Current treatment of *Staphylococcus aureus* bacteraemia

*Staphylococcus aureus* (S. aureus) bacteraemia is a common infection worldwide, with the elderly and those unwell in hospital being most at risk. In 2016 there were around 18 reports of S. aureus bacteraemia for every 100,000 population in England, Wales and Northern Ireland.

*S. aureus* bacteraemia is a serious condition, associated with mortality rates of around 20%. Yet despite its prevalence and high mortality, there is very little evidence on how best to treat it. Less than 1,600 participants have been enrolled in randomised controlled trials of antibiotic treatment for *S. aureus* bacteraemia over the last 50 years.

Current guidelines recommend that *S. aureus* bacteraemia should be treated with at least 14 days of an intravenous beta-lactam antibiotic, or a glycopeptide if the bacteria are meticillin-resistant. Combination antibiotic therapy is generally not recommended except in severe meticillin-resistant *S. aureus* (MRSA) infections (e.g. endocarditis or prosthetic joint infections). But these guidelines are weakened by the lack of high quality evidence to inform them.

This briefing paper explores the results of the ARREST trial, which looked at adding rifampicin to standard antistaphylococcal antibiotic treatment.

**Does adjunctive rifampicin improve outcomes from *Staphylococcus aureus* bacteraemia?**

**Why test adjunctive rifampicin?**

Adjunctive rifampicin has long been hypothesised to improve outcomes from serious *S. aureus* infections. It has good oral bioavailability and penetrates cells, tissues, and biofilms better than beta-lactams and glycopeptides; therefore, in combination with these agents, it may eradicate serious *S. aureus* infections more effectively.

The use of rifampicin in *S. aureus* bacteraemia treatment varies widely worldwide. Recent case-series from the UK and Germany reported nearly one third of all adults with *S. aureus* bacteraemia received rifampicin, more often in those with deep-seated infections. Supporting evidence of benefit is weak, however, and rifampicin is associated with hepatic toxicity and substantial interactions with other drugs.

A systematic review of relevant studies published before February 2013 found 3 randomised controlled trials and 1 cohort study, reporting a total of 98 patients with *S. aureus* bacteraemia

**Key points**

- Despite *Staphylococcus aureus* (S. aureus) bacteraemia being a common infection associated with high mortality, there is little reliable evidence on how best to treat it
- The ARREST trial randomised 770 adults with *S. aureus* bacteraemia to receive either adjunctive rifampicin or placebo plus standard antistaphylococcal antibiotic therapy
- Adjunctive rifampicin provided no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia
- Rifampicin significantly complicated antibiotic and other drug treatment; patients who received rifampicin were more likely to need to change their antibiotics, or experience drug-interactions
(54 rifampicin-treated; 44 controls). A pooled analysis of data from these reports suggested rifampicin had no significant effect on all-cause mortality, but there was a trend for rifampicin to reduce clinical and/or bacteriologically proven treatment failure.

Did adjunctive rifampicin improve outcomes?

The ARREST trial found 16.8% of participants in the rifampicin arm and 18.3% in the placebo arm experienced bacteriological failure/recurrence or death. This difference is not statistically significant and probably just occurred by chance.

Breaking this composite outcome into its component parts, there was no statistically significant difference in bacteriological failures (1.1% in rifampicin arm vs 1.3% in placebo arm) or deaths (14.9% in rifampicin arm vs 12.9% in placebo arm). There was a small but statistically significant difference in recurrences (0.8% in rifampicin arm vs 4.1% in placebo arm).

Bacterial clearance in blood was similar in the two arms, refuting the hypothesis that adjunctive rifampicin enhances *S. aureus* killing in the blood. Rifampicin also did not lead to a reduction in deaths adjudicated as definitely or probably due to *S. aureus* by the blinded endpoint review committee (50% of deaths).

We conducted a planned analysis to see if any particular groups of patients benefitted from rifampicin. The results of one of these analyses suggest that the effect of rifampicin may have varied by antibiotics used at randomization, with any benefit restricted to those with meticillin-sensitive infection treated with flucloxacillin alone. The clinical significance of this result is uncertain. The effect was lost if flucloxacillin was used with vancomycin or another antibiotic, or if the subgroups were defined by antibiotic class. With 20 subgroups analysed, one statistically significant association may have occurred by chance.

Did rifampicin increase side-effects or complicate treatment?

Around a quarter of participants in both groups experienced serious adverse events by 12 weeks, with no statistically significant difference between the groups. Similar numbers in both groups experienced grade 3/4 adverse events, but there was a trend for people in the rifampicin group to be more likely to have a renal grade 3/4 adverse event (most were acute kidney injury) than those in the placebo group (5% vs 2%). Gastrointestinal and renal/urinary disorders were more common in the rifampicin group.

People in the rifampicin group were more likely to experience an antibiotic-modifying adverse event than those in the placebo group (17% vs 10%). Drug interactions were also more common in the rifampicin group (7% vs 2%).

What does this mean for treating patients with *S. aureus* bacteraemia?

The small but statistically significant reduction in recurrences in the rifampicin group indicates that the drug had some biological activity, although the clinical significance of this is debatable. The numbers-needed-to-treat to prevent bacteriologically and clinically-defined recurrences were 29 and 26 respectively and both short-term and long-term mortality was unaltered.

Clinicians need to weigh up the benefits of rifampicin (a small reduction in risk of recurrence) against the increase in gastrointestinal and renal toxicity, and the complications of drug interactions.
What next for the treatment of *S. aureus* bacteraemia?

While it is disappointing that adding rifampicin provides no overall benefit over standard antibiotic therapy, the results from the ARREST trial will enable clinicians to make treatment choices based on high-quality evidence. It is a substantial addition to the evidence-base for treating *S. aureus* bacteraemia, which, until now, had been very limited.

ARREST is the largest trial ever performed for patients with *S. aureus* bacteraemia, and is large in comparison to the observational studies on this condition. The data and samples collected by the trial will allow the researchers to understand more about the infection. Some of the questions it may help to answer include what the risk factors for recurrence are, and whether certain strains of bacteria, or gene variations in people, may affect the severity of the infection.

The ARREST trial demonstrates that it is possible to conduct a high quality randomised controlled trial in acute life-threatening infections in the UK. This should encourage clinicians and researchers to do more trials to strengthen the evidence base in this under-researched area.

### Conclusions

Adding rifampicin to standard antibiotic therapy provides no overall benefit to patients with *S. aureus* bacteraemia, while substantially complicating other drug treatment.

### Recommendations

- Patients with *S. aureus* bacteraemia should not routinely be given adjunctive rifampicin
- Further research (particularly randomised controlled trials) are needed to improve the treatment of patients with acute life-threatening infections

### Further information


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