

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

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**Abstract**

These evidence-based guidelines have been produced after a literature review of the treatment and prophylaxis of MRSA infection. The guidelines were further informed by the results of a postal survey of MRSA infections occurring recently in hospitals throughout the UK (appendix 1). These results included information on current antibiotic susceptibilities. 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 currently available antibiotics, which are suitable for use in the management of this problem and potentially useful new agents are continuing to emerge.

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*This exercise was initiated by the Specialist Advisory Committee on Antimicrobial Resistance (SACAR), an independent advisory committee, set up to provide expert scientific advice on resistance issues arising from medical, veterinary and agricultural use of antimicrobials.*

*Established in 2001 following recommendations in the House of Lords Select Committee on Science and Technology's original report "Resistance to Antibiotics and other Antimicrobial Agents", the Committee advises the Government on its strategy to minimise illness and death due to antimicrobial resistant infection and to maintain the effectiveness of antimicrobial agents in their medical, veterinary and agricultural use.*

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**Appendix 1:** National Survey of MRSA Infection and Therapy in UK Hospitals

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## **1. Introduction**

Guidelines for the control of meticillin (formerly methicillin) resistant *Staphylococcus aureus* (MRSA) infection in the UK have been previously published by a joint working party of the British Society of Antimicrobial Chemotherapy (BSAC), and the Hospital Infection Society (HIS) in 1986<sup>1,2</sup>, 1990<sup>3</sup> and together with the Infection Control Nurses Association (ICNA) in 1998<sup>4</sup>. 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 societies to revise the guidelines. Unlike the previous reports, which focussed 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. This report deals with the prophylaxis and therapy of MRSA infections in adults and children in hospital and the community.

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**Box 1. Summary of recommendations****We make no recommendations**

- for the treatment of impetigo and boils caused by MRSA.[Category e]
- deep eye and CNS infection. [Category e]

**We do not recommend:**

- the use of nasal mupirocin alone in patients, or staff, with skin breaks. [Category b].
- the use of oral vancomycin as prophylaxis or part of clearance regimens for MRSA.

**We recommend that:**

- If a threshold of 10% resistance in staphylococci is exceeded isoxazolyl penicillins and cephalosporins are not used for empirical treatment of staphylococci.
- Step down therapy to flucloxacillin from glycopeptides and linezolid should be used wherever possible once antibiotic susceptibilities of S.aureus are known.[category d]
- Belgian recommendations on empirical use of glycopeptides be followed except that on surgical prophylaxis where epidemiological criteria also influence choice of agents.[Category b].

*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 b]
- glycopeptides or linezolid be considered for use where the risk of bacteraemia or endocarditis is high. [Category a]
- in infections that have failed therapy with single active agents, use of either rifampicin and fusidic acid together or glycopeptides and fusidic acid be considered but only where these antibiotics remain active *in vitro*. Formal clinical trials of the use of these combinations are needed. [Category d]
- 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 b]
- intravenous glycopeptides or linezolid are used in severe intravenous site infection and other oral agents in mild infections. [Category b]

*In urinary infections*

- tetracyclines be considered as first line agents for the treatment of urinary infections caused by susceptible MRSA, with trimethoprim or nitrofurantoin as alternatives [Category d].

*In bone and joint infections*

- glycopeptides be used for parenteral treatment particularly of multi-resistant MRSA. [Category b]
- combination therapy should be used where monotherapy has failed and the antibiotics chosen remain active *in vitro*. Rifampicin and fluoroquinolones together or double combinations of rifampicin, a fluoroquinolone,

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trimethoprim, or fusidic acid may be considered as first line therapy if the strain is susceptible to both agents. [Category d]

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

*In bacteraemia*

- a minimum duration of 10 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 a]

*In respiratory infections*

- infections in bronchiectasis should be treated with non-glycopeptide agents according to *in vitro* susceptibilities as suggested for cellulitis. [Category e]
- particular care is taken to improve the certainty of diagnosis of lower respiratory tract infection as distinct from colonisation.
- the use of either glycopeptides or linezolid for pneumonic infections where MRSA is the aetiological agent. [Category a]

*In eye infections*

- Gentamicin or chloramphenicol may be used for superficial eye infections. [Category b].

*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 multi-centre 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 d]

*In surgical site prophylaxis*

- patients who require surgery and have a history of MRSA colonisation 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 d]
- the use of aminoglycosides be reassessed in patients not expected to have MRSA colonisation for prophylaxis of staphylococcal infections.

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. These references were supplemented from personal reference collections and searches of the working party members.

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 Centres for Diseases Control and Prevention's (CDC) evidence grades. Each recommendation is categorised on the basis of existing scientific data, theoretical rationale, applicability and economic impact. The categories are:

- a) Strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiological studies.
- b) Strongly recommended for implementation and supported by certain experimental, clinical or epidemiological studies and a strong theoretical rationale.
- c) Required for implementation, as mandated by federal or state regulation or standard (this includes Health and Safety regulations in the UK).
- d) Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale.
- e) No recommendation. Unresolved issue. Practices for which insufficient evidence or no consensus regarding efficacy exist.

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For the last ten years there has been an unenviable 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”<sup>5</sup>. The incidence of MRSA within hospitals and nursing and residential homes is of particular concern although it is now appearing increasingly in a community setting, as happened 50 years ago with penicillin resistance in staphylococci. MRSA presenting from the community is sometimes associated with silent acquisition in the healthcare environment <sup>6,7</sup>, or household contacts <sup>8</sup>, and one study suggests that silent acquisition is associated with in-patient care for more than 5 days within the last year <sup>9</sup>. There is also a less common emerging problem of truly community acquired MRSA with Panton Valentine leucocidin <sup>10,11,12,13</sup>. 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<sup>14,15</sup>, 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 <sup>16</sup>.

Selection of new clones of MRSA may follow changes made in policies for 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

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such as Finland <sup>17</sup>. The recent survey conducted by BSAC <sup>18</sup> provides some information on hospital antibiotic use in patients developing MRSA in the 14day period before diagnosis. This can only be compared with local information as we did not include a control group without MRSA and there are no national data on hospital use of antibiotics in the UK. Reversion to the use of first generation cephalosporins in surgery <sup>19</sup>, reduced use of third-generation cephalosporins and clindamycin <sup>20</sup>, and reduced use of ceftazidime and ciprofloxacin <sup>21</sup> have been described as contributing to reduced prevalence of MRSA in different hospitals. Reduced rates with modified antibiotic policies in limited healthcare settings are described but difficult to evaluate<sup>22,23,24</sup>. High usage of cephalosporins <sup>25,26,27,28</sup> and fluoroquinolones <sup>27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45</sup> apparently have been important in selecting for MRSA in some settings as has use of macrolides, penicillins and to some extent aminoglycosides<sup>28</sup> but evidence is not conclusive. Quinolone use has been associated in one study with prolongation of MRSA carriage <sup>46</sup>. Latest SHEA guidelines lay greater emphasis on good antibiotic stewardship and specifically fluoroquinolone use <sup>47</sup>.

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 Danish and Birmingham tetracycline-resistant MRSA <sup>48,49</sup>. However this is 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 diminishing MRSA selection is scanty and has not been sought but their role in

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selecting for resistant *Staphylococcus epidermidis* is well recognised especially with quinolones<sup>50,51</sup>. This may be important given the extensive use of macrolides, and increasingly fluoroquinolones, in the treatment of respiratory tract infection, and our survey's finding of wide susceptibility to tetracyclines of MRSA currently.

