones occurred in 19/25 hospitals. These clones can be recognized in laboratories from their characteristic resistance patterns, although continuous structured national surveillance is necessary to follow changes and sub-type development[80] that may be more frequent in community strains.[81] Molecular typing methods such as PFGE confirm both the major clonal types and allow discrimination of sub-types showing changes in antibiogram,[82,83] which are of importance when investigating an outbreak against a background of endemicity or change in susceptibilities with time.

3. Use of glycopeptides

In the UK vancomycin has been widely used as 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.[84]

These guidelines suggest that glycopeptides are used in empirical treatment of:

- intravascular catheter infection in neonates
- patients with burns in units with high MRSA prevalence
- severe vascular catheter-related sepsis where the catheter cannot be removed and the patient is haemodynamically unstable
- prosthetic valve endocarditis
- foreign body or post-surgical meningitis with inconclusive investigation

and that glycopeptides are not used for:

- mild or moderate *Clostridium difficile* colitis
- prophylaxis of endocarditis except high-risk patients with proven penicillin allergy
- surgical prophylaxis except in known MRSA carriers and, during an outbreak, for prosthetic implants
- prophylaxis of catheter insertion in CAPD, haemodialysis or other iv catheters.
- within the first 96 h of empirical treatment of neutropenic fever
- isolation of coagulase-negative staphylococci from a single blood culture

These guidelines are not designed for endemic MRSA situations where advice on surgical prophylaxis may require modification.

We endorse the Belgian recommendations on use of glycopeptides except that on surgical prophylaxis where the local epidemiology of antibiotic resistance in staphylococci also influences choice of agents, and in neutropenic sepsis if there is severe line infection and the patient has previously had cultures positive for MRSA. In these situations we would advocate early use of vancomycin. [Category IB]

Pharmacodynamic modelling of vancomycin suggests that for those patients with good renal function 12 hourly dosing is optimal[85] although there is evidence that vancomycin 2 g once daily is also satisfactory.[86] If teicoplanin is used, a loading dose and adequate doses, i.e. >6 mg/kg once daily[87] are essential and even so cases of intravascular infection treated with teicoplanin may fail.[88] The pharmacokinetics of teicoplanin are unpredictable and low dosages have been associated with treatment failure.[87,89] Therapeutic drug monitoring with teicoplanin is advocated but not widely practised.[90] Pre-dose blood levels of >10 mg/L in general infection,[91] and >20 mg/L in endocarditis,[92,93] are associated with good outcomes. Loading doses of 400 mg twice daily for the first day are important: an alternative is to give still higher doses once daily initially. The evidence on which recommendations[94] are based of pre-dose blood levels of vancomycin of 5–10 mg/L relates more to potentially toxic peak levels that can be deduced from the trough level.[95,96] The association of toxicity with pre-dose blood levels of >10 mg/L is not well established with the current purified vancomycin product and there are few publications on toxicity in the past 20 years.[97–99] There is evidence that pre-dose levels of vancomycin >10 mg/L are associated with quicker defervescence and halt in increase in peripheral white blood cell counts, and no toxicity was seen if the pre-dose level was <20 mg/L.[99] Even with target levels of 15–25 mg/L another study showed no evidence of change in efficacy or toxicity.[98] Therapeutic pre-dose levels relate to the MIC for the organism and it has been suggested that the existing recommended range is too low. We consider the evidence is that the upper limit of vancomycin pre-dose levels might best be set at 15–20 mg/L. The use of continuous infusion of vancomycin with a target plateau of 20–25 mg/L did not change clinical outcome or unwanted effects when compared with target trough doses of 10–15 mg/L.[55] The lack of evidence of improved outcome does not therefore justify an increase in levels of dose, but the absence of toxicity suggests this change in levels is acceptable. These observations on dosage are puzzling since it seems that failure in MRSA infection is particularly correlated with strains with higher but still apparently susceptible MICs.[48,54] It might be expected that in strains with MICs of >0.5 mg/L, higher doses and serum therapeutic levels would be appropriate and might be associated with a better outcome. There is evidence that in paediatrics current dosing regimens of vancomycin commonly produce pre-dose serum levels <5 mg/L which are below even current standards of dose optimization and dosage recommendations need to be changed.[100,101]

4. Skin and soft tissue infections

It is often difficult to differentiate between staphylococcal colonization and infection in skin and soft tissue infection. Fever, raised peripheral white blood cell count and raised inflammatory markers such as C-reactive protein may help indicate infection. In one institution's predictive model, the presence of ulcers and sores was an independent predictor that bacteraemia would be caused by MRSA and given that clearance of these sites without a systemically active antimicrobial is difficult, care in defining infection and colonization in these lesions is important.[102]

4.1 Impetigo and boils

Impetigo and boils are usually community acquired and the prevalence of MRSA causing this condition is unknown, but, in our experience, prevalence is low in the UK. We are, however, aware that there is an increasing incidence of MRSA in the community worldwide.[11,12] We note the increased resistance to tetracyclines, fusidic acid and kanamycin/neomycin in such strains in Europe.[11]

On this occasion we have decided not to make any recommendations for the treatment of impetigo and boils caused by MRSA. This will be reviewed in future guidelines. [Category II]

4.2 Ulcers and sores

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 (see below) or bacteraemia.

4.3 Cellulitis/surgical site infections

A recent sponsored report[103] on skin and soft tissue infection recommends that particular attention is given to the local resistance rates for several classes of antimicrobial and, in particular, to the occurrence of MRSA. Recommendations for treatment of infections in patients with co-morbidities such as diabetes, peripheral vascular disease, venous insufficiency or morbid obesity, or ill patients, are predicated on excluding MRSA. Ceftriaxone, cefazolin and flucloxacillin are all inactive against MRSA and clindamycin cannot be assumed to be active (see below). A range of alternative agents for limb infections in diabetics with MRSA is suggested.

We are limited in the recommendations we can make in this important area because, despite its prevalence, there is a dearth of published data on treatment of such infection caused by MRSA. In particular there are few data on treatment with tetracyclines, other than minocycline,[104] and none on the use of trimethoprim without a sulphonamide.

