ClinicalEvidence

MRSA: treating people with infection

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ABSTRACT

INTRODUCTION: Methicillin-resistant Staphylococcus aureus (MRSA) has a gene that makes it resistant to methicillin as well as to other beta-lactam antibiotics including flucloxacillin, beta-lactam/beta-lactamase inhibitor combinations, cephalosporins, and carbapenems. MRSA can be part of the normal body flora (colonisation), especially in the nose, but it can cause infection, especially in people with prolonged hospital admissions, with underlying disease, or after antibiotic use. About 20% of S aureus in blood cultures in England, Wales, and Northern Ireland is resistant to methicillin. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatment for MRSA infections at any body site? We searched: Medline, Embase, The Cochrane Library and other important databases up to November 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 11 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: clindamycin, daptomycin, fusidic acid, glycopeptides (teicoplanin, vancomycin), linezolid, macrolides (azithromycin, clarithromycin, erythromycin), quinolones (ciprofloxacin, levofloxacin, moxifloxacin), quinupristin–dalfopristin, pristinamycin, rifampicin, tetracyclines (doxycycline, minocycline, oxytetracycline), tigecycline, trimethoprim, and trimethoprim–sulfamethoxazole (co-trimoxazole).

QUESTIONS

INTERVENTIONS

Key points

- Methicillin-resistant *Staphylococcus aureus* (MRSA) has a gene that makes it resistant to methicillin as well as other beta-lactam antibiotics including flucloxacillin, cephalosporins, and carbapenems.

  MRSA can be part of the normal body flora (colonisation), especially in the nose, but it can cause infection, especially in people with prolonged hospital admissions, with underlying disease, or after antibiotic use.

  About 20% of *S aureus* in blood cultures in England, Wales, and Northern Ireland is resistant to methicillin.

- Glycopeptides (teicoplanin, vancomycin) and linezolid seem to have similar efficacy at curing MRSA infection. However, they have all been associated with adverse effects.
- We found limited evidence that tigecycline may have similar cure rates as vancomycin, however effectiveness is not yet clear.
- Trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX) may be as effective as vancomycin at curing MRSA infection in injecting drug users, with similar toxicity. However, we cannot draw conclusions on the effects of this drug in other populations.
- We don't know whether macrolides (azithromycin, clarithromycin, erythromycin), quinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline, minocycline, oxytetracycline), clindamycin, daptomycin, fusidic acid, pristinamycin, quinupristin–dalfopristin, rifampicin, and trimethoprim are effective at curing MRSA infection, because we found no adequate RCTs.

Ciprofloxacin has been used in combination with rifampicin or fusidic acid for MRSA bone and joint infections but we cannot confirm its effectiveness from adequate studies. Fusidic acid or rifampicin should not be used as monotherapy because resistance rapidly develops.

Clindamycin may be used in preference to macrolides in susceptible MRSA infections, as bioavailability may be better and resistance less likely, however we found no adequate trials.

Oral tetracyclines may be recommended for minor MRSA infections, however we found no adequate trials.

DEFINITION

Staphylococcus aureus mainly colonises the nasal passages, but it may be found regularly in most other anatomical sites. Carrier rates in adults vary from 20% to 50% with people being persistent carriers, intermittent carriers, or non-carriers. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an organism resistant to methicillin by means of the *mecA* gene. This confers resistance to all beta-lactam antibiotics, including flucloxacillin, oxacillin, cephalosporins, and carbapenems. Antimicrobial resistance is defined as the failure of the antimicrobial drug to reach a concentration in the infected tissue that is high enough to inhibit the growth of the infecting organism. Like methicillin-sensitive *S aureus* (MSSA), MRSA can be part of the normal flora (colonisation) or it can cause infection. For MRSA to cause infection, it must be transmitted to the individual, colonise the individual, and gain entry to the host or target tissues. Infection is dependent on the balance between the host defences and the virulence of the infectious agent. Therefore, it is important to recognise the difference between colonisation and infection because they are entirely different entities in terms of clinical management. **MRSA infection:** Growth of MRSA from a sterile body site (e.g., blood culture or cerebrospinal fluid, joint aspirate or pleural fluid) or growth of MRSA from a non-sterile body site (e.g., wound, skin, urine, or sputum) usually in the presence of symptoms or signs of infection. The presence of viable bacteria in blood without a documented primary source of infection is termed primary bacteraemia whereas secondary bacteraemia is the presence of viable bacteria in the blood secondary to a localised focus of infection. The majority of strains of MRSA in the UK are associated with the healthcare setting (healthcare-associated MRSA [HA-MRSA]). These are strains that are transmitted to and circulate between individuals who have had contact with healthcare facilities. These infections can present in the hospital or healthcare setting (hospital or healthcare onset) or in the community (community onset), for example after hospital discharge. These MRSA strains are resistant to the isoxazolyl penicillins (such as meticillin, oxacillin, and flucloxacillin), beta-lactam/beta-lactamase inhibitor combinations, cephalosporins, and carbapenems. They also show a variable level of resistance to other groups of antibiotics such as quinolones, macrolides, and others. MRSA is also becoming an increasingly important cause of community-acquired infection in people who have not been recently admitted to healthcare facilities or had medical problems. This is termed community-associated or community-acquired MRSA (CA-MRSA). This is defined as MRSA strains isolated from patients in an outpatient or community setting (community onset), or within 48 hours of hospital admission (hospital onset), who have no previous history of MRSA infection or colonisation, no history of hospital admission, surgery, dialysis, or residence in a long-term care facility within 1 year of the MRSA culture date, and absence of an indwelling catheter or percutaneous device at the time of culture. These infections are generally less severe and primarily cause skin and soft-tissue infections, although cases of fulminant disseminated disease and necrotising pneumonia are increasingly reported. [1] We have primarily excluded this population from this review. However, the boundaries between HA-MRSA and CA-MRSA are becoming blurred because of the movement of people and infections between hospitals and the community. For example, nosocomial outbreaks of CA-MRSA following admission of colonised or infected patients have been reported. [2] In the US, where CA-MRSA is now common, it is becoming increasingly difficult to distinguish between CA-MRSA and HA-MRSA on clinical and epidemiological assessment. Since HA-MRSA and CA-MRSA strains are often genotypically and phenotypically different, the microbiological characteristics of staphylococcal isolates may help to distinguish between healthcare-associated and community-associated infections. [3] Our population of interest in this review is primarily people with HA-MRSA, although we have included people with CA-MRSA from studies in which most people (>50%) had HA-MRSA infections. The investigation of treatment strategies for community-acquired compared with nosocomial MRSA is ongoing, and will not be covered here. **Population:** We include adults with predominantly nosocomial or healthcare-acquired MRSA infection; we exclude children under 16 years.

