Review of new guidelines for prophylaxis and treatment of MRSA infections

A joint working party has produced evidence-based guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK. These guidelines will help clinicians choose appropriate therapy and point to areas where further research is needed. This review summarizes the main recommendations and discusses their implementation into clinical practice.

UK guidelines on methicillin-resistant *Staphylococcus aureus* (MRSA) were last published in 1998 (Ayliffe et al, 1998); they were not based on a systematic literature review and focussed on infection control rather than therapy. Since then new agents with activity against MRSA (linezolid and quinupristin/dalfopristin) have been introduced and the epidemiology of MRSA has continued to evolve. The Department of Health's Special Advisory Committee on Antimicrobial Resistance requested a joint working party representing the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, the Infection Control Nurses Association and an observer from the Department of Health produce new evidence-based guidelines for laboratory diagnosis and susceptibility testing, the management of MRSA infections, and prevention and control. The guidelines on diagnosis and testing of MRSA were published in December 2005 (Brown et al, 2005) and the new guidelines on MRSA therapy and prophylaxis have just been published (Gemmell et al, 2006).

Table 1. Evidence categories used by the working party

Overview	Category	Recommendation	Evidence level
Strong evidence	IA	Strongly recommended for implementation	Strongly supported by well designed experimental, clinical or epidemiological studies
	IB	Strongly recommended for implementation	Supported by certain experimental, clinical or epidemiological studies and a strong theoretical rationale
Required practice	IC	Required for implementation	Mandated by federal or state regulation or standard or representing an established association standard
Weak evidence	II	Suggested for implementation	Supported by suggestive (non-definitive) clinical or epidemiological studies or a theoretical rationale
Insufficent evidence	Unresolved issue	No recommendation is offered	No consensus or insufficient evidence exists regarding efficacy

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Evidence base and evidence categories

The working party performed an electronic literature review, focusing on about 2500 references on human studies published in English between 1998, the date of the last published guidelines, and 2003. These were supplemented by references provided by the working party members. Just over 250 references were cited in the final report but the criteria for inclusion or exclusion were not given.

One of the problems with any guideline for MRSA treatment is that there are few reported trials of older agents used successfully for many years against methicillin-sensitive *Staph. aureus* (MSSA), such as trimethoprim and the tetracyclines. The evidence for the clinical effectiveness of these agents against susceptible strains of MRSA is largely derived by extrapolation from case series of patients treated for MSSA infections. However, there is evidence, quoted in the guidelines (Blot et al, 2002; Cosgrove et al, 2003; Engemann et al, 2003), that MRSA infections – even when treated appropriately – have worse outcomes than similar MSSA infections. Such extrapolations, therefore, should be treated with caution.

Recommendations on treatment and prophylaxis were classified by the Centers for Diseases Control and Prevention's criteria for the strength of supporting evidence (*Table 1*). Their category IB (strong evidence, strongly recommended for implementation) is based on 'certain experimental, clinical or epidemiological studies and a strong theoretical rationale'. Thus, some treatment recommendations in these guidelines are supported by theoretical considerations rather than clinical trial data.

Current antimicrobial susceptibilities of MRSA in the UK

Most recent UK isolates of MRSA are macrolide and fluoroquinolone resistant and belong to two clones: EMRSA15 (ST22-MRSA-IV, in the new nomenclature) and EMRSA 16 (ST36-MRSA-IV). EMRSA-16 is usually resistant to methicillin, erythromycin, ciprofloxacin, trimethoprim and gentamicin, and accounts for about 35% of isolates; EMRSA-15 is usually resistant to methicillin, erythromycin and ciprofloxacin and accounts for about 60%. The prevalence of EMRSA-16 may be declining.

The working party conducted a postal questionnaire survey of MRSA treatment in the UK in 2004. Details

were received of 309 patients with MRSA infection from 45 diagnostic laboratories, and the responses indicated that 92% and 72% of strains respectively were resistant to fluoroquinolones and macrolides but most were susceptible to the tetracyclines, fusidic acid, rifampicin and chloramphenicol (Gemmell et al, 2006).

The need to limit unnecessary antimicrobial use

Unnecessary antimicrobial therapy is well recognized to be a driver of increasing antimicrobial resistance. The guidelines found that no particular class of antibiotic specifically favours the emergence of MRSA, but the unnecessary use of glycopeptides may promote the emergence of glycopeptide resistance in enterococci and other organisms, including *Staph. aureus*. The guideline recommendations took into account the need to avoid unnecessary antimicrobial usage.