Tetracyclines or co-trimoxazole have been used alone or in combination. There is no published large comparison of minocycline and other tetracyclines. Minocycline has *in vitro* activity against some tetracycline-resistant strains but tetracycline and doxycycline are active against many EMRSA-15 in the UK and this trend increased between 1989 and 1995.[79] Minocycline activity against tetracycline-resistant strains can be a phenomenon restricted only to a minority of strains[105] but this may depend on clonal prevalence.[106] There are no BSAC interpretative guidelines for minocycline disc susceptibility testing. Minocycline has adverse effects that other tetracyclines lack, and choice of this tetracycline is not essential if the strain is susceptible to other tetracyclines. Co-trimoxazole has been largely abandoned in the UK because of the adverse effects associated with the sulphonamide component. In Europe co-trimoxazole resistance rates in MRSA have been reported as between 53 and 76%.[107]

We recommend that because of their *in vitro* activity against current UK strains tetracyclines should be more widely used in adults for treatment of skin and soft tissue infections unless these are considered so severe as to carry a high risk of bacteraemia or endocarditis. [Category IB]

Information on vancomycin efficacy in cellulitis is scanty. Cure rates for teicoplanin in excess of 80% have been reported in treatment of cellulitis.[108–110] The non-availability of an absorbed oral formulation of any glycopeptide has limited early discharge from hospital unless home-therapy with parenteral teicoplanin can be arranged. Nevertheless, other agents may also have similar success against sensitive strains and can be used as follow-on therapy. The successful use of linezolid in this way has been described.[111]

Linezolid may be considered as primary treatment as there is evidence that it is effective.[111–113] It has been used in diabetics but the comparator agent used was not active against MRSA and the number of patients with MRSA was small.[114] The expense of linezolid, however, may only be justified if it allows early discharge from hospital.[115,116] Data have been published on a subset analysis of surgical site infection in a randomized, open-label comparative study of vancomycin and linezolid in skin and soft tissue infection.[117] Clinical cure rates were equivalent but microbiological eradication was more frequently reported with linezolid.

Tigecycline is a new tetracycline derivative with a broader spectrum of activity including activity against MRSA. As of the middle of 2005, this drug is unlicensed in the UK and so the final indications and dose recommendations that may ultimately appear in prescribing information are unknown. The drug is licensed in the USA. Daptomycin, which is similarly unlicensed in the UK but licensed in the USA, has been used for soft tissue infections in shorter courses with equivalent success to vancomycin.[118] Initial reports indicate that parenteral quinupristin/dalfopristin[51,119] may also be useful. New vancomycin/teicoplanin congeners, including dalbavancin,[120,121] oritavancin[122] and telavancin,[123] are undergoing clinical trial and their pharmacokinetics will probably permit less frequent dosing and use in outpatient parenteral antibiotic therapy. Initial trials with dalbavancin show efficacy rates, when two doses are given a week apart, are equivalent to current regimens.[121] Oritavancin and telavancin are designed for daily dosing.

We recommend that glycopeptides or linezolid be considered for use in skin and soft tissue infection where the risk of bacteraemia is high. [Category IA]

Rifampicin and fusidic acid resistance rates in MRSA can be high in areas of the world where these agents are widely used.[124] Spread of a few clones appears to have contributed to rifampicin resistance rates of 30–60% in parts of Australia.[125] Resistance to these agents was quite uncommon internationally in the late 1980s[126] but rifampicin resistance rose in many European countries to 14–58%.[107] It is currently rare in the UK.[78] Rifampicin and fusidic acid or trimethoprim should not be used alone but may be useful in combination depending on the antibiotic susceptibility of the isolate. The evidence for usefulness for all of these combinations is not strong and there is only evidence for use of co-trimoxazole and not for use of trimethoprim without sulphonamides.[127–129]

Topical antibiotics, such as mupirocin and fusidic acid, have been used at superficial sites including infected pressure sores and as an ointment to the nose for prophylaxis for peritoneal dialysis exit site infection, haemodialysis catheter site infection[130,131] or orthopaedic surgical site infection.[132] Topical agents will be associated with the emergence of resistance in such large bacterial populations and also probably should not be used in the absence of systemic therapy. Combination prophylaxis has, however, not been evaluated. This advice is clearly different from that given in the earlier version of these guidelines.[1] High-level mupirocin resistance has become an increasing problem[133] and is common in EMRSA-16 but mupirocin resistance does not seem to be common in the UK (see the Appendix). Other topical biocides,

such as chlorhexidine, triclosan or povidone-iodine, may also be useful but the presence of resistance to chlorhexidine and cetrimide,[134–137] the potential for emergence of resistance to triclosan,[138] and the resistance of GISA and glycopeptide-resistant *S. aureus* (GRSA) to phenolics[139] should be noted.

In a double-blind, placebo-controlled study of the use of a high dose of rifampicin 600 mg twice daily with either oxacillin 3 g or vancomycin 2 g daily, rifampicin did not improve outcome, nor was rifampicin resistance detected.[140] Resistance to rifampicin,[141] quinolones, or sodium fusidate[142] frequently emerge on monotherapy with these antibiotics. The use of two effective agents, i.e. agents active *in vitro* against the particular or likely strain has been suggested in other infections to stop emergence of single-step mutation to resistance. In MRSA infection the use of a second agent with rifampicin has been assessed to some extent in both treatment of infection and clearance of carriage in the UK and several other countries.[143–147] Combination therapy has also been recommended for fusidic acid use.[124,142,147] In practice, rifampicin resistance may emerge despite the use of minocycline,[143,144,146] fusidic acid[147,148] or even vancomycin in combination.[145,149,150] There is less information about emergence of resistance to fusidic acid when combinations are used. Findings in animal models also vary: vancomycin may prevent or only reduce emergence of rifampicin[151,152] or fusidic acid resistance.[153] The reasons for these differences are not completely understood and it is therefore unwise to use rifampicin frequently in any given environment. In biofilms rifampicin resistance rates relate to the number of organisms present.[154] In trials of clearance of colonization, rifampicin resistance was more frequently noted with co-trimoxazole than with novobiocin combinations.[129]