The appearance of strains of MRSA with raised minimum inhibitory concentrations 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. In one case, the presence of the VanA gene suggests transfer from other Gram-positive organisms<sup>52</sup> but most isolates are resistant by non-transferable mechanisms<sup>53</sup>. The number of cases of vancomycin resistant and intermediate *S. aureus* in the UK and internationally remain low despite alarm at their initial emergence<sup>54</sup>. MRSA strains with reduced teicoplanin susceptibility have been sufficiently frequent in the UK to identify them as a new clone, EMRSA-17<sup>55</sup>. Teicoplanin-resistant strains have also been reported from France<sup>56</sup>. Vancomycin treatment failures occur with strains apparently susceptible *in vitro*<sup>57,58,59</sup>. The description of a genetic marker of clones that are likely to fail on vancomycin therapy and its association with strains that are described as susceptible but are more resistant (MICs >0.5mg/l.) needs confirmation as it would have the important implication of suggesting that other treatment or an increase in dose is used for MRSA infections with higher MICs<sup>60,61</sup>. It is important to note that in this study treatment failure was not associated with changed mortality.

Most published guidelines focus on infection control measures rather than the appropriate use of antibiotics either in long term care or acute facilities<sup>62,63,64,65</sup>.

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Previous guidelines from this Working Party<sup>3,1,4</sup> have short sections only on chemotherapy. The present guidelines are specifically associated with aspects of antimicrobial chemotherapy that relate to *S. aureus*.

Mortality rates with MRSA are be higher than MSSA and this appears to be attributable mortality but the difficulty of interpretation is that MRSA more frequently occurs in the setting of hospital acquisition and other cofactors of illness that require a hospital stay and so may not be due to the antibiotic resistance per se<sup>66,67,68,69,70,71</sup>.

For meticillin susceptible *Staphylococcus aureus* (MSSA) flucloxacillin is a preferable agent because it is available orally. It is safer and has higher cure rates than glycopeptides for susceptible strains in respiratory primary sites in patients with bacteraemia<sup>72,73,72,66</sup> although other factors than chemotherapy including acute physiological score have been shown to be more important in mortality in bacteraemia overall<sup>74</sup>. Overall 30 day mortality rates in bacteraemia due to MRSA compared with MSSA may not be significantly greater in patients treated with glycopeptides rather than  $\beta$ -lactams so the issue of use of B-lactams is one of overall patient safety, convenience and cost rather than survival<sup>74,75</sup>. The only data that show flucloxacillin produces a better outcome than glycopetides in non-respiratory sites relates to right-sided endocarditis<sup>76</sup>.

Flucloxacillin is still an important agent for treatment of staphylococcal infection in patients in the community but not within high MRSA prevalence environments e.g. some areas of hospitals. Flucloxacillin is the drug of choice for definitive treatment

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of MSSA and is also preferred for empirical therapy except *in situations* where MRSA is highly prevalent.

**The prevalence level at which flucloxacillin, 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<sup>77</sup> and we would recommend the same threshold is used for staphylococcal infections and isoxazolympenicillins and cephalosporins. 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 d]**

The remainder of this document addresses treatment of MRSA infection.

## **2 Prevalence of antibiotic resistance in MRSA in United Kingdom**

The Working Party has sought information on the prevalence of antibiotic resistance within MRSA infection in the United Kingdom 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 cultures isolates included in the European Antimicrobial Resistance Surveillance System (EARSS) programme, incidence of MRSA in bacteraemia (separate studies in England and Wales, and Scotland)<sup>78</sup> and a comprehensive questionnaire sent to hospitals throughout the United Kingdom in 2004. This questionnaire sought information, on the number, prescribing patterns and outcome of MRSA infection in hospitalised patients over a seven-day

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period. Details were received from 309 patients with MRSA infection from 45 diagnostic microbiology laboratories across the UK<sup>18</sup>. The significant findings were:

- MRSA was predominantly a problem in older patients (82% were aged 60 years or over)
- 88% of isolates were resistant to three or more classes of antibiotics, but there was generally a range of active antibiotics available for treatment
- 95% of isolates were susceptible to tetracyclines, fusidic acid, rifampicin and chloramphenicol and more than 99% were reported as fully susceptible to glycopeptides
- 93% and 81% of strains were respectively resistant to fluoroquinolones and macrolides.
- Over 50% of treatment regimens used included a glycopeptide alone or with other agents.
- 55% of patients improved on initial therapy where early outcome was recorded: a further 13% did not deteriorate. Information was not collected on underlying medical condition or final outcome.

The rates of resistance to tetracyclines, macrolides and rifampicin appear to have fallen generally when compared with previously published data for UK strains from bacteraemia<sup>79</sup>.

At present in the UK most MRSA are macrolide and fluoroquinolone resistant and belong to two clones: EMRSA15 (ST22-MRSA-IV, in new nomenclature) and EMRSA 16 (ST36-MRSA-IV). In 2001, 95% of MRSA reported from 26 hospitals to the European Antimicrobial Resistance Surveillance system from causing bacteraemias, belonged to either EMRSA15 (60%) or EMRSA 16 (35%)<sup>78</sup>. Both

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clones occurred in 19/25 hospitals. These clones can be recognised in laboratories from their characteristic resistance patterns, although continuous structured national surveillance is necessary to follow changes and sub-type development<sup>80</sup> that may be more frequent in community strains<sup>81</sup>. Molecular typing methods such as pulse field gel electrophoresis (PFGE) confirm both the major clonal types and allow discrimination of sub-types<sup>82,83</sup>, showing changes in antibiogram, which are of importance when investigating an outbreak against a background of endemicity or change with time. As judged from antibiotic susceptibilities taken from a wider selection of infections than bacteraemias and more hospitals in our recent survey<sup>18</sup> EMRSA 16 may have declined in prevalence. EMRSA 15 has also become a global problem: it is responsible for 40% of MRSA isolated in New Zealand<sup>5</sup> and elsewhere.

### **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<sup>84</sup>.

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 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

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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 intravenous catheters.
- within the first 96 hours 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 epidemiological criteria also influence choice of agents.**[Category b].

Pharmacodynamic modelling of vancomycin suggests that for those patients with good renal function 12-hourly dosing is optimal<sup>85</sup> although there is evidence that once daily vancomycin is also satisfactory<sup>86</sup>. If teicoplanin is used, adequate doses (>6mg/Kg)<sup>87</sup>, and a loading dose are essential and even so cases of intravascular infection treated with teicoplanin fail<sup>88</sup>. The pharmacokinetics of teicoplanin are unpredictable and low doses have been associated with treatment failure<sup>89,87</sup>. Therapeutic drug monitoring with teicoplanin to give trough levels >20mg/l is advocated but not widely practised<sup>90</sup>. An alternative is to give still higher doses. The evidence on which recommendations<sup>91</sup> are based of serum trough levels of

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vancomycin of 5-10 mg/l relates more to potentially toxic peak levels that can be deduced from the trough level<sup>92,93</sup>. Toxicity above these levels is not well established with the current purified product and there are few publications on toxicity in the last 20 years<sup>94</sup>. Therapeutic trough levels relate to the MIC of the organism and it has been suggested that the existing recommended range is too low. This correlates with information that success in MRSA infection is particularly correlated with strains with the lowest MIC<sup>61</sup>. There is evidence that in paediatrics current dosing regimens of vancomycin commonly produce pre-dose serum levels <5mg/l which are below even current standards of dose optimisation<sup>95,96</sup>.