Prophylaxis of MRSA infections

Clearance of MRSA carriage

It is recommended infection control practice to try to clear MRSA from colonized patients or staff to reduce the risks of MRSA cross-infection and surgical site infection. In the new guidelines, the only high level recommendation regarding such prophylaxis is a negative one:

The guidelines do not recommend the use of nasal mupirocin alone for patients or staff with skin breaks (category IB).

Mupirocin has been widely used to eliminate MRSA carriage, but it may fail (especially in individuals with skin breaks) and is often associated with the emergence of mupirocin resistance. A Cochrane review concluded that there was insufficient evidence to support the use of topical or systemic antimicrobial therapy for eradicating nasal or extra-nasal MRSA (Loeb et al, 2003). The guidelines suggest that while topical mupirocin may be useful in outbreaks in low-prevalence environments, it may not be effective in the control of endemic MRSA. They, like the Cochrane review, recommend that a large double-blind, placebo-controlled trial should be performed to confirm whether mupirocin remains useful in clearing MRSA carriage in patients or staff when low level mupirocin resistance is present. The working party also recommends that further investigations are needed of combinations of agents to eliminate MRSA from skin and soft tissue sites.

The guidelines do not recommend the use of oral vancomycin for prophylaxis or as part of clearance regimens for MRSA. They base this recommendation on the limited evidence of effectiveness and concerns about encouraging glycopeptide resistance. However, they note that there is evidence that oral vancomycin can clear gut carriage (which may be a site of persistent colonization) and a lack of evidence that this has been associated with the emergence of glycopeptide-resistant enterococci (GRE). There is obviously a need for more trials in this area.

Surgical prophylaxis

MRSA surgical site infection often occurs as endogenous infection in patients who are colonized with MRSA at the time of surgery but there is little trial evidence on which to base recommendations for surgical prophylaxis. The guidelines recommend preoperative screening for MRSA followed by attempts at decolonization before surgery.

Because patients may come to surgery without screening or before the results are known, perioperative glycopeptide prophylaxis is being increasing used in high-risk patients. The guidelines express caution on the use of glycopeptide prophylaxis because this may encourage the emergence of resistance. However, they recommend that patients who require surgery and have a history of MRSA colonization or infection (without documented eradication) should receive glycopeptide prophylaxis, either alone or in combination with other antibiotics active against other potential pathogens (category II). Glycopeptide prophylaxis is also appropriate if there is an appreciable risk that MRSA carriage may have recurred or if the patient comes from a facility with a high prevalence of MRSA. At present, glycopeptide prophylaxis in the UK is usually restricted to patients who are at risk of disastrous outcomes if MRSA infection occurs, such as those undergoing orthopaedic or cardiothoracic surgery. The new guidelines imply that a wider range of patients will fall into risk groups requiring glycopeptide prophylaxis. Further evidence is needed to support this recommendation.

Treatment of MRSA infections

Empirical treatment of severe infection

When patients present with suspected severe staphylococcal infection, the clinician must decide whether to treat empirically with agents such as the isoxazolyl penicillins (e.g. flucloxacillin) or cephalosporins, which are effective against MSSA but not MRSA.

The UK guidelines recommend flucloxacillin for empirical therapy of suspected staphylococcal infections except in situations where MRSA is highly prevalent when a glycopeptide or linezolid can be used. They propose that the cut-off point for 'high prevalence' should be methicillin resistance in ≥10% of *Staph. aureus* strains, but admit that this is not based on good evidence (category II). Other risk factors for MRSA include recent transfer from nursing home or other facility with a high MRSA prevalence rate, previous antibiotic therapy, particularly with glycopeptides, mechanical ventilation and long-term intravenous or urinary catheterization. However, there is little published evidence to quantitate these risks. Since many UK hospitals, especially the tertiary referral centres, have methicillin resistance rates higher than 10% and many patients with risk factors for colonization, this recommendation tends to support a more widespread use of

glycopeptides or linezolid for empirical therapy of suspected severe MRSA infections, especially if there is a risk of bacteraemia or endocarditis (category IA).

In order to reduce the risk of the emergence of resistance, the Belgian national guidelines (Gordts et al, 2000) suggest that the use of empirical glycopeptide therapy should be limited to:

- Intravascular catheter infection in neonates
- Burns patients in units with a high prevalence of MRSA
- 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.

The UK guidelines give a high level endorsement (category IB) to the Belgian national recommendations on the empirical use of glycopeptides, except for surgical prophylaxis where the risks of MRSA carriage should be taken into account. However, this endorsement is rather at odds with the previous recommendation to use glycopeptides empirically for suspected severe MRSA sepsis.

The guidelines recommended the use of flucloxacillin as 'step-down therapy' from empirical glycopeptides or linezolid if the infection is subsequently shown to be caused by MSSA (category II).