There are only occasional descriptions of clinical emergence of fusidic acid resistance in the presence of vancomycin. There are no published data on whether the use of vancomycin with fusidic acid improves outcome. The use of erythromycin with fusidic acid has also been recommended in bone and joint infection if the *S. aureus* is susceptible to both antibacterials.[155] Fusidic acid resistance was not seen when used in combination with co-trimoxazole.[127] Co-trimoxazole may be effective alone, although a comparison still suggests vancomycin is more effective.[156]

We recommend that consideration should be given to the use of the combinations of rifampicin and fusidic acid or glycopeptides and fusidic acid in infections that have failed therapy with single active agents but only where these antibiotics remain active *in vitro*. Formal clinical trials of the use of these combinations are needed. [Category II]

Clindamycin use alone is not generally recommended if the strain is erythromycin-resistant though the MLS_B mechanism as a single-step mutation to resistance can occur.[157] For this reason, clindamycin has been advocated for use alone against erythromycin-susceptible strains. For erythromycin-resistant strains, specific testing for clindamycin resistance is recommended in the presence of erythromycin and reporting as resistant if inducible resistance is demonstrated, although the evidence for frequent one stage mutation to resistance on treatment is poor.[158] New clones of MRSA susceptible to erythromycin are increasingly being described from France[159] and are being seen in some localities in England where the overall prevalence of erythromycin resistance has fallen.[79]

We recommend that clindamycin be considered for use in treatment of MRSA susceptible to erythromycin because emergence of clindamycin resistance requires two mutations and its bioavailability is better. [Category IB]

There is limited information on the treatment of MRSA infections at specific surgical sites. Treatment of established infection associated with orthopaedic prostheses is difficult. MRSA infection is now also the commonest cause of infection after placement of a vascular graft—and this, more frequently than other organisms, may lead to loss of the graft, death and amputation.[160–163] However, some multicentre studies from the UK report very low rates of infection.[164] Rifampicin-bonded vascular grafts, whilst effective in prevention of *S. epidermidis* infections,[165] do not seem effective in MRSA infections.[166]

4.4 Intravenous infusion sites

An assessment must be made of the severity of infection, based on whether the cellulitis and evidence of systemic sepsis are present and on the risk of infection of distant sites. If the infection is severe, e.g. pus, induration or cellulitis are present or a tunnel infection rather than just exit site erythema is present, iv antibiotics such as a glycopeptide or linezolid are indicated, as is urgent removal of the line.[167] Owing to the high risk of bacteraemia and associated mortality, treatment needs to be prompt and effective. Mild infections with limited erythema often respond to the removal of the line and oral therapy may be adequate.

We recommend that iv antibiotics are used in cases of severe iv site infection and in such cases a glycopeptide or linezolid should be prescribed. Mild infections may respond well to other oral agents. [Category IB]

5. Urinary tract infections

Treatment will depend on antibiotic sensitivity and achievable urinary levels of active drug. Because of the lack of data on the efficacy of glycopeptides in this condition, and their cost, toxicity and the availability of other agents, we do not recommend glycopeptide use. Alternatives include nitrofurantoin, trimethoprim, or tetracyclines. Tetracycline susceptibility is more common than trimethoprim susceptibility in MRSA and resistance to trimethoprim is rising.[78,79] The ease with which MRSA can acquire resistance to fluoroquinolones,[168] and the high number and density of organisms in urine suggests that alternative agents should be used if possible even if they appear susceptible *in vitro.*

We recommend that in patients with normal renal function tetracyclines be considered as first-line agents for the treatment of urinary infections caused by susceptible MRSA, with trimethoprim or nitrofurantoin as alternatives. [Category II]

6. Bone and joint infections

Prolonged therapy is often required in these conditions, and the choice of antibiotic will depend on the susceptibility of the infecting strain and the underlying condition of the patient. MRSA is rare in community-acquired infection. Systemic glycopeptides have been shown to be effective in acute cancellous bone infection with MRSA.[169–171] Vancomycin concentrations in cortical bone are less satisfactory.[172] Outpatient treatment with teicoplanin can reduce hospitalization costs.[171] In animal models vancomycin therapy is sometimes disappointing without rifampicin use.[173,174] Quinolones, despite activity in animal models, are seldom useful in clinical practice because resistance is very common.

In acute prosthetic infection, early surgery (often within 2 days of onset of symptoms) is important for successful maintenance of the prosthesis.[175] Otherwise, as with chronic infection,[176] surgical debridement with removal of the prosthesis, cement and sequestra is critical to high success rates. Vancomycin may be useful in cement beads and PROSTOLAC (prosthesis of antibiotic-loaded acrylic cement) at revision arthroplasty.[177]

Linezolid is not currently licensed for use for more than 28 days owing to the risk of bone marrow suppression, which is between 5 and 10% for course durations over 2 weeks.[178] Linezolid has been reported to produce clinical cure in 19/33 (57.5%) MRSA bone infections.[179] Haematological monitoring, including platelet counts, must be performed at least weekly. Linezolid has also been used successfully for 6–10 weeks in 11/14 patients to treat prosthetic joint infection with MRSA where patients declined further surgical intervention.[180] Quinupristin/dalfopristin has been used in a small number of cases of bone and joint infections.[51]

Fusidic acid may also be considered as an adjunct to glycopeptides because of apparently good penetration into bone but this has not been systematically clinically assessed. It is important to note that levels of fusidic acid in chronically inflamed bone and sequestra are much lower than in non-inflamed bone and may fall below the MIC.[181–184] Rifampicin may also be considered for use with glycopeptides because of its activity against biofilms *in vitro* and some evidence in experimental models.[151,185] Drug interactions are more frequently described with rifampicin than fusidic acid. Rifampicin and fusidic acid can be used in combination orally and this is successful in 55% of cases[186] but unwanted effects on liver function are frequent and may necessitate discontinuation.[187] There is *in vitro* evidence that resistance rarely appears to either or both when used in combination[188] but in clinical practice rifampicin resistance may emerge.[147] Fusidic acid is not licensed in the USA: it deserves further assessment. Clindamycin has been used effectively in bone or joint infections in community-acquired MRSA infection.[189] Co-trimoxazole has also been used,[190] although unwanted effects frequently lead to discontinuation of the drug and small-colony variants which are thymidine-dependent and trimethoprim-resistant may appear with this therapy as they may with aminoglycosides or glycopeptides.