#### **4. Skin and soft tissue infections**

It is often difficult to differentiate between staphylococcal colonisation 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 prediction model, the presence of ulcers and sores was an independent predictor that bacteraemia would be due to MRSA and given that clearance of these sites without a systemically active antimicrobial is difficult, care in defining infection and colonisation in these lesions is important<sup>97</sup>.

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

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**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 e]

#### **4.2 Ulcers and sores**

Colonisation is more common than infection. Occasionally colonised 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 guideline<sup>98</sup> on skin and soft tissue infection recommends that particular attention is given to the local resistance rates to several classes of antimicrobial and in particular to the occurrence of MRSA. These recommendations for 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). The guidelines for limb infections in diabetics are also affected by the presence of MRSA and the use of ceftriaxone with vancomycin would not be everyone's choice for severe infections involving MRSA.

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 with MRSA. In particular there are few data on treatment with tetracyclines,

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other than minocycline, and use of trimethoprim without a sulphonamide. Tetracyclines or co-trimoxazole have been used alone or in combination. There is no published 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<sup>79</sup>. Minocycline activity against tetracycline resistant strains can be a phenomenon restricted only to a minority of strains<sup>99</sup> but this may depend on clonal prevalence<sup>100</sup>. There are no BSAC interpretative guidelines for minocycline susceptibility. Minocycline has unwanted effects that other tetracyclines lack and choice of this tetracycline is not essential if the strain is susceptible to other tetracyclines. Tigecycline is a new tetracycline derivative with much broader spectrum activity against Gram-negatives than existing tetracyclines and activity against MRSA. It's place in treatment is yet to be defined. Co-trimoxazole has been largely abandoned in the UK because of the unwanted side effects associated with the sulphonamide component. In Europe co-trimoxazole resistance rates in MRSA have been reported as between 53 and 76%<sup>101</sup>.

**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 b]**

Information on vancomycin efficacy in cellulitis is scanty. Cure rates for teicoplanin in excess of 80% are reported in treatment of cellulitis<sup>102,103,104</sup>. The non-availability of an oral formulation of any glycopeptide has limited early discharge from hospital

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unless home-therapy with teicoplanin is organised. 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<sup>105</sup>.

Linezolid may be considered as primary treatment as there is evidence that it is effective<sup>106,105,107</sup>: Its expense, however, may only be justified if it allows early discharge from hospital<sup>108,109</sup>.

Initial reports indicate that parenteral daptomycin or quinupristin/dalfopristin<sup>110,57</sup> may also be useful. New vancomycin/teicoplanin congeners, including dalbavancin<sup>111,112</sup>, oritavancin<sup>113</sup>, and telavancin<sup>114</sup>, are in clinical trial and their pharmacokinetics will permit less frequent dosing and use in out-patient parenteral antibiotic therapy. Initial trials with dalbavancin show efficacy rates with two doses a week apart equivalent to current regimens<sup>112</sup>. 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 or endocarditis is high.**

[Category a]

Rifampicin and fusidic acid resistance rates in MRSA can be high in environments where these agents are widely used<sup>115</sup> although clonal spread appears to have contributed to rifampicin resistance rates of 30-60% in parts of Australia<sup>116</sup>. Resistance to these agents was internationally quite uncommon in the late 1980s<sup>117</sup> but rifampicin resistance rose in many European countries to 14-58%<sup>101</sup>. It is

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currently rare in the UK<sup>18</sup>. 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 but there is only modest supporting data<sup>118,119,120</sup>.

Topical antibiotics e.g. mupirocin and fusidic acid, if used at superficial sites (including antibiotic treatment of infected pressure sores and prophylaxis for peritoneal dialysis exit site infection, haemodialysis catheter site infection<sup>121,122</sup> or orthopaedic surgical site infection<sup>123</sup> will be associated with the emergence of resistance and also probably should not be used in the absence of systemic therapy; combination prophylaxis however has not been evaluated. This advice is clearly different from that given in the earlier version of these guidelines<sup>1</sup>. High-level mupirocin resistance has become an increasing problem<sup>124</sup> and is common in EMRSA-16 but this does not seem to be the case with the current dominant UK strain EMRSA-15<sup>18</sup>. Other topical biocides such as chlorhexidine, triclosan, or povidone-iodine may also be useful but the presence of resistance to chlorhexidine and cetrimide<sup>125,126,127,128,129</sup> and the potential for emergence of resistance to triclosan<sup>130</sup> and the resistance of glycopeptide intermediate resistant *S. aureus* (GISA) and glycopeptide resistant *S. aureus* (GRSA) to phenolics<sup>131</sup> should be noted.

In a double blind, placebo-controlled study of the use of a high dose of rifampicin 600mg b.d. with either oxacillin 3G or vancomycin 2G daily, rifampicin did not improve outcome, nor was rifampicin resistance detected<sup>132</sup>. 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. Although applicable to other agents such as fluoroquinolones, the use of a second

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agent is standard policy in the UK and several other countries if rifampicin<sup>133,134,135,136</sup> or fusidic acid<sup>137,138,139,115</sup> therapy are to be used. In practice rifampicin resistance may emerge despite the use of minocycline<sup>133,134,136</sup>, fusidic acid<sup>140,139</sup> or even vancomycin in combination<sup>135,141,142</sup>. Findings in animal models also vary: Vancomycin may prevent or only reduce emergence of rifampicin<sup>143,144</sup> or fusidic acid resistance<sup>145</sup>. 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<sup>146</sup>. In trials of clearance of colonisation, rifampicin resistance was more frequently noted with co-trimoxazole than with novobiocin combinations<sup>120</sup>.

There are as yet no 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<sup>147</sup>. Fusidic acid resistance was not seen when used in combination with co-trimoxazole<sup>118</sup>. Co-trimoxazole may be unexpectedly effective alone although a comparison still suggests vancomycin is more effective<sup>148</sup>.

**We recommend that consideration should be given to the use of either rifampicin and fusidic acid together 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 d]

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Clindamycin use alone is not generally recommended if the strain is erythromycin resistant through MLS<sup>B</sup> resistance as a single step mutation to resistance can occur. For this reason, clindamycin has been advocated for use alone against erythromycin-susceptible strains. For erythromycin resistant strains, specific testing for clindamycin resistance in the presence of erythromycin and reporting as resistant if inducible resistance is demonstrated, is recommended although the evidence for frequent one stage mutation to resistance on treatment is poor<sup>149</sup>. New clones of MRSA susceptible to erythromycin are increasingly being described from France<sup>150</sup> and are being seen in some localities in England where the overall incidence of erythromycin resistance has fallen<sup>79</sup>.

**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 b]

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, leads to loss of the graft, death and amputation<sup>151,152,153,154</sup>. However, some multi-centre studies from the UK report very low rates of infection<sup>155</sup>. Rifampicin-bonded vascular grafts, whilst effective in prevention of *Staphylococcus epidermidis* infections<sup>156</sup>, do not seem effective in MRSA infections<sup>157</sup>.

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#### 4.4 Intravenous infusion sites

An assessment must be made of the severity of infection, based on the whether 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, intravenous antibiotics such as a glycopeptide or linezolid are indicated. 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 intravenous antibiotics are only used in cases of severe intravenous site infection and in such cases a glycopeptide or linezolid should be prescribed. Mild infections may respond well to other oral agents.** [Category b]

#### 5. Urinary Tract Infections

Treatment will depend on antibiotic sensitivity and achievable urinary levels of active drug. Owing to 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. The ease with which MRSA can acquire resistance to fluoroquinolones<sup>158</sup>, 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 tetracyclines be considered as first line agents for the treatment of urinary infections caused by susceptible MRSA, with trimethoprim or nitrofurantoin as alternatives** [Category d].