INCIDENCE/ PREVALENCE

The incidence of MRSA varies from country to country. [4] The UK, Ireland, and southern Europe (e.g., Spain, Italy, and Greece) have a high incidence when compared with northern Europe and Scandinavia. [5] The most objective measure of incidence is the percentage of *S aureus* found in blood cultures that are resistant to methicillin. At the time of writing this review this stands at about 20% in the UK. [5] [6]

AETIOLOGY/ RISK FACTORS

A case-control study (121 people with MRSA infection, 123 people with MSSA infection) found that the following characteristics were associated with a significantly increased risk of MRSA infection: more comorbidities, longer length of hospital stay, greater exposure to antibiotics, previous hospi-

talisation, enteral feedings, and surgery. [7] A systematic review (search date 2006, 10 observational studies, 1170 people colonised, 791 colonised by MSSA, and 379 colonised by MRSA) found that MRSA colonisation was associated with a four-fold increased risk of infection compared with MSSA colonisation (OR 4.08, 95% 2.1 to 7.44). [8]

PROGNOSIS

The virulence of MRSA has been found to be equal to that of MSSA in animal models. However, a meta-analysis of 31 cohort studies found that mortality associated with MRSA bacteraemia was significantly higher than that associated with MSSA bacteraemia (mean mortality not reported; OR 1.93, 95% CI 1.54 to 2.42). [9] A subsequent cohort study (438 people, predominantly men, with *S aureus* infection complicated by bacteraemia, 193 [44%] of whom had MRSA) also found higher *S aureus*-related mortality with MRSA compared with MSSA in people without pneumonia (HR [adjusted for age, comorbidities, and pneumonia] 1.8, 95% CI 0.2 to 3.0; P <0.01). [10] However, these studies had various methodological weaknesses including no specific data given on the adequacy of treatment administered or severity of illness, or other confounders not consistently available or considered. A more recent prospective cohort study (1194 episodes of *S aureus* bacteraemia, 450 of these MRSA) found that MRSA infection was not an independent predictor of death and commented that the increased mortality associated with this invasive infection may be partly due to suboptimal treatment. [11] Another retrospective cohort study (334 adults with *S aureus* bacteraemia, 77 due to MRSA) found that empirical treatment was inadequate significantly more often with MRSA bacteraemia than it was with MSSA bacteraemia (proportion of people with inadequate empirical treatment with antimicrobials: 54/257 [21%] in people with MSSA *v* 40/77 [52%] in people with MRSA; P <0.001). However, it found that MRSA was not associated with increased mortality rates at 30 days. [12] Therefore, one cannot assume that invasive infection with MRSA *per se* is associated with a poorer clinical outcome. A range of confounders is likely to influence clinical outcome, and timeliness of treatment, among others, may be a factor.

AIMS OF INTERVENTION

To improve the clinical and microbiological cure rate; to decrease length of stay in hospital, with minimal adverse effects of treatment.

OUTCOMES

Mortality; clinical and microbiological cure rates; length of hospital stay; adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal November 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2009, Embase 1980 to November 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributors for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs, RCTs and cohort studies (prospective and retrospective, with or without a control group) in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We included studies that primarily addressed MRSA as the causative pathogen of the infection. We came across several studies of treatment of a range of gram-positive infections including MRSA. We have included these studies if MRSA was mentioned as one of the pathogens. We did not prospectively specify what percentage of the relevant population needed to have MRSA to include or exclude a study in our review. We have been explicit about these deficiencies in the studies included and their impact on the quality of the findings. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 17). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatment for MRSA infections at any body site?

OPTION LINEZOLID

Mortality
Compared with teicoplanin We don't know how effective linezolid or teicoplanin are, compared with each other, at reducing mortality (very low-quality evidence).

Compared with vancomycin in bacteraemia We don't know how effective linezolid or vancomycin are, compared with each other, at improving survival in adults with MRSA bacteraemia (very low-quality evidence).

Clinical or microbiological cure
Compared with vancomycin in infection at any body site Linezolid may be more effective at increasing clinical cure, bacterial clearance, and clinical effectiveness rates in people with MRSA infection or gram-positive infection, including MRSA, at any body site (very low-quality evidence).

Compared with vancomycin in nosocomial pneumonia Linezolid may be more effective at increasing clinical cure, bacterial clearance, and clinical effectiveness rates in people with MRSA infection or gram-positive infection, including MRSA, in the subgroup of people with nosocomial pneumonia (very low-quality evidence).

Compared with vancomycin in skin and soft-tissue infection Linezolid may be more effective at increasing clinical cure, bacterial clearance, and clinical effectiveness rates in people with MRSA infection or gram-positive infection, including MRSA, in the subgroup of people with skin and soft-tissue infection (very low-quality evidence).

Compared with vancomycin in bacteraemia We don't know how effective linezolid or vancomycin are, compared with each other, at improving clinical cure rate or microbiological success rate in adults or children with MRSA bacteraemia (very low-quality evidence).

Compared with teicoplanin We don't know how effective linezolid or teicoplanin are, compared with each other, at increasing clinical cure rate or microbiological success rate in people treated for microbiologically confirmed MRSA infection (very low-quality evidence).

Note
Linezolid has been associated with adverse effects including blood disorders.

For GRADE evaluation of the interventions included for MRSA, see table, p 17 .