We recommend that for prosthetic joint infection with MRSA combinations of vancomycin and rifampicin or vancomycin and sodium fusidate should be used. Other oral combinations, which could be considered in bone and joint MRSA infection are two-agent combinations of rifampicin, a fluoroquinolone, trimethoprim, or fusidic acid if the strain is susceptible to both agents. [Category II]

Clindamycin may be considered for treatment of infection with erythromycin-susceptible variants and can be used orally. [Category IB]

7. Bacteraemia and endocarditis

MRSA bacteraemia is often associated with previous hospitalization[191] even if the bacteraemia is diagnosed on admission to hospital: careful distinction from true community-acquired infection is important because of differences in virulence and antibiotic susceptibility.[7,11,12] Intravascular catheter-related infections must be adequately managed and associated endocarditis may affect the duration of antibiotic therapy.[167] Endocarditis may supervene in between 5 and 15% of cases. Recent data suggest that the incidence of MRSA bacteraemia in children has increased since 1990, although the number of MSSA has remained largely static over the same time period.[192]

Glycopeptides are widely regarded, except in bacteraemic pneumonia, as the drugs of choice for MRSA bacteraemia[111,156] although it is not always clear that comparator drugs were active against MRSA.[193,194] There is some evidence that vancomycin is less satisfactory for MSSA than β-lactams and if vancomycin has been used empirically because of a need to provide effective antibacterials for MRSA, treatment may be changed to an active β-lactam. Data suggesting the superiority of β-lactam antibiotics comes from studies in right-sided endocarditis[195] and also bacteraemia.[73] In the latter study, in MSSA bacteraemia, both presence of endocarditis and therapy with vancomycin independently predict relapse or persistence of bacteraemia, even when iv catheters have been removed. Treatment with nafcillin was not associated with persistent bacteraemia or relapse. High relapse rates with vancomycin treatment and the failure to remove catheters have also been reported by others in patients with *S. aureus* bacteraemia, including both MRSA and MSSA, in the absence of endocarditis.[73,75] MRSA infection in the presence of haemodialysis is also associated with a high incidence of endocarditis and septic arthritis with similar associations with leaving an intravascular catheter *in situ* and either with MRSA specifically or possibly with vancomycin therapy,[74] and with a higher all-cause mortality at 3 months and much higher costs than MSSA bacteraemias.[61] Improved antibiotic and infection control management in dialysis centres may therefore be of particular importance. Vancomycin is preferred to teicoplanin for treatment of *S. aureus*, including MRSA, bacteraemia unless teicoplanin levels are measured or high dosages (>6 mg/kg and probably 800 mg/day) are used empirically. Early studies with low dosages (200 mg/day) of teicoplanin without the use of loading doses were complicated by failure[196] and doses up to 1200 mg/day may be needed[87] but are expensive.

It has been suggested that using rifampicin with vancomycin improves outcome in uncomplicated bacteraemia but this comes from one uncorroborated study.[149] Fusidic acid in combination with vancomycin may be relevant as an alternative to rifampicin. There is no evidence that the use of aminoglycosides with glycopeptides improves outcome in MRSA bacteraemia or endocarditis, and using aminoglycosides with vancomycin should be avoided, where possible, because of the risk of increased toxicity.[197–199]

Linezolid appeared to be superior to teicoplanin in one study[113] but equivalent in a randomized double-blind control trial.[93]

In neutropenic patients with fever, from whom MRSA has been isolated previously, the presence of serious iv catheter-related infection is an indication to use glycopeptides,[167] immediately rather than waiting 96 h as suggested in Belgian guidelines.

Other antibacterials may need consideration as alternatives depending on the source of the bacteraemia and regional resistance rates.[78] Failures with chloramphenicol- and amikacin-containing combinations are described.[170] There are limited data to show that linezolid or quinupristin/dalfopristin are as effective as vancomycin in uncomplicated bacteraemia, and in the unlikely event of a GISA or GRSA bacteraemia these would appear to be the agents of choice,[200] although the diverse agents used in these infections[44,201] make conclusions based on evidence impossible. Resistance to quinupristin/dalfopristin in MRSA is already described in France where pristinamycin has been widely used.[202] Linezolid resistance

in *S. aureus* has also been described but is rare.[203,204] A preliminary report on daptomycin resistance has also been made.[205] Guidelines for treatment of endocarditis and other intracardiac infections (e.g. pacemaker wires), including infections due to MRSA, have been recently published by the BSAC.[206] Infection of a pacemaker box requires removal of the box and the same antibiotic treatment as for prosthetic joint infections.

