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RESEARCH NEWS

Is there still a role for adjunctive rifampicin in *S. aureus* bacteraemia?

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Article

Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Thwaites GE, et al. Lancet. 2018 Feb 17; 391 (10121): 668-78.

Why was this research done?

Staphylococcus aureus bacteraemia is one of the most common and serious infections worldwide and has an associated mortality of approximately 20%. Most treatment recommendations are based on observational studies and clinical experience. Current guidelines recommend treatment for a minimum of 14 days with an intravenous β-lactam antibiotic or in the case of methicillin resistance, with a glycopeptide. Combined antibiotic therapy is only recommended in severe methicillin-resistant *S. aureus* infections. Because of good oral bioavailability and better penetration of cells, tissues and biofilms compared with β-lactams and glycopeptides, adjunctive rifampicin might be more effective in the eradication of *S. aureus* infections. Russell et al. showed in a systematic review that addition of rifampicin is associated with reduced mortality and reduced clinical or bacteriological failure; however this systematic review included four studies with only 98 patients in total.[1]

Research question

Does adjunctive rifampicin reduce bacteriologically confirmed treatment failure, disease recurrence or death by enhancing early killing of *S. aureus* and thereby reduce the risk of dissemination and metastatic infection?

How was this investigated?

A multicentre, randomised, double-blind, placebo-controlled trial was performed in 29 UK hospitals. Adult patients (≥18 years) with suspected *S. aureus* infection were included, in whom methicillin-susceptible *S. aureus* (MSSA) or methicillin-resistant *S. aureus* (MRSA) was grown from at least one blood culture. Participants were included within 96 hours after starting active antibiotic therapy. Patients who had contraindications for rifampicin were excluded, as were those with pre-existing evidence of *S. aureus* rifampicin non-susceptibility. Furthermore, patients were ineligible if *S. aureus* was considered a blood culture contaminant or mixed with another organism likely contributing to the current infection. Further exclusion criteria were suspected active tuberculosis, previous randomisation of the subject in ARREST and if rifampicin was considered mandatory for any reason. Patients were randomly assigned to receive either rifampicin or placebo for two weeks, with standard backbone antibiotic therapy as chosen by the attending physician. Success of blinding was assessed at the final visit at 12 weeks, when physicians were asked which treatment they believed they had prescribed.

Depending on their weight, patients either received 600 mg or 900 mg of rifampicin daily (either a divided dose twice a day or a single dose once a day). These were administered orally or intravenously for 14 days or until cessation of backbone antibiotic therapy. Backbone antibiotics could be changed according to clinical need and rifampicin could be used after 14 days. In cases judged clinically necessary, it was possible to use open-label rifampicin within the 14-day period. Clinical assessments were done on days 0, 3, 7, 10 and 14, and once a week until discharge or at 12 weeks.

The primary outcome was time to bacteriologically confirmed treatment failure or disease recurrence or death (all-cause), from randomisation to 12 weeks. Secondary outcomes were time to all-cause mortality from randomisation to 2 weeks; time to death or clinically defined treatment failure or disease recurrence from randomisation to 12 weeks; duration of bacteraemia; grade 3-4 adverse events, serious adverse events, antibiotic or trial-drug modifying adverse events; the proportion for whom treatment was modified because of drug interactions; and the proportion who developed rifampicin-resistant *S. aureus*.

Main conclusions

A total of 758 patients with *S. aureus* bacteraemia were included in the analysis (placebo, n=388 and rifampicin, n=370). Another 12 patients were included unintentionally, and were excluded before randomisation. Rifampicin did not have a significant effect on any of the efficacy measures, including the combined primary outcome of bacteriologically confirmed treatment failure or disease recurrence, or mortality (17% in the rifampicin group vs. 18% in the placebo group, respectively, p=0.81). There was no difference in duration of bacteraemia, or development of rifampicin-resistant *S. aureus*. Rifampicin was associated with a small, statistically significant reduction in bacteriologically (bacteriological failure or recurrence (4% vs. 1%, placebo vs. rifampicin), p=0.01) and clinically defined disease recurrences (clinical failure or recurrence (6% vs. 2%, placebo vs. rifampicin), p=0.01).

Consequences for daily practice

This was a large randomised, double-blind, placebo-controlled trial that included 770 participants. Both patients with community-acquired *S. aureus* bacteraemia and nosocomial infection were included. Of the patients, 9% were admitted to the ICU. Slow recruitment resulted in a reduction of the sample size; however this number of participants still doubles the number in the biggest previous trial in *S. aureus* bacteraemia. Of the non-randomised participants, 11% were excluded because rifampicin was considered mandatory. Even though additional details are unknown, anecdotal evidence suggests many of these patients had prosthetic-related infections. The exclusion of this group may bias the outcome of this study. The choice of first-line anti-staphylococcal penicillin for the treatment of MSSA infections varies, however there is no evidence to support clinically relevant differential anti-staphylococcal activity between these antibiotics.[2,3] Furthermore, in this study mainly flucloxacillin was prescribed (82%), which is also first-line therapy in the Netherlands. MRSA prevalence in the current study was 6%.

Adjunctive rifampicin did not enhance the killing of *S. aureus* in the blood and thereby reduce the risk of dissemination and death; however, it was associated with a small significant reduction in bacteriologically and clinically defined disease recurrences. These findings might support the hypothesis of rifampicin enhancing the sterilisation of deep infection foci, hereby reducing disease recurrences.[4] The uncertainty of this effect needs to be weighed against the toxicity and possible complications that rifampicin may cause. Of the screened patients, 11% were not enrolled because of predicted drug interactions or pre-existent liver disease. Moreover, there were significantly more antibiotic-modifying adverse events and drug interactions in the rifampicin group. This, together with the absence of improved survival in those receiving adjunctive rifampicin, suggests that rifampicin does not replace the need to define, drain and remove the infection focus when possible. This study provides evidence that adjunctive rifampicin does not improve outcomes from *S. aureus* bacteraemia; therefore adjunctive rifampicin might not provide overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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