MRSA skin and soft tissue infections

The working party could find little evidence to guide therapy of impetigo and boils caused by MRSA and make no recommendation for treatment of these conditions.

High level recommendations

The guidelines recommend that tetracyclines should be used more widely in adults for skin and soft tissue infections where there is judged to be little risk of bacteraemia or endocarditis (category IB).

The guidelines recommend glycopeptides or linezolid for treatment of skin and soft tissue infections where the risk of bacteraemia or endocarditis is high (category IA).

Intravenous glycopeptides or linezolid should be used in severe intravenous site infection. Mild infections may respond well to removal of the line and treatment with oral agents (category IB).

The guidelines recommended clindamycin for treatment of MRSA susceptible to erythromycin because the emergence of clindamycin resistance requires two mutations and its bioavailability is better than erythromycin (category IB).

There is good trial evidence for the effectiveness of both glycopeptides and linezolid in the treatment of complicated skin and soft tissue MRSA infections (Moise et al, 2002; Stevens et al, 2002; Wilcox et al, 2004). The glycopeptides are only available parenterally and the guidelines suggest that the higher cost of oral linezolid therapy can be justified if it allows early discharge from hospital (Li et al, 2001; Nathwani, 2003).

The category IB recommendation for increased use of tetracyclines in simple skin and soft tissue infections with MRSA is based on in-vitro susceptibilities of current UK strains of MRSA and evidence of clinical efficacy in MSSA infections. There are no clinical trial data to support this recommendation and there is now a need to conduct such trials. This also applies to the use of clindamycin for the treatment of susceptible strains of MRSA.

There is limited evidence of any improved efficacy of combination therapy in staphylococcal infections. However, although both fusidic acid and rifampicin are effective agents for susceptible staphylococci, they are used in combinations because of the risk of resistance emerging to these agents during monotherapy. The guidelines suggest using fusidic acid in combination with rifampicin or a glycopeptide for patients who have failed with monotherapy (category II) but recommend that formal clinical trials of these combinations should be done. The guidelines also note that resistance to rifampicin or fusidic acid may develop despite the use of combination therapy (Garraud et al, 1985; Shanson, 1990; Eng et al, 1998).

MRSA bacteraemia/endocarditis

High level recommendation

For uncomplicated bacteraemia, the guidelines recommend a minimum of 10 days' treatment with a glycopeptide or linezolid. Longer treatment will be required in patients with, or at higher risk of, endocarditis (category IA).

The guidelines indicate a preference for vancomycin over teicoplanin for glycopeptide treatment of MRSA bacteraemia. There is probably little difference in the effectiveness of the two glycopeptides when teicoplanin is used at high doses, but clinicians should be aware that teicoplanin therapy with low doses and/or without loading doses has been associated with clinical failures (Glupczynski et al, 1986). Because of the poor predictability of teicoplanin serum levels, the guidelines recommend that teicoplanin dosage should be adjusted by serum monitoring. This will complicate the use of teicoplainin which is not routinely monitored in this way and most hospital do not have facilities for assaying serum levels locally. The guidelines note that linezolid appears to be superior to teicoplanin in bacteraemia (Wilcox et al, 2004).

For the treatment of MRSA endocarditis, the guidelines refer to the British Society of Antimicrobial Chemotherapy endocarditis guidelines (Elliott et al, 2004); these recommend the use of vancomycin in combination with an appropriate second antibiotic (rifampicin, gentamicin or fusidic acid) according to organism susceptibility.

MRSA lower respiratory tract infections

Although MRSA is being isolated with increasing frequency from patients with suspected hospital-acquired and ventilator-associated pneumonia, there are considerable difficulties in confirming the diagnosis and in distinguishing colonization from infection.

High level recommendation

The guidelines recommend that care is taken to distinguish true lower respiratory tract infection with MRSA from colonisation. For true infection, a glycopeptide or linezolid is recommended for treatment (category IA).

The guidelines note that vancomycin has proved less effective than flucloxacillin and other anti-staphylococcal penicillins in the treatment of pneumonia caused by MSSA (Gonzalez et al, 1999; Moise and Schentag, 2000). Linezolid, unlike the glycopeptides, produces high drug concentrations in lung tissue (Honeybourne et al, 2003) and, in clinical trials in adults, linezolid appears to have been superior to vancomycin in patient subsets with MRSA pneumonia (Wunderink et al, 2003; Kollef et al, 2004). Another smaller adult trial (Stevens et al, 2002) and a small paediatric one (Jantausch et al, 2003) showed equivalence between linezolid and vancomycin and the working party suggests that further studies are needed to compare these two agents for the treatment of MRSA lower respiratory tract infection.