A minimum duration of 14 days' antibiotic treatment is required for uncomplicated bacteraemia,[72,75,167,207] but oral therapy may be substituted for initial parenteral agents. It is important that the duration of treatment is adequate and any local focus of infection is eliminated. A strategy using trans-oesophageal echocardiography to determine the need for more prolonged treatment in catheter-associated bacteraemia has been explored.[208] In *S. aureus* bacteraemia trans-oesophageal echocardiography is three times more likely to detect vegetations on heart valves than trans-thoracic echocardiography.[209]

We recommend a minimum duration of 14 days' treatment with glycopeptides or linezolid for uncomplicated bacteraemia. Longer treatment will be required in patients with, or at higher risk of, endocarditis, and trans-oesophageal echocardiographic assessment is important. [Category IA]

8. Respiratory tract infections

MRSA-associated upper respiratory tract infection, e.g. sinusitis, is rare and tends to be restricted to patients after ENT surgery or healthcare staff. Agents such as those suggested as alternatives to glycopeptides in cellulitis should be considered according to *in vitro* susceptibilities. Lower respiratory tract infection with MRSA occurs in patients with bronchiectasis of any aetiology including cystic fibrosis. Children with chronic disease, such as cystic fibrosis, are at particular risk of developing chest infections. Miall *et al*.[210] studied 300 patients with cystic fibrosis to analyse whether infection with MRSA led to a worse respiratory outcome. It was concluded that MRSA infection in children with cystic fibrosis does not alter respiratory function significantly, but might have an adverse effect on growth. There is no good evidence that it is important to treat MRSA in adult bronchiectasis or chronic obstructive pulmonary disease as infection and colonization may be difficult to distinguish. Trimethoprim and co-trimoxazole should be avoided in chronic pulmonary sepsis with staphylococci because of the risk of development of resistant thymidine-dependent strains.[211] As alternatives in adults, a tetracycline or chloramphenicol could be considered.

We recommend that infections in bronchiectasis without pneumonia should be treated with non-glycopeptide agents according to *in vitro* susceptibilities as suggested for cellulitis. [Category II]

In pneumonia vancomycin proved less effective than flucloxacillin or other penicillinase-stable penicillins for MSSA although the presence of shock was a confounding factor.[70] Further reports of vancomycin treatment failure have followed.[52] Linezolid has been reported to be as, but not more, effective than vancomycin for empirical therapy of hospital-acquired, ventilator-associated pneumonia in two adult studies.[212,213] Subset analysis amalgamating the two trials in adults in hospital-acquired pneumonia[214] and ventilator-associated pneumonia[215] suggested that there was significant benefit in the use of linezolid in those patients from whom MRSA was grown. However, a third small study in adults[111] and one small study in children[216] found equivalence between linezolid and vancomycin in MRSA pneumonia. Larger studies are required to compare conclusively vancomycin with linezolid for MRSA chest infections, but the differences in outcome seem to be small. Quinupristin/dalfopristin has also been assessed as rescue therapy in ITU patients with MRSA, and in pneumonia, without significant differences being found.[53,217] The diagnosis of ventilator-associated pneumonia, as distinct from respiratory tract colonization, is difficult but critical when making the decision to use antibiotics. Rigorous clinical and laboratory criteria should be applied. There is evidence that vancomycin is effective in community-acquired pneumococcal pneumonia but no similar evidence is available in influenza-associated staphylococcal pneumonia.

Newer fluoroquinolones with improved Gram-positive spectra have not been shown, as yet, to be effective against ciprofloxacin-resistant MRSA pulmonary infection and caution in their use in hospitals is advised given the selective influence of earlier fluoroquinolones. The selective influence for MRSA is important in hospitals but has not been systematically studied.

We recommend that particular care be taken to improve the certainty of diagnosis of lower respiratory tract infection as distinct from colonization. We recommend the use of either glycopeptides or linezolid for pneumonic infections where MRSA is the aetiological agent. [Category IA]

9. Eye and CNS infections

Postoperative surgical infections in the eye are commonly treated with intravitreal vancomycin, the low pH of which can be damaging to tissues. Teicoplanin given by local injection into the eye, which has a neutral pH, has not been clinically evaluated in endophthalmitis but has been given into the vitreous humour of rabbits at concentrations of 0.75 mg in 0.1 mL without retinal toxicity.[218] Fusidic acid,[219] clindamycin,[220] linezolid[221] and fluoroquinolones all penetrate the vitreous humour. Clindamycin and linezolid require individual clinical assessment in infections with susceptible strains. There is evidence that vancomycin or amikacin systemically are ineffective in the prophylaxis of staphylococcal endophthalmitis but quinolones were effective with susceptible strains of MRSA.[222] Quinolone resistance is now so common in MRSA that fluoroquinolones should not be used for prophylaxis. Superficial eye infections can be treated with topical chloramphenicol,[223] fusidic acid or gentamicin, if the strain is susceptible.

In staphylococcal brain abscess and meningitis, vancomycin has been used[224] but consideration should be given to the use of chloramphenicol if the strain is susceptible. Rifampicin, clindamycin and fusidic acid may also be useful in combinations on the basis of evidence of penetration of the abscess[225] or their use in some other CNS infections.[226] Evidence on use of linezolid for these indications is awaited.

There is insufficient evidence to make a specific recommendation in deep eye and CNS infection. [Category Unresolved issue] **Gentamicin or chloramphenicol may be used for superficial eye infections.** [Category IB]

10. Elimination of carriage

In the pre-Medline older literature, use of prophylactic nasal neomycin creams was initially described as useful in reducing wound

sepsis rates with susceptible staphylococci.[227] Later studies showed this was ineffective[228–230] even when selectively applied.[231] Emergence of resistant strains was a problem and the use of local neomycin was generally abandoned.[232] There is little information on clearance of MRSA strains with neomycin but use of neomycin–chlorhexidine on an individual basis may be considered for mupirocin-resistant strains. The important older literature on staphylococcal infection that precedes the arrival of literature abstraction and computerized databases has been widely forgotten but it contains numerous important experiments on control measures with modern applications to MRSA. This literature was well summarized just before the advent of data abstraction.[233,234]

In recent times, tea tree preparations have also been assessed in a double-blind controlled comparison with mupirocin and have been found to be disappointing in the nose, although slightly more promising at skin sites.[235]

Considerable reliance has been placed in the past on eradication therapy and the use of mupirocin in the control of epidemic, if not endemic, MRSA. Alternative measures are also of critical importance. Standardization of culture technique and follow up of eradication has not been achieved and limits the assessment of studies of mupirocin. The use of mupirocin in eradicating mupirocin-susceptible strains from the nose is well established and in early studies before the description of resistance about 85% of nasal carriers were cleared, although relapse did occur.[236] A more recent study confirmed this.[237] Carriage in the nose alone is more likely in staff than in patients, the latter often having soft tissue lesions. Clearance of nasal *S. aureus* with mupirocin in staff is associated with clearance of hand carriage, which may be important in control of outbreaks.[130]