Benefits:

Linezolid versus vancomycin:
We found one systematic review (search date 2006, 7 RCTs [reported in 8 publications], 756 adults with MRSA infection) [13] and one subsequent RCT (144 adults with known/suspected gram-positive bacterial infection [69/114 {61%} of pathogens isolated at baseline were MRSA] and clinical diagnosis of pneumonia or complicated skin or soft-tissue infection). [14] The review and subsequent RCT presented results for infection at any body site and also presented subgroup analyses by site of infection — nosocomial pneumonia; skin and soft-tissue infection. We found another two systematic reviews (search dates not reported [15] and 2009 [16]) that presented subgroup analyses in people with bacteraemia. The second review included five RCTs, four of which were also found by the first systematic review (144 people with secondary *S aureus* bacteraemia, 73/144 [51%] with MRSA). [15] The third systematic review included seven RCTs in adults and children with bacteraemia, one of which was identified by the first review (unclear how many people in the total population had MRSA infection). [16]

Any body site: The first systematic review found that linezolid significantly improved clinical cure rates compared with vancomycin (time frame not reported). It also found that linezolid significantly improved bacterial clearance rates compared with vancomycin (see table 1, p 15 for results). The systematic review had limitations in that no information was provided on blinding or allocation concealment in the included RCTs. [13] The subsequent RCT did not present clinical and microbiological cure rates specific to MRSA infection, and therefore results should be interpreted with caution. It also allowed concomitant use of aztreonam in people with mixed gram-positive and gram-negative infections. It found that linezolid significantly improved the proportion of people with gram-positive bacterial infection with clinically effective treatment (defined as resolution of at least 3 of the following outcomes: signs, symptoms, haematology and chemistry, microbiology) compared with vancomycin at 72 hours and 7 to 28 days post treatment. The RCT found no significant difference between linezolid and vancomycin in the subgroup of people with *S aureus* with eradication

at 7 to 28 days post treatment, however the follow-up for this outcome was low (<80% of the randomised study population) and so we have not reported it further. [14]

Nosocomial pneumonia: The first systematic review found that linezolid significantly improved clinical cure rates and bacterial clearance compared with vancomycin in the subgroup of people with MRSA nosocomial pneumonia (see table 1, p 15 for results). [13] The subsequent RCT reported on the subgroup of people with clinical diagnosis of pneumonia (80 people in intention-to-treat [ITT] population; pneumonia was hospital acquired in 90% of people). The RCT found that linezolid significantly improved the proportion of people with clinically effective treatment compared with vancomycin at 72 hours post treatment for gram-positive pneumonia. However, the RCT found no significant difference between linezolid and vancomycin in the proportion of people with clinically effective treatment at 7 to 28 days post treatment for gram-positive pneumonia (see table 1, p 15 for results). The RCT found similar eradication rates between linezolid and vancomycin in the subgroup of people with *S aureus* at 7 to 28 days post treatment; however, the follow-up for this outcome was low (<80% of the randomised study population) and so we have not reported it further. [14]

Skin and soft-tissue infection: The first systematic review found that linezolid significantly improved clinical cure rates and bacterial clearance compared with vancomycin in the subgroup of people with skin and soft-tissue MRSA infections (see table 1, p 15 for results). [13] The subsequent RCT reported on the subgroup of people with a clinical diagnosis of complicated skin or soft-tissue infection (62 people in ITT population). It found that linezolid significantly improved the proportion of people with clinically effective treatment compared with vancomycin at 72 hours for gram-positive skin or soft-tissue infection. However, the RCT found no significant difference between linezolid and vancomycin in the proportion of people with clinically effective treatment at 7 to 28 days post treatment for skin or soft-tissue infection (see table 1, p 15 for results). The RCT found similar eradication rates between linezolid and vancomycin in the subgroup of people with *S aureus* at 7 to 28 days post treatment; however, the follow-up for this outcome was low (<80% of the randomised study population) and so we have not reported it further. [14]

Bacteraemia: The second systematic review found no significant difference between linezolid and vancomycin in mortality for MRSA bacteraemia (see table 1, p 15 for results). It also found no significant difference between groups in clinical cure; however, the follow-up for this outcome was low (<80% of the randomised study population) and so we have not reported it further. The review did not separately report microbiological outcomes for the subgroup of people with MRSA infection. Two of the identified RCTs were blinded, and three were not. [15] The third systematic review found that there was no significant difference between linezolid and vancomycin in clinical cure (time frame not reported; see table 1, p 15 for results). The results of this systematic review should be interpreted with caution, because it had several limitations: four RCTs included children aged <12 years, which do not meet our reporting criteria, details of blinding were available in only one RCT, and no sensitivity analyses were undertaken. [16]

Linezolid versus teicoplanin:

We found no systematic review. We found one RCT comparing linezolid versus teicoplanin (see table 1, p 15). [17] The RCT found no significant difference in clinical or microbiological cure in the subgroup of people treated for microbiologically confirmed MRSA infection, but no figures were reported. It found no significant difference in clinical cure for all gram-positive infections between linezolid and teicoplanin (see table 1, p 15). It found no significant difference between groups in microbiological success for all gram-positive infections; however, the follow-up for this outcome was low (<80% of the randomised study population) and so we have not reported it further. The RCT also found that there were significantly fewer deaths in the linezolid group compared with the teicoplanin group for all people regardless of MRSA infection, although the cause of death was usually multifactorial.

Linezolid versus any other antibiotic listed in review:

We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms:

Linezolid versus vancomycin:

The systematic review did not report on adverse effects of treatment. [13] Three RCTs identified by the systematic review reported adverse effects. In the first RCT, 10 people in each group discontinued treatment owing to adverse effects. [18] There was a higher rate of drug-related adverse effects in the linezolid group compared with the vancomycin group (460 people; drug-related adverse effects: 44/240 [18%] with linezolid *v* 18/220 [8%] with vancomycin; P = 0.001). These were mostly gastrointestinal disturbance for linezolid. There were two cases each of anaphylaxis and renal disturbance in the vancomycin group. In the second RCT, there was no significant difference in the rate of treatment discontinued owing to adverse effects or drug-related adverse effects (1080 people; drug-related adverse effects; 131/592 [22%] with linezolid plus aztreonam *v* 121/588 [21%] with vancomycin plus aztreonam; P = 0.516). [19] Gastrointestinal disturbance and thrombocytopenia were significantly more common with linezolid and rash, anaphylaxis, allergic reaction, and phlebitis occurred significantly more often in the vancomycin group. In the third RCT, there was no significant

difference in the rate of treatment discontinued owing to adverse effects or drug-related adverse effects. [20]

The subsequent RCT found similar rates of drug-related clinical adverse effects in both groups (18/71 [25%] people with linezolid *v* 12/71 [17%] people with vancomycin; significance not assessed). [14] Common adverse effects included rash, fever, dyspepsia, nausea, allergic reaction, leukopenia, and thrombocytopenia. One serious adverse effect (acute renal failure 1 week after the end of treatment visit) was considered to be treatment-related in one person taking linezolid.

