Adjunctive use of rifampin for the treatment of Staphylococcus aureus infections: a systematic review of the literature

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CRD summary
This review evaluated the effectiveness of rifampin as an adjunctive therapy to treat Staphylococcus aureus infections. The evidence suggests that rifampin may be promising in certain clinical scenarios, but this conclusion may not be reliable given the limitations in the review data, particularly with regard to methodological quality.

Authors’ objectives
To evaluate the effectiveness of rifampin as an adjunctive therapy to treat Staphylococcus aureus (S. aureus) infections.

Searching
Two independent reviewers searched PubMed, the Cochrane Library and EMBASE for English language articles published between 1 January 1966 and 31 January 2006; the search terms were reported. In addition, the bibliographies of review articles were checked and experts in the field of adjunctive rifampin therapy were contacted for unpublished articles.

Study selection
Studies comparing quantitative bacterial measurements, cure rates or staphylococcal-related mortality rates of one or more antibiotics alone and in combination with rifampin, and studies of the efficacy of one or more antibiotics alone and in combination with rifampin, were eligible for inclusion. Studies of the efficacy of rifampin alone compared with other antibiotics, rifampin as prophylaxis to prevent infection in uninfected hosts, and the use of rifampin impregnated devices or catheters, were excluded.

Studies of patients with a wide range of conditions were included in the review (cellulitis, wounds, pneumonia, urinary tract infection, endocarditis, bacteraemia, osteomyelitis, septic arthritis, catheter related empyema, orthopaedic hardware infections and other conditions). The authors reported that the included patients varied in terms of co-morbidities, sites of infection and acuity of infection. The included studies investigated a variety of doses and dosing regimens of the antibiotics vancomycin, pefloxacin, ciprofloxacin, oxacillin, fleroxacin and nafcillin, given orally and intravenously. Rifampin doses varied from 300 to 1,200 mg/day and was given orally and intravenously. Where reported, the included studies reported results for the methicillin-susceptible and methicillin-resistant S. aureus strains. A variety of outcomes, including cure, clinical improvement and persistence of bacteraemia, were reported. The included studies were randomised prospective and randomised prospective placebo-controlled trials, randomised prospective cohort analysis and a retrospective study. The follow-up period varied from several days to over 3 years.

Two reviewers independently selected the studies and a third reviewer resolved any disagreements.

Assessment of study quality
Methodological quality was assessed using the Jadad scale, a 5-point scale evaluating randomisation, blinding and allocation concealment.

Two independent two reviewers performed the assessment and a third reviewer resolved any disagreements.

Data extraction
Clinical cure, failure to respond, improvement, bacteriologic failure, duration of bacteraemia, duration of fever, cure negative, explanted hardware, cure without hardware removal, possible cure, probable cure, remission, definite relapse, persistent infection and overall favourable response were extracted. Statistical analysis was performed for studies that had reported results but no analysis. Dichotomous outcomes were analysed using a $\chi^2$ or Fisher exact test, and for studies comparing means the Wilcoxon rank sum test was used (if standard deviations and group sample sizes were
Two independent reviewers extracted the data into a standardised form and checked for accuracy; any discrepancies in the data were resolved through discussion.

Methods of synthesis
Differences between the studies precluded a quantitative analysis. The studies were grouped according to the antibiotic used and summarised in a narrative with accompanying data tables.

Results of the review
Seven studies were included in the review: two randomised, prospective placebo-controlled trials, three randomised prospective trials, one randomised prospective cohort analysis and one retrospective study. The number of participants in each study was not reported, but the authors stated that the study populations were between 15 and 65 patients.

The mean Jadad score of the included studies was two, the median one (range: 0 to 5).

Two trials investigated oxacillin or vancomycin in patients with a variety of infection types. These showed a statistically significant improvement in clinical cure rates in the dual therapy group (p=0.02 and p<0.05). The authors also reported that a trial that treated hardware infections with fluoroquinolones achieved clinical cure more often with dual therapy (p=0.002), and cure rates were statistically significantly improved in patients treated with dual therapy compared with the monotherapy group in an as-treated analysis (p=0.04).

There were no statistically significant differences between dual and monotherapy groups in the studies of nafcillin, vancomycin, pefloxacin and ciprofloxacin (it is unclear which specific outcomes the p-values corresponded to in the tables).

Authors’ conclusions
Although it was difficult to draw conclusions given the limitations in the data, rifampin as an adjunctive therapy may be promising in certain clinical scenarios, for example in the treatment of prosthetic device infections and bone infections.

CRD commentary
The review addressed a clear research question. The inclusion criteria were clear for the interventions and outcomes, but did not address participant characteristics or study design, which may have led to subjective decisions regarding inclusion. The searches included three relevant databases but only papers published in English were sought; this might have introduced language bias. The authors attempted to identify unpublished studies, thereby reducing the risk of publication bias. The study selection and validity assessment were performed independently by two reviewers, thus minimising the risk of errors and bias in the review process. In addition, the data extraction was checked by a second reviewer, which minimises the risk of errors. The quality of the studies was assessed and taken into consideration. The studies were discussed narratively, which was appropriate given the heterogeneity between them. However, important characteristics of the individual studies were poorly reported, such as the numbers of participants in each study and adverse effects, which the authors discussed but did not report. The primary studies were also generally of a poor quality. Since most of the studies were conducted in the early to mid 1980s there may also be issues with applicability, which the authors do not appear to have addressed. The authors’ conclusions may be considered strong given the limitations of this review.

Implications of the review for practice and research
Practice: The authors stated that rifampin therapy may be reasonable in infections where cure rates are not high, assuming patients are at low risk for toxic effects for rifampin or significant drug-drug reactions. The use of rifampin is questionable in cases where this treatment may compromise patient safety.

Research: The authors stated that adequately powered clinical studies are needed to assess outcomes with or without rifampin in the clinical scenarios in which poor outcomes are common. The role of rifampin also needs to be better defined for the treatment of clinical *S. aureus*. 
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