Careful consideration should be given as to whether reliance should be placed on the use of mupirocin to aid control of endemic MRSA in hospitals,[238] although it is undoubtedly useful in outbreaks in low-prevalence environments. The use of blind intranasal mupirocin in an outbreak situation may be effective[239,240] but increases exposure to the drug and may increase the risk of selecting resistant strains. Repetitive or prolonged use of mupirocin is unwise.[241] A Cochrane systematic review[242] of randomized, controlled trials published from 1966 to 2003 of systemic and topical regimens to clear carriage concluded that there was insufficient evidence to support the use of topical or systemic antimicrobial therapy for eradicating nasal or extra-nasal MRSA although this has been successful in one more recent randomized, double-blind, placebo-controlled trial.[237]

The natural history of carriage without treatment is that persistence occurs in some 40% of patients, particularly if skin breaks are present.[243] The effect of skin breaks as predictors of failed therapy is also confirmed from placebo-controlled double-blind studies of nasal mupirocin, with rates of failure reaching 79%.[35]

We do not recommend the use of nasal mupirocin alone in patients, or staff, with skin breaks. [Category IB]

The increasing prevalence of mupirocin-resistant (EMRSA-16) strains in some areas, although not apparent generally in the UK, (see the Appendix) also means that eradication treatment with mupirocin should now only be considered in especially vulnerable preoperative patients, such as those undergoing joint replacement, stent placement, vascular and cardiothoracic surgery or for patients in a unit where MRSA has a low prevalence and the intention is to eliminate the risk of spread. The international prevalence of mupirocin resistance is unknown. The required duration and frequency of treatment is not clear: Dutch guidelines recommend a maximum of a 5 day course.[58] Clinical trial data has shown efficacy with 14 days of treatment twice daily.[237]

As mupirocin is a topical agent used in high local concentration, it may be important to test strains by using high-content antibiotic discs to see if the MIC is likely to be particularly high. Whether mupirocin will clear carriage may depend on whether high MICs are present. Data on the level of resistance was only partially available in some of the studies included in the Cochrane review.[242] An important recent study reported clearance rates of the nose of ~80% at 3 days post-treatment if mupirocin-susceptible or low-level mupirocin-resistant MRSA were present and only 27% clearance of high-level mupirocin-resistant strains.[244] The number of mupirocin low-level resistant strains was very small in this study. In eradication or suppression therapy with mupirocin in high-risk situations, this implies that susceptibility testing should be performed with high content discs to detect high-level resistance.[245,246] High-level resistance is usually plasmid-mediated. An uncorroborated small study[244] showed that whereas nasal clearance persists at 4 weeks with mupirocin-susceptible strains, 80% of low-level mupirocin and 95% of high-level resistant strains reappear. This study suggests that eradication therapy will not work with low-level resistant strains and is partially supported by findings in an underpowered study in which clearance rates in patients with nasal cultures alone positive decline from 86 to 44% in the presence of resistance and from 55 to 33% when other sites are positive as well.[247] Both of these studies are small, however. Epidemiological data on low-level resistance is therefore important.

We recommend, like the Cochrane review, that a large double-blind placebo-controlled study is now needed to confirm whether mupirocin remains useful in clearing carriage in patients or staff when low-level mupirocin resistance is present. This study should be multicentre and matched for presence of skin lesions.

Because of the high relapse rate when mupirocin is used alone, in highly vulnerable patients with peripheral colonized or infected lesions, or if the MRSA strain is mupirocin-resistant, the use of alternative nasal topical agents, e.g. bacitracin,[128] has been investigated. Bacitracin in combination with co-trimoxazole and rifampicin produces persistent clearance rates of 65%. Co-trimoxazole plus nasal fusidic acid has been reported as being as successful as nasal mupirocin.[127] Nasal clearance rates at 28 days were 95% declining at 3 months to 71%. Soft tissue clearance at 28 days was 69% compared with 45% with mupirocin but the number of participants followed up is not stated and these results were not considered significant. No study has been carried out with trimethoprim and this is needed to avoid the risks of sulphonamide use in the co-trimoxazole combination. Oral fusidic acid must not be used alone.[145] Novobiocin in combination with rifampicin has produced similar eradication rates to co-trimoxazole with rifampicin (67% versus 53%) but was less likely to select for rifampicin resistance.[129] Novobiocin is not generally available. Colonization with rifampicin-resistant strains at 4 weeks was also a problem when rifampicin was used alone or with minocycline for 5 days.[146] Combinations involving fluoroquinolones are not recommended because of the high prevalence of fluoroquinolone-resistant strains in the UK and the selective effect of fluoroquinolones for resistance on the normal skin flora.[39,40] The use of systemic agents in clearance depends on *in vitro* susceptibilities, the underlying clinical condition and risk. Overall, this collection of small trials on

alternative therapies to mupirocin suggests that various combinations of co-trimoxazole, rifampicin, tetracyclines, mupirocin and fusidic acid have some efficacy (50–75%) but this cannot be considered as established clinical management. Further investigation is urgently needed on the use of currently available and alternative agents, including lysostaphin, in combination to eliminate MRSA from skin and soft tissue sites as well as from the nose.

If treatment is required, we recommend that mupirocin should only be used with a systemically active agent in treatment of patients with carriage, or infection, at extra-nasal sites. [Category II]

Systemic vancomycin does not clear nasal, throat, or gut sites at least at conventional doses of 20 mg/kg daily but there is evidence of suppression at doses of 40 mg/kg daily, which is above the normal dosage recommendation.[248] No data are available for teicoplanin but it is likely that this is ineffective. Three trials show that the use of oral vancomycin[249–251] improves clearance rates, presumably acting against gastrointestinal carriage of MRSA.[252] Selection by parenteral vancomycin use of glycopeptide-resistant enterococci (GRE) has not been substantiated in numerous publications including a recent meta-analysis, systematic review and a carefully controlled observational study.[253–255] Nevertheless it would be counter-intuitive for there not to be a risk of oral glycopeptides, particularly at low dose, selecting for GRE and, more importantly, for GRSA and GISA. This risk is unacceptable at a time when other agents have not yet fully established their longevity and efficacy as alternative options.