The second systematic review found a significantly higher rate of new-onset thrombocytopenia with linezolid compared with vancomycin (5/36 [14%] with linezolid *v* 0/70 [0%] with vancomycin; P = 0.02). It found no significant difference between groups in rates of any adverse effect, rates of serious adverse effects (as assessed by investigators), or rates of discontinuation from treatment (any adverse effect: 59/74 [80%] with linezolid *v* 48/59 [70%] with vancomycin; P = 0.16; serious adverse effects: 35/74 [47%] with linezolid *v* 26/70 [37%] with vancomycin; P = 0.22; discontinuation from treatment: 27/74 [37%] with linezolid *v* 27/70 [39%] with vancomycin; P = 0.80). [15]

The third systematic review comparing linezolid versus vancomycin for gram-positive infections found that there was no significant difference between groups in overall adverse effects or anaemia (overall adverse effects: P = 0.64; anaemia: P = 0.48; absolute results not reported). However, it found that renal inadequacy was significantly lower with linezolid compared with vancomycin (0.47% with linezolid *v* 2.51% with vancomycin; P = 0.0003; absolute results not reported), and that thrombocytopenia was significantly higher with linezolid compared with vancomycin (4.39% with linezolid *v* 1.35% with vancomycin; P=0.01; absolute results not reported). [16]

Linezolid versus teicoplanin:
The RCT comparing linezolid versus teicoplanin found no significant difference in the rate of adverse effects overall or for any particular adverse effect. [17]

Linezolid versus any other antibiotic listed in review:
We found no RCTs or cohort studies.

Comment:

We found one retrospective cohort study comparing linezolid versus teicoplanin in gram-positive infection. [21] However, the study did not present a direct comparison between linezolid and teicoplanin monotherapy in people with MRSA infection.

Three methodological aspects must be considered when interpreting the results of these studies. First, most were open label, which could be a problem in view of the subjective nature of the main outcome measure in most RCTs, clinical cure. Second, people with MRSA, and those with particular types of MRSA infection, usually formed a subgroup within a larger investigation of presumed gram-positive infection. Third, the population size was often small and microbiological clearance of MRSA was not consistently measured. A recent meta-analysis of trials evaluating parenteral antimicrobial therapy for skin and soft-tissue infections found that although 88% (15/17 trials) had reported infection with MRSA, only 10/17 (59%) reported separate cures for the pathogens. [22] Furthermore, FDA guidance recommended that at least 70% of the clinically evaluable population should be microbiologically evaluable; however, very few studies complied with this.

Clinical guide:
Linezolid was not found to be consistently better than glycopeptides across all groups analysed, which undermines the reliability of significant results from individual studies. Theoretically, the superior tissue penetration of linezolid should give it an advantage when treating infections where high antibiotic levels are difficult to achieve, such as in the lungs and poorly perfused lower limbs. However, a recent open-label RCT comparing early microbiological efficacy of linezolid versus vancomycin for ventilator-associated pneumonia caused by MRSA found no significant difference between the two antibiotics for bacterial clearance. It commented that there may be other factors that may explain differences found between antibiotics in clinical cure. This study was small, had low follow-up, and might have been underpowered to detect a difference between groups. [23] The availability of an oral preparation of linezolid makes treatment at home an easier prospect than for vancomycin and teicoplanin, which cannot be given by this route.

OPTION TEICOPLANIN, VANCOMYCIN (GLYCOPEPTIDES)

Mortality
Vancomycin compared with quinupristin–dalfopristin for MRSA nosocomial pneumonia We don't know how effective vancomycin and quinupristin–dalfopristin are, compared with each other, in improving mortality (low-quality evidence).

Teicoplanin compared with linezolid for MRSA infection of any body site We don't know how effective teicoplanin and linezolid are, compared with each other, at reducing mortality (very low-quality evidence).

Clinical or microbiological cure

Vancomycin compared with linezolid in infection at any body site Vancomycin may be less effective at increasing clinical cure, bacterial clearance, or clinical effectiveness rates in people with MRSA infection or gram-positive infection, at any body site (very low-quality evidence).

Vancomycin compared with linezolid in nosocomial pneumonia Vancomycin may be less effective at increasing clinical cure, bacterial clearance, or clinical effectiveness rates in people with MRSA infection or gram-positive infection, in the subgroup of people with nosocomial pneumonia (very low-quality evidence).

Vancomycin compared with linezolid in skin and soft-tissue infection Vancomycin may be less effective at increasing clinical cure, bacterial clearance, or clinical effectiveness rates in people with MRSA infection or gram-positive infection, in the subgroup of people with skin and soft-tissue infection (very low-quality evidence).

Vancomycin compared with linezolid in bacteraemia We don't know how effective vancomycin and linezolid are, compared with each other, at improving clinical cure rate or microbiological success rate in adults or children with MRSA bacteraemia (very low-quality evidence).

Vancomycin compared with quinupristin–dalfopristin for MRSA nosocomial pneumonia We don't know how effective vancomycin and quinupristin–dalfopristin are, compared with each other, in improving clinical cure rates (very low-quality evidence).

Vancomycin compared with trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX) for MRSA infection of any body site We don't know how effective vancomycin and TMP-SMX are, compared with each other, at increasing clinical cure in injecting drug users (very low-quality evidence).

Vancomycin compared with tigecycline We don't know how effective tigecycline and vancomycin are, compared with each other, at increasing cure rates in hospitalised people with serious MRSA infection (low-quality evidence).

Teicoplanin compared with linezolid for MRSA infection of any body site We don't know how effective teicoplanin and linezolid are, compared with each other, at increasing clinical cure rate or microbiological success rate (very low-quality evidence).

Note

Teicoplanin and vancomycin have been associated with adverse effects.

For GRADE evaluation of the interventions for MRSA, see table, p 17 .

Benefits:

Vancomycin versus linezolid:
See benefits of linezolid, p 4 .

Vancomycin versus quinupristin–dalfopristin:
See benefits of quinupristin–dalfopristin, p 9 .

Vancomycin versus trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX):
See benefits of trimethoprim–sulfamethoxazole, p 10 .