MRSA bone and joint infections

High level recommendations

The guidelines recommend glycopeptides for parenteral treatment of MRSA bone and joint infections, particularly those caused by multi-resistant MRSA strains (category IB).

They recommend clindamycin for oral treatment of infection with erythromycin susceptible MRSA (category IB).

The guidelines note that prolonged therapy is often required for bone and joint infections, and that the choice of agent depends on the susceptibility of the infecting strain and whether parenteral therapy can be given. Glycopeptides are effective in acute cancellous bone infections (Cafferkey et al, 1985; Graninger et al, 1995; Dacquet, 1996), but penetrate less well into cortical bone (Graziani et al, 1988).

In acute prosthetic infection, prompt surgical debridement within 2 days of onset of symptoms is recommended (Brandt et al, 1997). Where revision arthropathy is required, the guidelines suggest the inclusion of vancomycin in bone cement (Youngman et al, 2003).

The guidelines recommend combination therapy for MRSA-associated bone and joint infections if monotherapy has failed and the strain is susceptible to both agents. Suggested combinations include glycopeptides plus rifampicin or fusidic acid, or combinations selected from rifampicin, a fluoroquinolone, fusidic acid or trimethoprim. Such combinations may be considered as first-line therapy if the MRSA strain is susceptible to both the chosen agents. However, the evidence level for this recommendation is category II, reflecting the lack of clinical trial data in this area.

Other MRSA infections

Topical gentamicin or chloramphenicol are recommended for the treatment of superficial MRSA eye infections (category IB). However, the working party found insufficient evidence to make specific recommendations on the treatment of deep eye or CNS infections caused by MRSA. The guidelines recommend tetracyclines as first-line agents for the treatment of urinary tract infections caused by susceptible MRSA strains, with trimethoprim or nitrofurantoin as alternatives, but there is limited published work in this area and the evidence level is category II.

New agents

The guidelines support the use of the oxazolidinone linezolid as an alternative to glycopeptides for the treatment of certain MRSA infections as described earlier, especially where an oral agent is required or the patient is glycopeptide intolerant. Owing to the potential for reversible bone marrow suppression with prolonged therapy, linezolid treatment is normally limited to 28 days or less. The working party recommends that more clinical trials should be done to determine whether linezolid is superior to the glycopeptides for some conditions.

The streptogramin combination quinopristin/dalsopristin has been available for several years and is active against susceptible strains of MRSA. Because of vascular irritation, it usually has to be given by central line, and the guidelines suggest it should be reserved for glycopeptide-intermediately susceptible *Staph. aureus* (GISA) and GRE.

Some other new agents active against MRSA are in development. Those mentioned in the guidelines include tigecycline (a tetracycline derivative), the cyclic lipopetide daptomycin and the glycopeptide-related agents dalbavancin, oritavancin and telavancin; however, the working partly makes no recommendations on the use of these agents that are not yet (or only recently) licensed in the UK.

Discussion

Although the aim of the working party was to produce evidence-based guidelines, the evidence base for MRSA treatment and prophylaxis is limited and, in many cases, more studies are needed for stronger recommendations. Furthermore, some of the strong recommendations made at category IB were based more on theoretical or in vitro considerations than on clinical trial data. The frequent citation of older references on treatment of MSSA also reflects the lack of good quality recent studies on the

treatment and prophylaxis of MRSA. The guidelines should act as a catalyst for new, high quality clinical research into theses areas.

The guidelines will need to be studied by trust formulary committees to update local clinical guidance, taking into account local antibiotic resistance patterns. Recommended antibiotics should be included in local MRSA susceptibility testing protocols.

The control of MRSA infections in our hospitals is an urgent national priority. Implement of effective prophylaxis and treatment guidelines is one of the key steps to achieve this goal, together with the other essential elements of early detection of MRSA and improved infection control practice. It is important to ensure that evidence-based guidance in these areas is being followed. The British Society of Antimicrobial Chemotherapy is proposing that audits of MRSA therapy and prophylaxis parallel the introduction of local policies based on these new guidelines. Many trusts now have antibiotic pharmacists who have an important role in facilitating such audits and promoting best practice in MRSA prophylaxis and therapy. **BJHM**

Conflict of interest: Professor French has acted as a consultant and as a symposium speaker for Pfizer.

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KEY POINTS

- The new guidelines provide evidence-based recommendations for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in different types and severity of infections and in different patient groups, and include new agents not discussed in previous guidelines.
- Evidence categories indicate the level of evidence that supports the recommendations.
- In several treatment areas or antimicrobial classes, the amount of published evidence is limited and in these cases further clinical trials are needed.
- All trusts should review their local treatment guidelines for MRSA therapy and prophylaxis to ensure they are in accordance with the new guidelines.

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