We do not recommend the use of oral vancomycin as prophylaxis or part of clearance regimens for MRSA. [Category II]

High concentrations of linezolid have been demonstrated in the skin and might be expected to be selectively active on the skin flora. Nevertheless, the importance of the agent in other therapeutic situations and the availability of data showing that relapse in carriage sites occurs after normal treatment mean that it cannot be currently recommended for use in clearance regimens.

11. Surgical site infection prophylaxis

Patients who undergo clean elective surgical procedures and who are colonized or infected with MRSA are usually given MRSA-colonization eradication therapy, which is usually successful short term. However, as part of risk reduction, they should probably in any case receive operative prophylaxis active against MRSA. Glycopeptides are commonly used as part of prophylactic regimens in patients colonized or infected with MRSA but few authorities recommend general glycopeptide prophylaxis, which should be limited to reduce the risk of emergence of resistant organisms. Patients known to be colonized or infected with MRSA or who have been a hospital inpatient on units with a high incidence of MRSA are candidates for systemic prophylaxis specifically directed against MRSA. However, the sensitivity of a history of hospitalization as an indicator of MRSA colonization may be low.[256] In addition, preoperative screening for MRSA has been recommended in elective surgery followed by attempts at clearance of carriage. Conjunctival carriers of MRSA have been cleared of MRSA by topical therapy prior to ophthalmic surgery.[257]

Evidence from a study of MSSA carriage showed that mupirocin alone does not reduce *S. aureus* infection rates to a statistically significant extent.[132] However, there is evidence that a reduction both in surgical site infection and nasal colonization with MRSA can be made before elective orthopaedic surgery with an anti-staphylococcal regimen including the use of 1 day preoperative and 4 days postoperative nasal mupirocin.[258] The reason for this difference is not apparent. Further studies in emergency orthopaedic surgery suggest that admission from long-term care facilities, or other hospitals,[9] rather than the patient's own home is an adequate predictive factor for MRSA carriage and may usefully indicate those who would benefit from vancomycin prophylaxis.[259] However, in orthopaedics, sepsis can apparently occur regardless of carriage status and appropriate prophylaxis, so changing prophylaxis may not be indicated at all.[26] The routine use of mupirocin to treat MRSA carriers has been associated with the emergence of resistance and consequent failure to clear carriage.[260]

In general surgery, antimicrobial prophylaxis regimens such as those using cephalosporins,[261] have not been reassessed for efficacy since the advent of a high prevalence of MRSA—resistant to cephalosporins—in the UK from 1992 onwards. These general surgical prophylactic regimens need to be critically reviewed because efficacy of prophylaxis may, in part, be related to prevention of susceptible staphylococcal infections as well as anaerobic infection, as seen with trials of aminoglycoside and either lincosamine or metronidazole prophylaxis.[262,263] It is important to note that the use of lincomycin and clindamycin[262] was abandoned in favour of metronidazole in the UK because of *C. difficile* colitis.[263] Gentamicin and other current aminoglycosides are active against EMRSA-15 but not classical EMRSA-16, although there are now gentamicin-susceptible EMRSA-16.[264] The role of aminoglycosides in surgical prophylaxis and treatment as part of non-glycopeptide regimens requires reassessment if staphylococci locally are susceptible to these agents. Toxic effects limit the prolonged use of aminoglycosides in treatment but to a lesser extent in prophylaxis. Aminoglycosides may be useful substitutes in prophylactic combination regimens.[265] Caution is necessary in gentamicin use. Hetero-GISA in France and Belgium are specifically noted to be frequently gentamicin-resistant.[45,46,266] Reports of failure with amikacin against gentamicin-resistant MRSA[170] are in retrospect not surprising given the bi-functional phosphoacetyl-transferase enzyme responsible for aminoglycoside resistance in staphylococci[193] and this compound offers no advantage over other aminoglycosides for staphylococci.

We recommend that patients who require surgery and have a history of MRSA colonization or infection without documented eradication 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. [Category II]

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

12. Conclusions

Our summarized recommendations for the treatment of MRSA infection are shown in Table 1. Special features of antibiotics used in the treatment of MRSA infections are shown in Table 2.