Vancomycin versus tigecycline:
See benefits of tigecycline, p 11 .

Teicoplanin versus linezolid:
See benefits of linezolid, p 4 .

Harms:

Teicoplanin, vancomycin (glycopeptides) versus no antibiotics:
We found no RCTs or cohort studies.

Vancomycin versus linezolid:
See harms of linezolid, p 4 .

Vancomycin versus quinupristin–dalfopristin:
See harms of quinupristin–dalfopristin, p 9 .

Vancomycin versus trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX):
See harms of trimethoprim–sulfamethoxazole, p 10 .

Vancomycin versus tigecycline:
See harms of tigecycline, p 11 .

Teicoplanin versus linezolid:
See harms of linezolid, p 4 .

Comment: None.

OPTION AZITHROMYCIN, CLARITHROMYCIN, ERYTHROMYCIN (MACROLIDES)

We found no direct information from RCTs on the effects of macrolides (azithromycin, clarithromycin, erythromycin) in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits: **Azithromycin, clarithromycin, erythromycin (macrolides) versus any other antibiotic listed in review:**
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms: **Azithromycin, clarithromycin, erythromycin (macrolides) versus any other antibiotic listed in review:**
We found no RCTs or cohort studies.

Comment: **Clinical guide:**
Macrolides are not recommended for the treatment of MRSA infections in UK guidelines. [9]

OPTION CIPROFLOXACIN, LEVOFLOXACIN, MOXIFLOXACIN (QUINOLONES)

We found no direct information from RCTs on the effects of quinolones (ciprofloxacin, levofloxacin, moxifloxacin) in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits: **Ciprofloxacin, levofloxacin, moxifloxacin (quinolones) versus any other antibiotic listed in review:**
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms: **Ciprofloxacin, levofloxacin, moxifloxacin (quinolones) versus any other antibiotic listed in review:**
We found no RCTs or cohort studies.

Comment: **Clinical guide:**
Ciprofloxacin has been used in combination with rifampicin or fusidic acid for MRSA bone and joint infections.

OPTION CLINDAMYCIN

We found no direct information from RCTs on the effects of clindamycin in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits: **Clindamycin versus any other antibiotic listed in review:**
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms: **Clindamycin versus any other antibiotic listed in review:**
We found no RCTs or cohort studies.

Comment: **Clinical guide:**
Clindamycin is used in preference to macrolides in clinical practice for susceptible MRSA infections because bioavailability is considered to be better and resistance is less likely to occur. [9]

OPTION DAPTOMYCIN

We found no direct information from RCTs on the effects of daptomycin in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits: **Daptomycin versus any other antibiotic listed in review:**
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms: **Daptomycin versus any other antibiotic listed in review:**
We found no RCTs or cohort studies.

Comment: **Clinical guide:**
Daptomycin is a new drug but there is evolving experience in the UK and globally of use in clinical practice.

OPTION DOXYCYCLINE, MINOCYCLINE, OXYTETRACYCLINE (TETRACYCLINES)

We found no direct information from RCTs on the effects of tetracyclines (minocycline, doxycycline, and oxytetracycline) in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits: **Doxycycline, minocycline, oxytetracycline (tetracyclines) versus any other antibiotic listed in review:**
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms: **Doxycycline, minocycline, oxytetracycline (tetracyclines) versus any other antibiotic listed in review:**
We found no RCTs or cohort studies.

Comment: **Clinical guide:**
Tetracyclines are often used in clinical practice as an oral treatment for minor MRSA infections as recommended by UK national guidelines. [9]

OPTION FUSIDIC ACID (SODIUM FUSIDATE)

We found no direct information from RCTs on the effects of fusidic acid (sodium fusidate) in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits: **Fusidic acid versus any other antibiotic listed in review:**
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms: **Fusidic acid versus any other antibiotic listed in review:**
We found no RCTs or cohort studies.

Comment: **Clinical guide:**
Fusidic acid alone or in combination is no longer recommended in the UK guidelines for MRSA infections. [9]

OPTION QUINUPRISTIN–DALFOPRISTIN

Clinical or microbiological cure
Compared with vancomycin for MRSA nosocomial pneumonia We don't know how effective quinupristin–dalfopristin and vancomycin are, compared with each other, in improving clinical cure rates (very low-quality evidence).

Mortality
Compared with vancomycin for MRSA nosocomial pneumonia We don't know how effective quinupristin–dalfopristin and vancomycin are, compared with each other, in improving mortality (low-quality evidence).

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits:

Quinupristin–dalfopristin versus vancomycin for MRSA nosocomial pneumonia:
We found no systematic review. We found one multicentre RCT (298 people with nosocomial pneumonia, 51 of whom had MRSA, age range not reported) comparing quinupristin–dalfopristin with vancomycin. [25] It found no significant difference in the clinical cure rate (defined as the disappearance of signs and symptoms) with quinupristin–dalfopristin (7.5 mg/kg 3 times daily intravenously [iv] for 5–14 days) compared with vancomycin (1 g twice daily iv for 5–14 days) in the subgroup of people with MRSA pneumonia (clinical cure: 6/31 [19%] with quinupristin–dalfopristin *v* 8/20 [40%] with vancomycin; difference –21%, 95% CI –46% to –5%). It found no significant difference in mortality between quinupristin–dalfopristin compared with vancomycin at 30 days' follow-up for all people with nosocomial pneumonia regardless of MRSA infection (38/150 [25%] with quinupristin–dalfopristin *v* 32/148 [22%] with vancomycin; P = 0.45). [25] The number of people in the RCT with confirmed MRSA was small and was not sufficient to detect a clinically significant difference in the cure rate. [25]

Quinupristin–dalfopristin versus any other antibiotic listed in review:
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms:

Quinupristin–dalfopristin versus vancomycin:
The RCT found no significant difference between groups in adverse effects (non-venous adverse effects: 145/150 [97%] with quinupristin–dalfopristin *v* 138/148 [93%] with vancomycin; P = 0.18; venous adverse effects: 36/150 [24%] with quinupristin–dalfopristin *v* 29/148 [20%] with vancomycin; P = 0.36). [25] There was also no significant difference in withdrawal rates because of adverse effects (23/150 [15%] with quinupristin–dalfopristin *v* 14/148 [9%] with vancomycin; P = 0.12). [25]

Quinupristin–dalfopristin versus any other antibiotic listed in review:
We found no RCTs or cohort studies.