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## 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<sup>159,160,161</sup>. Vancomycin concentrations in cortical bone are less satisfactory<sup>162</sup>. Outpatient teicoplanin can reduce hospitalisation costs<sup>161</sup>. In animal models vancomycin therapy is sometimes disappointing without rifampicin use<sup>163,164</sup>. Quinolones, despite activity in animal models, are seldom useful in clinical practise because of resistance.

In acute prosthetic infection, surgery within two days of onset of symptoms is critical to successful maintenance of the prosthesis<sup>165</sup>. Otherwise as with chronic infection<sup>166</sup>, surgical debridement with removal of the prosthesis, cement and sequestra is critical to high success rates. Vancomycin is useful in cement beads and prostolacs at revision arthroplasty<sup>167</sup>.

Linezolid is not currently licensed for use for more than 28 days owing to the risk of bone marrow suppression, which may approach 10%<sup>105</sup> but it has been reported to produce clinical cure in 19/33 (57.5%) treated MRSA infections<sup>168</sup>. Haematological monitoring, including platelet counts, must be performed at least weekly. Quinupristin/dalfopristin has been used in a small number of cases of bone and joint infections<sup>57</sup>.

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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<sup>169,170,171,172</sup>. Rifampicin may also be considered for use with glycopeptides because of its activity against bio-films *in vitro* and some evidence in experimental models<sup>173,143</sup>. Drug interactions are more frequently described with rifampicin than fusidic acid. Rifampicin and fusidic acid can be used in combination and is successful in 55% of cases<sup>174</sup> but unwanted effects are frequent and may necessitate discontinuation<sup>175</sup>. There is *in vitro* evidence that resistance rarely appears to either or both when used in combination<sup>176</sup> but in clinical practice rifampicin resistance may emerge<sup>139</sup>. 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<sup>177</sup>. Co-trimoxazole has also been used although unwanted effects frequently lead to discontinuation of the drug and small-colony variants may appear on this therapy<sup>178</sup>.

**We recommend that glycopeptides be used for parenteral treatment of bone and joint infection particularly multi-resistant MRSA. [Category b]**

**We recommend that combination therapy should be used where monotherapy has failed and the antibiotics chosen remain active *in vitro*. Use of, for example, rifampicin and fluoroquinolones together or double combinations of rifampicin, a fluoroquinolone, trimethoprim, or fusidic acid may be considered as first line therapy if the strain is susceptible to both agents. [Category d]**

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

## **7. Bacteraemia and endocarditis**

MRSA bacteraemia is often associated with previous hospitalisation<sup>179</sup> 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<sup>7,11,12</sup>. Intravascular catheter-related infections must be adequately managed and associated endocarditis may affect the duration of antibiotic therapy<sup>180</sup>. 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<sup>181</sup>.

Glycopeptides are widely regarded as the drugs of choice<sup>148,105</sup> except in bacteraemic pneumonia, although it is not always clear that comparator drugs are active against MRSA<sup>182,183</sup>. Vancomycin is preferred to teicoplanin unless teicoplanin levels are measured or high doses (>6mg/Kg and probably 800mg/day) are used empirically. Early studies with low doses (200mg/day) of teicoplanin without the use of loading doses were complicated by failure<sup>184</sup> and doses up to 1200mg/day may be needed<sup>87</sup> but are expensive. It is suggested that rifampicin use with vancomycin improves outcome in uncomplicated bacteraemia but this comes from one uncorroborated study<sup>141</sup>. 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

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improves outcome in MRSA bacteraemia or endocarditis, and with vancomycin should be avoided where possible because of the risk of increased toxicity<sup>185,186,187</sup>. Linezolid appears to be superior to teicoplanin<sup>107</sup>

Other antibacterials may need consideration as alternatives depending on the source of the bacteraemia. Failures with chloramphenicol -and amikacin- containing combinations are described<sup>160</sup>. There is limited data that linezolid and 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<sup>188</sup> although the diverse agents used in these infections<sup>189,54</sup> make conclusions based on evidence impossible. Resistance to quinupristin/dalfopristin in MRSA is already described in France where pristinamycin has been widely used<sup>190</sup>. Linezolid resistance in *S.aureus* has also been described but is rare<sup>191,192</sup>. Guidelines for treatment of endocarditis and other intracardiac infections (e.g. pacemaker wires), including infections due to MRSA, have been recently published by the British Society for Antimicrobial Chemotherapy<sup>193</sup>. Infection of a pacemaker box requires removal of the box and the same antibiotic treatment as with prosthetic joint infections. It should be noted that the treatment of right-sided *S.aureus* endocarditis is one of the rare situations where glycopeptides have proved inferior to isoxazolyl penicillins<sup>76</sup>.

A minimum duration of 10 days' antibiotic treatment is required for uncomplicated bacteraemia, but oral therapy may be substituted for initial parenteral agents<sup>194</sup>. Scottish guidelines recommend 2-3 weeks for uncomplicated bacteraemia and 6-12 weeks for deep-seated infection but there is no trial evidence to support this<sup>195</sup>. It is

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important that the duration of treatment is adequate and any local focus of infection is eliminated.

**We recommend a minimum duration of 10 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 a]

## **8. Respiratory tract infection**

MRSA-associated upper respiratory tract infection e.g. sinusitis is rare and tends to be restricted to patients after ENT surgery or health-care 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<sup>196</sup>. studied 300 patients with cystic fibrosis to analyse if 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 may have an adverse effect on growth. Trimethoprim and co-trimoxazole should be avoided because of the risk of development of resistant thymidine - dependent strains<sup>197</sup>. As an alternative in adults, a tetracycline or chloramphenicol can be considered.

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**We recommend that infections in bronchiectasis should be treated with non-glycopeptide agents according to *in vitro* susceptibilities as suggested for cellulitis.**

[Category e]

In pneumonia vancomycin proved less effective than flucloxacillin or other isoxazolylic penicillins for MSSA although shock was an additional factor<sup>72</sup>. Further reports have followed of vancomycin treatment failure<sup>58</sup>. Linezolid produces high concentrations in lung epithelial lining fluid<sup>198</sup> unlike glycopeptides. 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<sup>199</sup>. A subset analysis amalgamating the two adult trials suggested that there was significant benefit in the use of linezolid in those patients from whom MRSA was grown<sup>200</sup>. However, a third small adult study<sup>105</sup> and one small paediatric study<sup>201</sup> also found equivalence between linezolid and vancomycin in MRSA pneumonia. Larger studies are required to compare 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<sup>202,59</sup>. The diagnosis of ventilator-associated pneumonia, as distinct from respiratory tract colonisation, 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.

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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, despite its importance in hospitals this has not been systematically studied.

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

## **9. Eyes and CNS infections**

Postoperative surgical infections in the eye are commonly treated with intravitreal vancomycin whose low pH can be tissue damaging. 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 of rabbits at concentrations of 0.75mg in 0.1ml without retinal toxicity<sup>203</sup>. Fusidic acid<sup>204</sup>, clindamycin<sup>205</sup>, linezolid<sup>206</sup> and fluoroquinolones all penetrate the vitreous and these require clinical assessment with susceptible strains. There is evidence that vancomycin or amikacin systemically are ineffective in the prophylaxis of staphylococcal endophthalmitis but quinolones might be effective with susceptible strains of MRSA<sup>207</sup>. Superficial eye infections can be treated with topical chloramphenicol<sup>208</sup> fusidic acid, or gentamicin if the strain is susceptible.

