In adults with *S. aureus* bacteremia, adding rifampin to standard antibiotic therapy did not improve outcomes

**Question**
In adults with *Staphylococcus aureus* bacteremia, does adding rifampin to standard antibiotic therapy improve outcomes?

**Methods**
**Design:** Randomized placebo-controlled trial (Adjuvant Rifampicin to Reduce Early Mortality from *Staphylococcus aureus* bacteraemia [ARREST] trial). ISRCTN37666216.

**Allocation:** Concealed.*

**Blinding:** Blinded* (patients, investigators, clinicians, and primary outcome adjudicators).

**Follow-up period:** 12 weeks.

**Setting:** 29 hospitals in the UK.

**Patients:** 770 inpatients ≥ 18 years of age (median age 65 y and 65% men in 758 patients analyzed) who had signs or symptoms of *S. aureus* infection, ≥ 1 blood culture with methicillin-resistant or -susceptible *S. aureus* (MRSA or MSSA) growth, ≤ 96 hours of antibiotic treatment for the current infection, and no evidence of *S. aureus* rifampin nonsusceptibility. Exclusion criteria included need for rifampin, *S. aureus* as a blood culture contaminant or mixed with another infection-causing organism, or suspected active tuberculosis.

**Intervention:** Standard antibiotic therapy plus oral or IV rifampin, 600 mg/d or 900 mg/d based on patient weight (n = 374), or standard antibiotic therapy plus placebo (n = 396) for 2 weeks.

**Outcomes:** Primary outcome was a composite of bacteriologically confirmed treatment failure (ongoing infection signs or symptoms for > 14 d and isolation of *S. aureus* from blood or another sterile site), disease recurrence (isolation of *S. aureus* from a sterile site after > 7 d of apparent clinical improvement), or all-cause mortality. Other outcomes included all-cause mortality at 2 weeks and serious adverse events. Based on a revised power calculation due to slow recruitment, the trial had 80% power to detect an absolute 10% reduction in the primary outcome with rifampin from 35% to 25% at 12 weeks (2-sided α = 0.05).

**Patient follow-up:** 90% completed the trial or died (intention-to-treat analysis).

**Main results**
The main results are in the Table.

**Conclusion**
In adults with *S. aureus* bacteremia who had received ≤ 96 hours of antibiotics, adding rifampin to standard antibiotic therapy did not improve a composite clinical outcome at 12 weeks.

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*Rifampin vs placebo, added to standard antibiotic therapy, in adults with *S. aureus* bacteremia†

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Event rates (n)</th>
<th>RRR/RRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>17/102</td>
<td>RRR 3.6 (1.30-10)</td>
</tr>
<tr>
<td>Serious adverse events at 12 wk</td>
<td>27/102</td>
<td>RRI 1.86 (1.75-9)</td>
</tr>
<tr>
<td>All-cause mortality at 2 wk</td>
<td>7/102</td>
<td>RRI 5.58 (1.14-2)</td>
</tr>
</tbody>
</table>

†Abbreviations defined in Glossary. RRR, RRI, and CI calculated from hazard ratios and placebo event rates in article.

*See Glossary.

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For correspondence: Professor Guy E. Thwaites, University of Oxford, Oxford, England, UK. E-mail: g.thwaites@oucu.ox.ac.uk.

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**Commentary**
*S. aureus* bacteremia, increasingly with MRSA in most of the industrial world, is associated with 10% to 30% mortality (1). In the ARREST trial, Thwaites and colleagues found that adding rifampin to standard (backbone) antistaphylococcal antimicrobial therapy for *S. aureus* bacteremia did not improve a composite outcome of treatment failure, disease recurrence, or death. Rifampin was well-tolerated but associated with a low but increased incidence of potentially serious side effects, including acute kidney injury (5% vs 2%, P value not reported) and drug interactions (6% vs 2%, P < 0.001).

Our capacity to draw definitive clinically applicable conclusions from ARREST is limited by combining MSSA and MRSA in the overall analyses; heterogeneity of backbone regimens; a 3-day delay from initiation of backbone therapy to start of study drug (rifampin or placebo); with 13% of the control group receiving post-protocol rifampin; and only 4% of patients with endocarditis and 6% with MRSA infection.

Subgroup analysis in 367 patients with MSSA bacteremia who received backbone therapy solely with fluoroquinolone showed benefit with adjunctive rifampin (hazard ratio [HR] 0.45, 95% CI 0.25 to 0.81), and rifampin showed a nonsignificant benefit in the 40 patients with endocarditis (HR 0.30, CI 0.60 to 1.54). This suggests that adjunctive rifampin may provide benefit in these settings and mandates further study in focused multicenter randomized controlled trials. ARREST was not powered to draw conclusions about potential benefits of adjunctive rifampin in MRSA bacteremia or, especially, prosthesis valve *S. aureus* endocarditis, for which current national guidelines recommend its use, based on limited clinical data (2).

> > 70% of clinical and bacteriologic failures were associated with delayed or inadequate source control, reaffirming the importance of early source control, especially prompt removal of infected vascular catheters (3).

The results of ARREST should impel urgently needed similar, large, multicenter RCTs of overarchings questions for managing *S. aureus* bacteremia.

Dennis G. Maki, MD, MACP
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin, USA

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References

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