Comment:

None.

OPTION RIFAMPICIN

We found no direct information from RCTs on the effects of rifampicin in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits:

Rifampicin versus any other antibiotic listed in review:
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms:

Rifampicin versus any other antibiotic listed in review:
We found no RCTs or cohort studies.

Comment:

Clinical guide:
Rifampicin can be used in combination with other oral agents (such as trimethoprim) but not alone because *S aureus* rapidly develops resistance. However, its use in most MRSA infections — except for perhaps in combination with parenteral glycopeptides or other agents for bone and joint infections and endocarditis — is no longer recommended. [9]

OPTION TRIMETHOPRIM

We found no direct information from RCTs on the effects of trimethoprim alone in people with MRSA infection.

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits:

Trimethoprim versus any other antibiotic listed in review:
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms:

Trimethoprim versus any other antibiotic listed in review:
We found no RCTs or cohort studies.

Comment:

None.

OPTION TRIMETHOPRIM–SULFAMETHOXAZOLE (CO-TRIMOXAZOLE; TMP-SMX)

Clinical or microbiological cure

Compared with vancomycin for MRSA infection of any body site We don't know how effective TMP-SMX and vancomycin are, compared with each other, at increasing clinical cure in injecting drug users (very low-quality evidence).

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits:

Trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX) versus vancomycin for MRSA infection of any body site:
We found no systematic review. We found one RCT (101 people who were injecting drug users requiring admission to hospital for *S aureus* infection of any site; 47 of whom had MRSA, age range not reported) comparing TMP-SMX (320 mg/1600 mg intravenously [iv] twice daily) versus vancomycin (1 g iv twice daily). [26] All people with MRSA in both groups were cured clinically (21/21 [100%] with TMP-SMX *v* 26/26 [100%] with vancomycin; RR 1.0).

Trimethoprim–sulfamethoxazole versus any other antibiotic listed in review:
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms:

Trimethoprim–sulfamethoxazole versus vancomycin:
The RCT found similar rates of toxicity in both groups (26/112 [23%] with TMP-SMX *v* 22/110 [20%] with vancomycin; P value not reported). [26] Three people in each group withdrew owing to adverse events (2 people with TMP-SMX and 3 people with vancomycin owing to rashes, and 1 person with TMP-SMX owing to serum sickness). The RCT did not report subgroup analysis in people with MRSA.

Trimethoprim–sulfamethoxazole versus any other antibiotic listed in review:
We found no RCTs or cohort studies.

Comment:

This was a double-blind study of injecting drug users with *S aureus* bacteraemia. As such, there was an unusually large number of people with tricuspid endocarditis.

Clinical guide:
The use of TMP-SMX in endocarditis/bacteraemia is not recommended in the UK although TMP-SMX has been recommended in the management of skin and soft-tissue infections in non-hospitalised patients and for oral therapy of simple urinary tract infection for clinical practice in the UK. [9]

OPTION TIGECYCLINE New

Clinical or microbiological cure
Compared with vancomycin We don't know how effective tigecycline and vancomycin are, compared with each other, at increasing cure rates in hospitalised people with serious MRSA infection (low-quality evidence).

For GRADE evaluation of interventions for MRSA, see table, p 17 .

Benefits:

Tigecycline versus vancomycin for MRSA infection at any body site:
We found no systematic review. We found one RCT (157 hospitalised people with serious MRSA infection; complicated skin or soft-tissue infection [108 people], complicated intra-abdominal infection [21 people], primary bacteraemia [15 people], hospital-acquired pneumonia [10 people], or community-acquired pneumonia [2 people]; median age 51 years) comparing tigecycline (100 mg intravenously [iv] loading dose followed by 50 mg every 12 hours) versus vancomycin (1 g iv every 12 hours). [24] The RCT found similar clinical cure rates with tigecycline and vancomycin at 12 to 37 days after the last dose (intention-to-treat [ITT] analysis: proportion of people with clinical cure: 85/118 [72%] with tigecycline *v* 29/39 [74%] with vancomycin; significance not reported; proportion of test-of-cure attendees with clinical cure: 75/100 [75%, 95% CI 65% to 83%] with tigecycline *v* 27/33 [82%, 95% CI 65% to 93%] with vancomycin). Microbiological cure rates were also similar between groups (ITT analysis: proportion of people with microbiological cure [eradication of the organism, documented or presumed]: 74/100 [74%] with tigecycline *v* 27/33 [82%] with vancomycin; significance not reported). [24]

Tigecycline versus any other antibiotic listed in review:
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms:

Tigecycline versus vancomycin:
The RCT found similar rates of drug-related adverse effects in both groups (45% with tigecycline *v* 33% with vancomycin; absolute numbers and P value not reported). [24] Adverse events affecting the digestive system (nausea, vomiting, and diarrhoea) were significantly more common with tige-

cycline than with vancomycin (58/117 [50%] with tigecycline *v* 12/39 [31%] with vancomycin; P <0.05). Treatment discontinuation for adverse events was similar between treatment groups (8/117 [7%] with tigecycline *v* 2/39 [5%] with vancomycin; reported as not significant). Eight people died but the deaths were not thought to be treatment related (all-cause mortality during the study [timescale not defined]: 6/117 [5%] with tigecycline *v* 2/39 [5%] with vancomycin).

Tigecycline versus any other antibiotic listed in review:
We found no RCTs or cohort studies.

Comment: This double-blind study of hospitalised patients with serious MRSA infections found similar cure rates between tigecycline and vancomycin, but was not powered to demonstrate superiority of either agent. [24] The population in the study was heterogeneous and its effectiveness for any specific infection site is difficult to ascertain.

Clinical guide:
Recent UK guidelines recommend that tigecycline be regarded as an alternative treatment for MRSA skin and soft-tissue infections in clinical situations where other agents are deemed inappropriate or failing. [9]

OPTION PRISTINAMYCIN New

We found no direct information from RCTs on the effects of pristinamycin alone in people with MRSA infection.

For GRADE evaluation of the interventions included for MRSA, see table, p 17 .

Benefits: **Pristinamycin versus any other antibiotic listed in review:**
We found no systematic review, RCTs, or cohort studies satisfying *Clinical Evidence* inclusion criteria.