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In staphylococcal brain abscess and meningitis, vancomycin has been used<sup>209</sup> 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 to the abscess<sup>210</sup> or their use in some other CNS infections<sup>211</sup>.

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

## **10. Elimination of carriage**

In the pre-Medline older literature, use of nasal neomycin creams was initially described as useful in reducing wound sepsis rates with susceptible staphylococci<sup>212</sup> but was shown to be ineffective<sup>213,214,215</sup> even when selectively applied<sup>216</sup>. Appearance of resistant strains was a problem and its use was generally abandoned<sup>217</sup>. There is little later information on clearance in MRSA strains 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 computerised data bases has been widely forgotten and contains numerous important experiments on control measures with modern applications to MRSA. This literature was well summarised just before the advent of data abstraction<sup>218,219</sup>. Coming to recent times, tea tree preparations have also been recently assessed in a double blind controlled comparison with mupirocin and have

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been found to be disappointing in the nose, although slightly more promising at skin sites<sup>220</sup>.

Considerable reliance has been placed in the past on eradication therapy and mupirocin use in the control of epidemic if not endemic MRSA. Alternative measures are also of critical importance. Standardisation of culture technique and follow up of eradication has not been achieved and limits the assessment of studies. . 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<sup>221</sup>. Newer studies confirm this<sup>222</sup>. 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 is associated with clearance of hand carriage, which may be important in control of outbreaks<sup>121</sup>.

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<sup>223</sup>, although it is undoubtedly useful in outbreaks in low-prevalence environments. The use of blind intranasal mupirocin in an outbreak situation may be effective<sup>224,225</sup> but increases exposure to the drug and may make it less useful in future if it selects resistant strains and use is repetitive or prolonged<sup>226</sup>. A Cochrane systematic review<sup>227</sup> of randomised 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 is still being advocated as a routine treatment for all carriers in

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Scotland<sup>195</sup> and has been successful in one more recent randomised, double-blind, placebo-controlled trial<sup>222</sup>. Further analysis of the trials in the Cochrane review is justified: excluded trials are not considered further.

The natural history of carriage without treatment is that persistence occurs in some 40% of patients, particularly if skin breaks are present<sup>228</sup>. 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%<sup>46</sup>.

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

The increasing prevalence of mupirocin resistant (EMRSA-16) strains in some areas, although not apparent generally in the UK<sup>18</sup>, also means that eradication treatment with mupirocin should now only be considered in especially vulnerable patients such as those undergoing joint replacement, stent placement, vascular and cardiothoracic surgery or where MRSA has a low prevalence. 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<sup>64</sup>. Scottish guidelines recommend a course length between 3 and 5 days<sup>195</sup>. Trial data has shown efficacy with 14days twice daily<sup>222</sup>.

Levels of mupirocin resistance may require testing to predict clearance. This is only partially available in some of the studies included in the Cochrane review. An important recent study illustrates ~80% clearance rates of the nose at 3 days post

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treatment of mupirocin-susceptible or low level mupirocin-resistant MRSA and only 27% clearance of high level mupirocin-resistant strains<sup>229</sup> The numbers of mupirocin low level resistant strains were very small.. 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<sup>230,231</sup>. High-level resistance is usually plasmid-mediated. An uncorroborated small study<sup>229</sup> shows that whereas nasal clearance persists at 4 weeks with mupirocin susceptible strains, 80% of low-level mupirocin and 95% high level resistant strains re-appear. This study is partially supported by findings in an underpowered study that 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<sup>232</sup>. 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 multi-centre and matched for presence of skin lesions.**

Because of these findings of relapse when mupirocin is used alone, if peripheral colonised or infected lesions are present in highly vulnerable patients or if the MRSA strain is mupirocin resistant, the use of alternative nasal topical agents e.g. bacitracin<sup>119</sup> has been investigated. and in combination with co-trimoxazole and rifampicin produces persistent clearance rates of 65%. Co-trimoxazole plus nasal

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fusidic acid has been reported as being as successful as nasal mupirocin<sup>118</sup>. Nasal clearance rates at 28 days were 95% subsiding 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<sup>137</sup>. Novobiocin in combination with rifampicin has produced similar eradication rates to co-trimoxazole with rifampicin (67% vs 53%) but was less likely to select for rifampicin resistance<sup>120</sup>. Novobiocin is not generally available. Colonisation with rifampicin resistant strains at 4 weeks was also a problem when rifampicin was used alone or with minocycline for 5 days<sup>136</sup>. Combinations involving fluoroquinolones are not recommended because of the high prevalence of fluoroquinolone-resistant strains in the UK and the selective effect for resistance on the normal skin flora<sup>50,51</sup>. The use of systemic agents in clearance depends on *in vitro* susceptibilities, the underlying clinical condition, and risk. These trials suggest that various combinations of co-trimoxazole, rifampicin, tetracyclines, mupirocin and fusidic acid have some efficacy (50-75%) but this cannot be considered established. 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 d]**

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Systemic vancomycin does not clear nasal, throat, or gut sites at least at conventional doses of 20mg/Kg/d but there is evidence of suppression at doses of 40mg/Kg/d, which is above the normal dosage recommendation<sup>233</sup>. No data is available for teicoplanin but it is likely that this is ineffective. Three trials show that the use of oral vancomycin<sup>234,235,236</sup> improves clearance rates, presumably acting against gastrointestinal carriage of MRSA<sup>237</sup>. The issue of the ongoing risk of selection by parenteral vancomycin use of glycopeptide resistant enterococci (GRE) has not been substantiated by numerous publications including systematic review as recent meta-analysis, systematic review and a carefully controlled observational study make clear<sup>238,239,240</sup>. 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 & 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.**

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**

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Patients who undergo clean elective surgical procedures and who are colonised or infected with MRSA may have undergone successful eradication therapy and should in any case receive prophylaxis active against MRSA. Glycopeptides are commonly used as part of prophylactic regimens in patients colonised 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 colonised or infected with MRSA or who have been a hospital in-patient on units with a high incidence of MRSA are candidates for systemic prophylaxis specifically directed against MRSA. 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<sup>241</sup>.

Evidence in MSSA carriage shows that mupirocin alone does not reduce *S. aureus* infection rates to a statistically significant extent<sup>123</sup>. However, there is evidence that a reduction both in surgical site infection and nasal colonisation can be made before elective orthopaedic surgery with an anti-staphylococcal regimen including 1 day preoperative and 4 days postoperative nasal mupirocin<sup>242</sup>. 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<sup>9</sup> 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<sup>243</sup>. However, in orthopaedics, sepsis can apparently occur regardless of carriage status and appropriate prophylaxis so changing prophylaxis may not be indicated at all<sup>27</sup>. The

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routine use of mupirocin to treat MRSA carriers has been associated with the emergence of resistance and consequent failure to clear carriage<sup>244</sup>.