Table 1. Summary of recommendations

We make no recommendations for	• the treatment of impetigo and boils caused by MRSA. • the treatment of deep eye and CNS infection.
We do not recommend	• the use of nasal mupirocin alone for clearance of nasal carriage in patients, or staff, who also have skin breaks. [Category IB] • the use of oral vancomycin as prophylaxis or part of clearance regimens for MRSA. [Category II]
We recommend that	• if a threshold of 10% resistance in staphylococci is exceeded isoxazolyl penicillins and cephalosporins are not used for empirical treatment of serious staphylococcal infection. [Category II] • step-down therapy to flucloxacillin or cloxacillin from glycopeptides and linezolid should be used wherever possible once antibiotic susceptibilities of *S. aureus* are known. [Category II] • Belgian recommendations on empirical use of glycopeptides are followed except that on surgical prophylaxis where epidemiological criteria also influence choice of agents [Category IB] and on neutropenic patients with a past history of MRSA and obvious line sepsis.
In skin and soft tissue infections	• in the UK, tetracyclines should be more widely used in adults for treatment unless infections are so severe as to carry a high risk of bacteraemia or endocarditis. [Category IB] • glycopeptides or linezolid be considered for use where the risk of bacteraemia is high. [Category IA] • in infections that have failed therapy with single active agents, combined use of rifampicin and fusidic acid, or glycopeptides and fusidic acid or glycopeptides and rifampicin be considered but only where these antibiotics remain active *in vitro*. Formal clinical trials of the use of these combinations are needed. [Category II] • clindamycin be considered for use in treatment of MRSA susceptible to erythromycin because emergence of clindamycin resistance requires two mutations and its bioavailability is better. [Category IB] • iv glycopeptides or linezolid are used in severe iv site infection and that other oral agents are used in mild infections. [Category IB]
In urinary infections	• tetracyclines are considered as first-line agents for the treatment of urinary infections caused by susceptible MRSA, with trimethoprim or nitrofurantoin as alternatives. [Category II]
In bone and joint infections	• glycopeptides be used for parenteral treatment particularly of multiresistant MRSA and combination with rifampicin or fusidic acid should be considered. [Category IB] • combination therapy with two antibiotics that remain active *in vitro* should be used where monotherapy has failed. Agents that may be used in such combinations include rifampicin, a fluoroquinolone, trimethoprim or fusidic acid. Such a combination may be considered as first-line therapy if the strain is susceptible to both agents. [Category II] • clindamycin may be considered for treatment of infection with erythromycin-susceptible variants and can be used orally. [Category IB]
In bacteraemia	• a minimum duration of 14 days' treatment with glycopeptides or linezolid for uncomplicated bacteraemia. Longer treatment will be required in patients with, or at higher risk of, endocarditis, and echocardiographic assessment is important. [Category IA]
In respiratory infections	• infections in bronchiectasis should be treated with non-glycopeptide agents according to *in vitro* susceptibilities as suggested for cellulitis. [Category II] • particular care is taken to improve the certainty of diagnosis of lower respiratory tract infection as distinct from colonization. • the use of either glycopeptides or linezolid for pneumonic infections where MRSA is the aetiological agent. [Category IA]
In eye infections	• gentamicin or chloramphenicol may be used for superficial eye infections. [Category IB]
In clearance of carriage	• a large double-blind placebo-controlled study, is needed to confirm whether mupirocin remains useful in clearing carriage in patients or staff when low-level mupirocin resistance is present. This study should be multicentre and matched for presence of skin lesions. • mupirocin should only be used with a systemically active agent in treatment of patients with carriage, or infection, at extra-nasal sites. [Category II]
In surgical site prophylaxis	• patients who require surgery and have a history of MRSA colonization or infection without documented eradication 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. [Category II] • the use of aminoglycosides is reassessed in patients not expected to have MRSA colonization for prophylaxis of staphylococcal infections.

Table 2. Special features of antibiotics used in the treatment of MRSA infections

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	*Clostridium difficile* 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	Marrow hypoplasia and sulphonamide allergy	Trimethoprim alone may be preferred
Fusidic acid	Never	Skin and soft tissue infections Elimination of carriage	Jaundice on parenteral therapy	Resistance—an emerging problem with topical and systemic use Hepatic excretion
Linezolid	Yes	Pneumonia Serious soft tissue infections Bacteraemia GISA and GRSA infection	5–10% incidence of marrow suppression Caution in pre-existing liver insufficiency Peripheral neuropathy	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)	Not recommended for therapeutic use Use in eradication therapy	Minor	Established and increasing 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	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)		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
Trimethoprim	No	Urinary tract infection Other use in combination therapy		Dearth of data in MRSA infection
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

There are a number of existing licensed antimicrobial agents that can be used. We recommend the reassessment of current prophylactic regimens for surgical site infection to cover appropriately the possibility of MRSA infection. These guidelines will require updating as evidence emerges on the use of newer antimicrobial agents active against MRSA, including a number still under development.

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Transparency declarations

C. G. G. declares that during the preparation of this document he was not in the employment of any pharmaceutical firm with interests in the content of the guidelines but he did accept appointment to the advisory boards of two, Pfizer and Chiron. D. I. E., A. P. F., F. K. G., G. L. R. and R. E. W. declare that during the preparation of this document they were not in the employment of, nor receiving funding from, any pharmaceutical firm or other organization that may have resulted in a conflict of interest.

Comment on editorial process

This Working Party Report was put out for consultation on 11 April 2005 (consultation period closed on 6 May 2005) and amended in light of the comments prior to its submission to this journal. This national consultation exercise amongst major stakeholders and other interested parties replaced the journal's peer review process.

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Appendix. UK survey of antibiotic therapy for infections with MRSA

Microbiologists from the UK were invited to participate via the Association of Medical Microbiologists mailing list. Where there was more than one microbiologist per hospital trust, participants were encouraged to nominate a co-ordinator for that Trust.

The survey was carried out over a 7 day period between 6 February and 12 February 2005. Participants were requested to complete a questionnaire for each inpatient who had a clinical specimen positive for MRSA during the study period. Patients who had positive surveillance cultures only were excluded. Participants were asked to record the antibiotic sensitivity of the MRSA.

Results

A total of 309 questionnaires were returned from 45 Trusts.

Trusts which identified themselves were from the following locations: Belfast, Birmingham, Berkshire, Blackpool, Cumbria, Cheshire, Cambridge, Chester, Devon, Durham & Darlington, Edinburgh, Essex, East Sussex, Glasgow, Gloucester, Hartlepool, Kent, London, Newcastle, Nottingham, Portsmouth, Surrey, Salford, Sheffield, Shrewsbury, Somerset, Tyneside, Taunton and Worcester.

Table A1 describes the antibiotic resistance pattern of the MRSA isolates from the clinical specimens included in the survey.

Table A1. Antibiotic resistance in addition to methicillin

	Number and % resistant
Fluoroquinolone	258 (92% of tested)
Macrolide & fluoroquinolone	209 (72% of tested)
additionally mupirocin	33 (12% of tested)
additionally gentamicin	7
additionally tetracycline	3

Table A2. Choice of new antibiotic to treat MRSA when microbiology results are available

	Number
β-Lactam	4
Glycopeptide	80
Tetracycline	16
Trimethoprim	12
Rifampicin	14
Fusidic acid	12
Linezolid	8
Gentamicin	3
Other[a]	10
Any combination	40

Total number of patients = 151.
[a]Includes chloramphenicol, dalfopristin/quinupristin, clindamycin, nitrofurantoin and fosfomycin.