Harms: **Pristinamycin versus any other antibiotic listed in review:**
We found no RCTs or cohort studies.

Comment: **Clinical guide:**
Oral pristinamycin is not widely available in the UK but there have been some reports (mainly uncontrolled studies or retrospective observational studies) of its use in management of MRSA skin and soft-tissue infections and osteoarticular infections. It is not referred to in the UK guidance. [27] [28]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Tigecycline New option added, for which we found one RCT. [24] It found similar clinical cure rates and microbiological cure rates with tigecycline and vancomycin in people with serious MRSA infections. Categorised as Unknown effectiveness as we cannot draw conclusions from a single RCT.

Pristinamycin New option added, for which we found no systematic review or RCTs. Categorised as unknown effectiveness.

Linezolid One systematic review added comparing linezolid versus vancomycin, which included six RCTs previously reported separately in this *Clinical Evidence* review. [13] One subsequent RCT also added. [14] The review and RCT presented results for infection at any body site and also subgroup analyses for nosocomial pneumonia; and skin and soft-tissue infection; all analyses suggested that linezolid was more effective than vancomycin in reducing infection rates. Two systematic reviews added that presented data separately for people with bacteraemia and found no significant difference in this outcome between linezolid and vancomycin. [15] [16] However, the analyses in both reviews had important limitations owing to weak original RCT data. Categorisation unchanged (Trade-off between benefits and harms).

Teicoplanin, vancomycin (glycopeptides) One systematic review added comparing vancomycin versus linezolid, which included six RCTs previously reported separately in this *Clinical Evidence* review. [13] One subsequent RCT also added, again comparing vancomycin versus linezolid. [14] The review and RCT presented results for infection at any body site and also subgroup analyses for nosocomial pneumonia; and skin and soft-tissue infection; all analyses suggested that vancomycin was less effective than linezolid. Two systematic reviews added also comparing linezolid versus vancomycin and presented data separately for people with bacteraemia and found no significant

difference in this outcome between vancomycin and linezolid. [15] [16] However, the analyses in both reviews had important limitations owing to weak original RCT data. One RCT added comparing tigecycline versus vancomycin. [24] It found similar clinical cure rates and microbiological cure rates with tigecycline and vancomycin in people with serious MRSA infections. Categorisation unchanged (Trade-off between benefits and harms).

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TABLE 1 **Studies comparing linezolid with vancomycin or teicoplanin**

Ref	Intervention	Participants	Outcomes	Results
Linezolid *v* vancomycin for MRSA infection of any body site				
[13]	Linezolid (600 mg every 12 hours iv or orally for 7–21 days) *v* vancomycin (1 g every 12 hours iv for 7–21 days)	756 adults with MRSA infection	Proportion of people with clinical cure	301/379 (79%) with linezolid *v* 252/377 (67%) with vancomycin; OR 2.48, 95% CI 1.68 to 3.64
		756 adults with MRSA infection	Proportion of people with bacterial clearance (time frames not reported)	262/337 (78%) with linezolid *v* 195/328 (59%) with vancomycin; OR 2.68, 95% CI 1.29 to 5.57); however, there was significant statistical heterogeneity for this outcome (P = 0.005; heterogeneity defined as P = 0.10). The review included a diverse group of clinical infections and ages and healthcare settings, which may have contributed to this heterogeneity
[14]	Linezolid (600 mg iv every 12 hours for 7–21 days) *v* vancomycin (0.75–1 g iv every 12 hours for 7–21 days)	144 people with known or suspected infection with gram-positive bacteria randomised, 131 people available for this analysis	Proportion of people with clinically effective treatment at 72 hours post treatment	53/61 (87%) with linezolid *v* 37/70 (62%) with vancomycin; 95% CI for the difference in rates 10.3 to 40.2; P = 0.0015
		144 people with known or suspected infection with gram-positive bacteria randomised, 116 people available for this analysis	Proportion of people with clinically effective treatment at 7 to 28 days post treatment. Data for MRSA infection not reported	49/59 (83%) with linezolid *v* 37/57 (65%) with vancomycin; 95% CI for the difference in rates 2.5 to 33.8; P = 0.03
Linezolid *v* vancomycin for MRSA nosocomial pneumonia				
[13]	Linezolid (600 mg every 12 hours iv or orally for 7–21 days) *v* vancomycin (1 g every 12 hours iv for 7–21 days	Subgroup analysis of adults with MRSA nosocomial pneumonia (number of RCTs and people in this analysis not reported)	Proportion of people with clinical cure	OR 3.45, 95% CI 1.90 to 6.26; favours linezolid; absolute results per group not reported
		Subgroup analysis of adults with MRSA nosocomial pneumonia (number of RCTs and people in this analysis not reported)	Proportion of people with bacterial clearance (time frames not reported)	OR 2.60, 95% CI 1.31 to 5.15; favours linezolid; absolute results per group not reported
[14]	Linezolid (600 mg iv every 12 hours for 7–21 days) *v* vancomycin (0.75–1 g iv every 12 hours for 7–21 days)	Subgroup analysis of 62 people with known or suspected infection with gram-positive pneumonia	Proportion of people with clinically effective treatment at 72 hours post treatment	Data for MRSA infection not reported. 22/28 (79%) with linezolid *v* 18/34 (53%) with vancomycin; 95% CI for the difference in rates 2.99 to 48.3
		Subgroup analysis of 59 people with known or suspected infection with gram-positive pneumonia	Proportion of people with clinically effective treatment at 7 to 28 days post treatment	Data for MRSA infection not reported. 19/26 (73%) with linezolid *v* 18/33 (55%) with vancomycin; 95% CI for the difference in rates –5.5 to +42.6
Linezolid *v* vancomycin for MRSA skin and soft-tissue infection				
[13]	Linezolid (600 mg every 12 hours iv or orally for 7–21 days) *v* vancomycin (1 g every 12 hours iv for 7–21 days)	Subgroup analysis of adults with MRSA skin and soft-tissue infection (number of RCTs and people in this analysis not reported)	Proportion of people with clinical cure (time frame not reported)	OR 2.84, 95% CI 1.47 to 5.49; favours linezolid; absolute results per group not reported
		Subgroup analysis of adults with MRSA skin and soft-tissue infection (number of RCTs and people in this analysis not reported)	Proportion of people with bacterial clearance (time frame not reported)	OR 4.56, 95% CI 2.65 to 7.83; favours linezolid; absolute results per group not reported
[14]	Linezolid (600 mg iv every 12 hours for 7–21 days) *v* vancomycin (0.75–1 g iv every 12 hours for 7–21 days)	Subgroup analysis of 59 people with known or suspected complicated skin or soft-tissue infection with gram-positive bacteria	Proportion of people with clinically effective treatment at 72 hours post treatment	Data for MRSA infection not reported. 31/33 (94%) with linezolid *v* 19/26 (73%) with vancomycin; 95% CI for the difference in rates 1.97 to 39.8