In general surgery, antimicrobial prophylaxis regimens such as those using cephalosporins<sup>245</sup>, have not been reassessed for efficacy since the advent of widespread MRSA in the UK in 1992: these need to be critically reviewed because efficacy of prophylaxis may, in part, related to prevention of susceptible staphylococcal infections as well as anaerobic infection as seen with aminoglycoside and either lincosamine or metronidazole prophylaxis<sup>246,247</sup>. It is important to note that the use of lincomycin and clindamycin<sup>246</sup> was abandoned in favour of metronidazole in the UK because of *C.difficile* colitis<sup>247</sup>. Gentamicin and other current aminoglycosides are active against EMRSA15 but not EMRSA16 and their role in prophylaxis and treatment as part of non-glycopeptide regimens requires reassessment. Toxic effects limit their prolonged use in treatment but to a lesser extent in prophylaxis. Aminoglycosides may be useful substitutes in prophylactic combination regimens although this has not been recently assessed. Reports of failure with amikacin against gentamicin-resistant MRSA<sup>160</sup> are in retrospect not surprising given the bi-functional phosphoacetyl-transferase enzyme responsible for aminoglycoside resistance in staphylococci<sup>182</sup> and this compound offers no advantage over other aminoglycosides for staphylococci.

**We recommend that patients who require surgery and have a history of MRSA colonisation 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**

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**an appreciable risk that patients' MRSA carriage may have recurred or they come from facilities with a high prevalence of MRSA. [Category d]**

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

## **12. Conclusion**

Our summarised recommendations for the treatment of MRSA infection are shown in Box 1. 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 up-dating as evidence emerges on the use of newer antimicrobial agents active against MRSA, including a number still under development.

## **13. Acknowledgements**

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## Special features of antibiotics in treatment of MRSA infections

Agent	Use as monotherapy	Key indications	Unwanted effects	Comments
Aminoglycosides	No	Use in prophylaxis.	Ototoxicity in renal impairment.	
Chloramphenicol	Yes	CNS infections.	Rare cause of marrow aplasia.	
Clindamycin	Yes	Skin and soft tissue infections. Bone and joint infections.	<i>Clostridium difficile</i> colitis and antibiotic-associated diarrhoea.	Evidence of efficacy as sole agent against strains with macrolide resistance but risk of emergence of resistance.
Co-trimoxazole	Yes	Skin and soft tissue infections and eradication therapy in combination.	Stevens Johnson syndrome and marrow hypoplasia associated with sulphonamide usage.	Trimethoprim alone may be preferred
Fusidic acid	Never	Skin and soft tissue infections. Elimination of carriage.	Jaundice on parenteral therapy. Highly protein bound.	Resistance-emerging problem with topical and systemic use. Hepatic excretion
Linezolid	Yes	Pneumonia. Serious soft tissue infections. Bacteraemia. GISA and VRSA of infection.	5-10% incidence of marrow suppression. Hepatotoxicity in pre-existing liver disease.	No information on combination therapy. No information on treatment in renal impairment. Recommended maximum duration of Rx of 28 days limits use in bone and joint infection. Availability of oral agent attractive.

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<b>Agent</b>	<b>Use as monotherapy</b>	<b>Key indications</b>	<b>Unwanted effects</b>	<b>Comments</b>
Mupirocin	Yes (nasal carriage as sole site)	Not recommended for therapeutic use. Use in eradication therapy.	Minor.	Established and increasing high level resistance problem.
Quinupristin/ Dalfopristin	Yes	Reserve drug. GISA and GRSA infections	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)	Few	Not orally absorbed. Poorly predictable blood levels mean monitoring essential in serious infection.

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<b>Agent</b>	<b>Use as monotherapy</b>	<b>Key indications</b>	<b>Unwanted effects</b>	<b>Comments</b>
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 aminoglycoside concurrent use.	Not orally absorbed. Poorly predictable blood levels mean monitoring essential in serious infection.

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**NB: In this document 'meticillin' has been used in place of the established 'methicillin' in accordance with the new International Pharmacopoeia guidelines.**

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## National Survey of MRSA Infection and Therapy in UK Hospitals

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## Introduction

Shortly after the introduction in 1960 of semi-synthetic penicillinase-resistant  $\beta$ -lactams, of which methicillin was the first, the observed level of resistance to this class of antibiotics among *Staphylococcus aureus* began to rise (Jevons 1961) leading to the first documented hospital outbreak of MRSA three years later (Cookson 2003). At this time, the incidence of MRSA in our hospitals was just 0.4%. Within 10 years (Livermore 2000) this had risen to 10% and today estimates indicate that 43% of laboratory reported *S. aureus* are methicillin resistant (Griffiths 2004). These figures are mirrored by surveillance schemes in the UK and Europe, with particular emphasis being placed on isolates from cases of bacteraemia.

It was against this background that concern was raised that patients with MRSA may or may not be receiving the most appropriate antibiotic therapy. Evidence from a preliminary study involving six hospitals over a four week period suggested some degree of diversity in antibiotic choice amongst 258 patients whose details matched the criteria for a questionnaire sent to each of the hospitals early in 2004. In almost half the cases (49.3%) antibiotics were prescribed before the microbiology results became available. When these results did become available antibiotic therapy was initiated in a further 28%. It was likely that the remainder of patients were merely colonised with MRSA. In many cases antibiotic therapy was changed following release of the laboratory results.

The present paper is an extension of these studies. A larger number of hospitals were asked to participate but for a much shorter period (seven days) but with a 28 day follow-up in an attempt to relate outcome of infection to choice of antibiotics used in therapy.

## **Methods**

A pilot survey was carried out over a four-week period in June/July 2003 in six centres across the UK. Based on the feed back from this pilot the survey questionnaire was refined.

Microbiologists from the United Kingdom 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<sup>th</sup> February and 12<sup>th</sup> February 2004. Participants were requested to complete a questionnaire for each in-patient 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 anonymised demographic details including length of hospital stay, antibiotic sensitivity of the MRSA and treatment decisions. Participants were then, where possible asked to complete a 28-day follow up to ascertain outcomes and the questionnaires then returned to a central point for analysis.

## **RESULTS**

A total of 309 questionnaires were returned from 45 Trusts representing a wide spread of both geographical area and hospital type. (Figure1)

A total of 244 questionnaires from 34 Trusts.

A total of 65 questionnaires were received anonymously.

Table I represents the age range of patients from whom MRSA was isolated. Fifty-three percent of patients were male

The admission source of patients is demonstrated in Table II

The relationship between the date of admission and the isolation of MRSA is recorded in Figure 2, and the number of days between date of isolation and date of discharge/death can be seen in Figure 3.

Table III demonstrates the range of specimens from which MRSA was isolated

Table IV describes the resistance patterns of all isolates compared with MRSA isolated from blood cultures. The patterns of antibiotic resistance are demonstrated in Tables V.

The antibiotic sensitivity testing method used for each isolate can be seen in Table VI. In 13 cases this was confirmed by the detection of the Mec A gene.

When participants were asked whether the isolate represented an on-going infection, 41% said 'definitely yes', 22% 'probably yes' and 31% 'probable colonisation'

77% of patients were received antibiotics in the 14 days prior to the isolation of MRSA (Table VII). In 47% of cases, this therapy was changed when the result of the positive MRSA culture was available. The antibiotic(s) chosen when MRSA positive culture was available is outlined in Table VIII.

173 (56%) of patients were followed up after 28 days. Of the remainder 41 (13%) were lost to follow up and the rest were assessed at an earlier date, either because they died, or had been discharged from hospital. Details of outcome can be found in Table IX.

The final question asked the Infection Control Teams to give their opinion as to where the MRSA was acquired. Responses are summarised in Table X.

## **Acknowledgements**

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Finally we would like to thank all the Microbiologists and Infection Control Teams for their input, without which we would not have been able to conduct this survey.