Ref	Intervention	Participants	Outcomes	Results
		Subgroup analysis of 57 people with known or suspected complicated skin or soft-tissue infection with gram-positive bacteria	Proportion of people with clinically effective treatment at 7 to 28 days post treatment	Data for MRSA infection not reported. 30/33 (91%) with linezolid *v* 19/24 (79%) with vancomycin; 95% CI for the difference in rates –7.2 to +30.7
Linezolid *v* vancomycin for MRSA bacteraemia				
[15]	Linezolid *v* vancomycin	144 people with secondary *S aureus* bacteraemia, subgroup analysis in 73/144 (51%) people with MRSA	Survival for MRSA bacteraemia	24/36 (67%) with linezolid *v* 24/37 (65%) with vancomycin; OR 1.08, 95% CI 0.41 to 2.85
[16]	Linezolid (10 mg/kg to 600 mg iv every 8–12 hours) *v* vancomycin (10 mg to 1 g iv every 6–24 hours)	7 RCTs, subgroup analysis in adults and children with MRSA bacteraemia	Proportion of people with clinical cure (time frame not reported)	65/92 (71%) with linezolid *v* 41/68 (60%) with vancomycin; RR 1.22, 95% CI 0.97 to 1.53; P = 0.10
Linezolid *v* teicoplanin for MRSA infection of any body site				
[17]	Linezolid (600 mg every 12 hours) *v* teicoplanin (400 mg every 12 hours for 3 doses, then 400 mg every 24 hours iv)	202 people with suspected or confirmed gram-positive infections in an intensive care population; 82 people had confirmed MRSA	Clinical cure rate	Data for MRSA infection not reported. For all people: 71/90 (79%) with linezolid *v* 67/92 (73%) with teicoplanin; P = 0.39; RR 1.10, 95% CI 0.92 to 1.27
		202 people with suspected or proved gram-positive infections in an intensive care population; 82 people had proved MRSA	Mortality	Data for MRSA infection not reported. For all people: 18% with linezolid *v* 25% with teicoplanin; P = 0.3

iv, intravenous; ref, reference.

TABLE **GRADE evaluation of interventions for MRSA: treating people with infection**

Important outcomes	Clinical or microbiological cure, length of hospital stay, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatment for MRSA infections at any body site?									
5 (73) [15]	Mortality	Linezolid *v* vancomycin in bacteraemia	4	–3	0	0	0	Very low	Quality points deducted for sparse data, methodological weaknesses (no blinding), and subgroup analysis
7 (900) [13] [14]	Clinical or microbiological cure	Linezolid *v* vancomycin in infection at any body site	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting and methodological weaknesses (no blinding). Directness points deducted for population issues (inclusion of people with non-MRSA infections in some studies), unclear/subjective outcome (clinical cure), and inclusion of co-intervention in one study (aztreonam)
more than 1 RCT (>62 people) [13] [14]	Clinical or microbiological cure	Linezolid *v* vancomycin in nosocomial pneumonia	4	–3	0	–2	0	Very low	Quality points deducted for incomplete reporting, methodological weaknesses (no blinding), and subgroup analysis. Directness points deducted for population issues (inclusion of people with non-MRSA infections in some studies), unclear/subjective outcome (clinical cure), and inclusion of co-intervention in one study (aztreonam)
more than 1 RCT (>80 people) [13] [14]	Clinical or microbiological cure	Linezolid *v* vancomycin in skin and soft-tissue infections	4	–3	0	–2	0	Very low	Quality points deducted for incomplete reporting, methodological weaknesses (no blinding) and subgroup analysis. Directness points deducted for population issues (inclusion of people with non-MRSA infections in some studies), unclear/subjective outcome (clinical cure), and inclusion of co-intervention in one study (aztreonam)
12 (223) [15] [16]	Clinical or microbiological cure	Linezolid *v* vancomycin in bacteraemia	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting and methodological weaknesses (no blinding). Directness points deducted for population issues (inclusion of people with non-MRSA infections in some studies, inclusion of children in some studies), and unclear/subjective outcome (clinical cure)
1 (182) [17]	Clinical or microbiological cure	Linezolid *v* teicoplanin	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and inclusion of people without MRSA. Directness points deducted for low follow-up and use of unclear/subjective outcome (clinical cure)
1 (182) [17]	Mortality	Linezolid *v* teicoplanin	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and inclusion of people without MRSA. Directness point deducted for highly selected population (on intensive care)
1 (51) [25]	Clinical or microbiological cure	Quinupristin–dalfopristin *v* vancomycin	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and subgroup analysis. Directness point deducted for use of unclear/subjective outcome (clinical cure)
1 (298) [25]	Mortality	Quinupristin–dalfopristin *v* vancomycin	4	–1	0	–1	0	Low	Quality point deducted for inclusion of people without MRSA. Directness point deducted for lack of subgroup analysis in people with MRSA only, hence, limited generalisability to this population group

Important outcomes	**Clinical or microbiological cure, length of hospital stay, mortality, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (47) [26]	Clinical or microbiological cure	Trimethoprim–sulfamethoxazole (co-trimoxazole) *v* vancomycin	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and subgroup analysis. Directness points deducted for highly selected population (injecting drug users) and for use of unclear/subjective outcome (clinical cure)
1 (157) [24]	Clinical or microbiological cure	Tigecycline *v* vancomycin	4	–2	0	0	0	Low	Quality points deducted for sparse data and no statistical assessment

Type of evidence: 4 = RCT; Consistency: similarity of results across studies; Directness: generalisability of population or outcomes; Effect size: based on relative risk or odds ratio.