**Table I Patient Age**

<b>Age</b>	<b>Number</b>	<b>Percent</b>
0 – 19	4	1.3
20 – 39	13	4.2
40 – 59	39	12.6
60 – 79	149	48.2
80 and over	104	33.7
<b>Total</b>	<b>309</b>	<b>100.0</b>

**Range:** 5 years – 97 years  
**Mean:** 70.9 years  
**Median:** 74.0 years  
**Mode:** 82.0 years

**Table II Admission Source**

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<b>Answer</b>	<b>Number</b>	<b>Percent</b>
Another Country	1	0.3
Own home	220	71.2
Nursing home/Residential home	40	12.9
Another Hospital	26	8.4
GP referral	4	1.3
Not recorded	18	5.8
<b>Total</b>	<b>309</b>	<b>100.0</b>

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**Table III Specimen Type**

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<b>Specimen Type</b>	<b>Number</b>	<b>Percent</b>
Urine	23	7.4
Surgical wound	83	26.9
Sputum / BAL	52	16.8
Blood culture	33	10.7
Skin and soft tissue infection	68	22.0
IV line / site eye infection	11	3.6
Mixed	6	1.9
Other	25	8.1
Not recorded	8	2.6
<b>Total</b>	<b>309</b>	<b>100.0</b>

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**Table IV Antibiotic Resistance**

	<b>All Isolates</b>		<b>Blood culture Isolates</b>	
	<b>Number</b>	<b>%of total Tested</b>	<b>Number tested</b>	<b>% of Tested</b>
Methicillin	296	100.0	32	100.0
Tetracycline	5	1.8	1	3.2
Fusidic acid	10	3.3	4	12.1
Rifampicin	8	2.7	3	9.4
Gentamicin	12	4.0	3	9.1
Trimethoprim	47	16.4	6	18.2
Macrolide	238	100.0	27	100.0
Fluroquinolone	262	93.2	28	96.6
Vancomycin	2	0.7	-	-
Teicoplanin	1	0.4	-	-
Mupirocin	20	7.1	4	13.8
Chloramphenicol	3	1.1	-	-
Clindamycin	60	24.1	8	36.4
Cotrimoxazole	1	0.4	-	-
Linezolid	1	0.4	-	-
Penicillin	204	72.6	26	86.7

**Table V Antibiotic Resistance Patterns (1)**

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	<b>Number</b>
Methicillin & Fluroquinolone	258
Methicillin, Macrolide & Fluroquinolone	209
Methicillin, Macrolide, Fluroquinolone & Gentamicin	7
Methicillin, Macrolide, Fluroquinolone & Tetracycline	3

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**Table VI Sensitivity testing method**

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	<b>Number of Patients</b>	<b>Percent</b>
BSAC	157	50.8
BSAC & VITEK	2	0.6
BSAC & High level Mupirocin	10	3.2
BSAC & other	2	0.6
NCCS	16	5.2
Stokes	58	18.8
Break point	1	0.3
Other – type not specified	46	14.9
Not recorded	17	5.5
<b>Total</b>	<b>309</b>	<b>100.0</b>

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**Table VII Antibiotics prescribed in 14 days before specimen collected, either as monotherapy or in combination with another antibiotic.**

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	<b>Number</b>
Betalactam	95
Glycopeptide	34
Macrolide	37
Fluroquinolone	75
Tetracycline	4
Other(s) *	94
None	52
Any Combination	100

---

Total number of patients: **269**

\* Includes Trimethoprim, Rifampicin, Linezolid, Chloramphenicol fusidic acid, Dalfopristin/Quinopristin and Fosfomycin

**Table VIII Choice of new antibiotic to treat MRSA when Microbiology results available.**

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	<b>Number</b>	<b>Percent</b>
Betalactam	4	2.6
Glycopeptide	80	53.0
Macrolide	4	2.6
Fluroquinolone	6	4.0
Tetracycline	16	10.6
Other *	89	58.9
Any Combination	40	26.5

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Total number of patients: **151**

\*\* Includes Trimethoprim, Rifampicin, Linezolid, Chloramphenicol fusidic acid, Dalfopristin/Quinopristin and Fosfomycin

**Table I X Outcome**

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	<b>Number</b>	<b>Percent</b>
Deteriorating	2	0.6
Deteriorating after initial improvement	1	0.3
Deteriorating then patient died	3	1.0
Improving on therapy	54	17.5
Improving on therapy then patient died	2	0.6
Resolved	96	31.1
Resolved then patient died	1	0.3
Unchanged	36	11.7
Patient died	76	24.6
No antibiotics prescribed yet during admission	1	0.3
Improved without antibiotics	2	0.6
Not recorded	35	11.3
<b>Total</b>	<b>309</b>	<b>100.0</b>

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**Table X According to ICT opinion, how / where was MRSA acquired?**

	<b>Number</b>	<b>Percent</b>
Acquired in hospital in this admission	152	49.2
Likely to have been present but undetected	70	22.7
Previously known MRSA positive	28	9.1
Unknown	35	11.3
Not recorded	24	7.8
<b>Total</b>	<b>309</b>	<b>100.0</b>

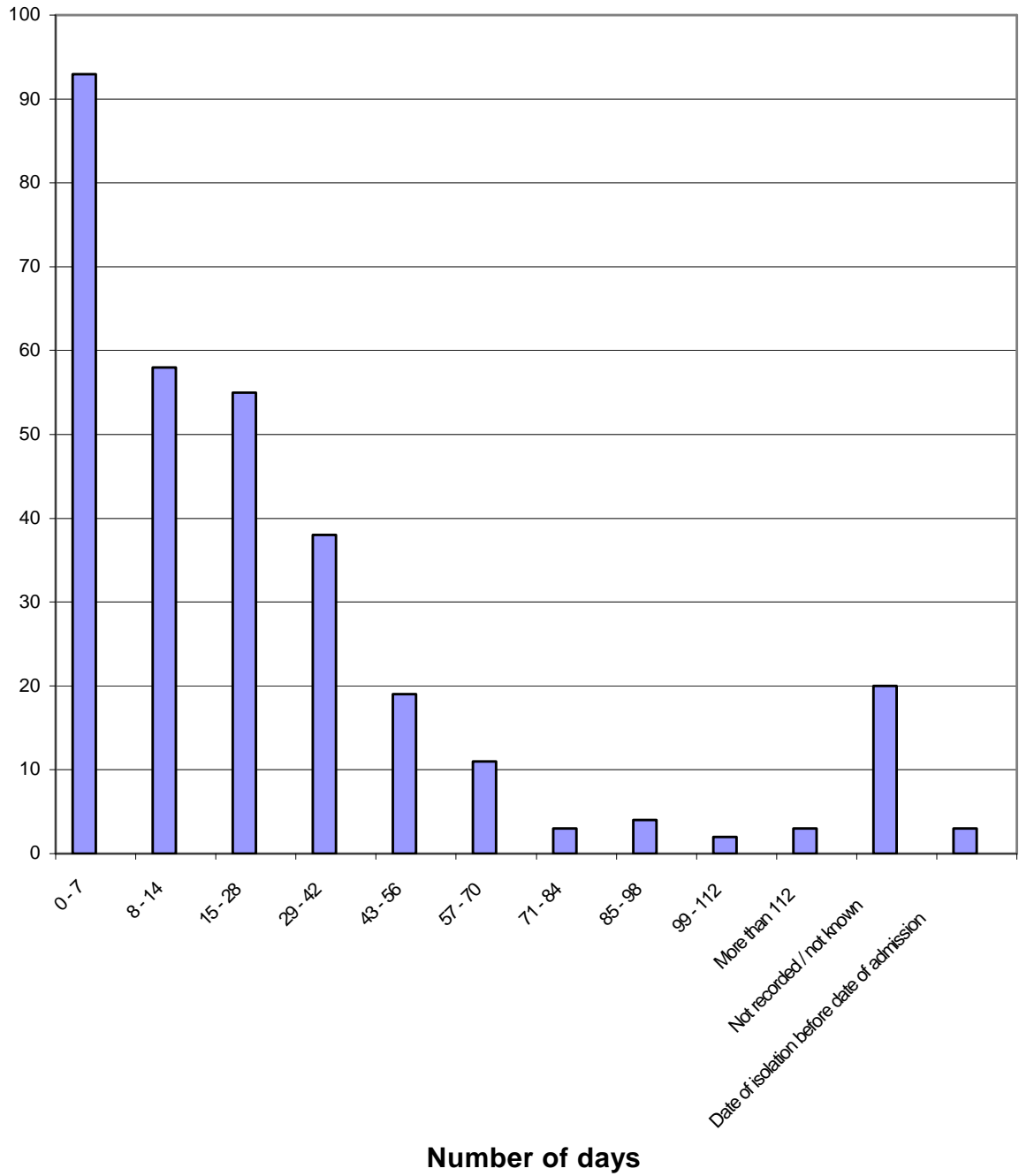


Figure 1



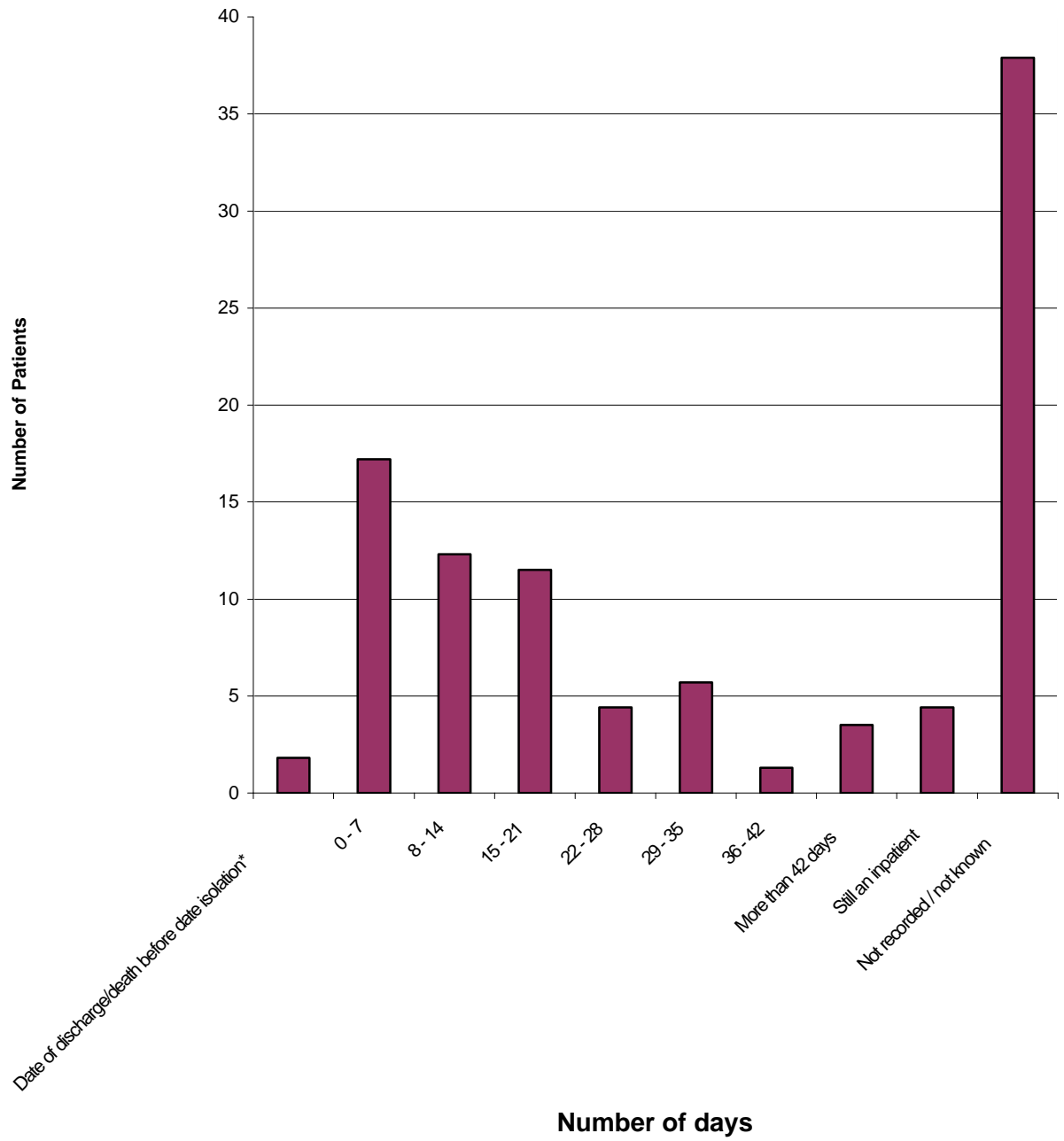
**Figure 2**

**Number of days between date of hospital admission and date of isolation**



**Figure 3**

**Number of days between date of isolation and date of discharge / death**



## **Discussion**

Although in a number of cases the respondents failed to identify themselves, there was a good geographical distribution amongst those who did. Data from a meaningful number of patients with proven MRSA infection were provided allowing useful interpretation of the result.

Significantly patients aged 60 or over predominated (81.7%) in this survey. This is higher than predicted from figures of hospital in-patients in England in 2002-03 which reveals only 34.9% over 65 and 21.7% between 45-64 years.

The figures suggest a higher susceptibility to MRSA amongst the elderly. No evidence was obtained from our survey suggested that this high frequency was due to transfer of patients from residential/nursing homes to hospital. Indeed 71.2% of patients included came from their own home.

Most infections began within the first seven days after admission. Of these the sources of the infection based on the specimen provided for the laboratory was predictable with a high incidence of skin/soft tissue/surgical wound specimens (40.7%). In the majority of instances the MRSA infection was acquired in hospital (11.9%) with an additional 9.1% of patients previously known to be MRSA positive.

The typical antibiotic resistance patterns seen in the MRSA isolates showed that they belonged mainly to EMRSA15 and EMRSA16 clones which are generally distributed 70-75% and 25-30% throughout the UK respectively. Interestingly some 56 (or 18.1%) of isolates were resistant to five antibiotics.

In terms of antibiotic prescribing,  $\beta$ -lactams with/without other agents (21.3%) had been prescribed for the patients in the 14 days prior to collection of the specimen from which MRSA was isolated. Quinolones alone or with another agent (13.4%) was the next most frequently used agent. The significance of these findings is uncertain. However the choice of antibiotic made after laboratory results were available clearly showed a switch to glycopeptide use either alone (29%) or with other agents (21.7%). Thus just over 50% of patients infected with MRSA were given glycopeptide following disclosure of laboratory results.

In terms of outcome there was good evidence that choice of antibiotic following confirmation of MRSA and laboratory antibiotic sensitivities influenced outcome. In 49.5% the patient's infection either was resolved or improved. In an additional 11.7% the patient's condition remained unchanged. Mortality (and not necessarily attributed to the MRSA infection) was 24.6% in this survey.

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