Adjunctive rifampicin may improve outcomes in *Staphylococcus aureus* bacteraemia: a systematic review

Clark D. Russell,¹ Aaron Lawson McLean,² Christopher Saunders³ and Ian F. Laurenson¹

¹Clinical Microbiology, Laboratory Medicine, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK
²Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London, London E1 4NS, UK
³Centre for Immunology and Infection, University of York, York YO10 5DD, UK

*Staphylococcus aureus* bacteraemia (SAB) is associated with substantial morbidity and mortality. By surviving within leukocytes, *S. aureus* can evade both immunological defences and antimicrobial drugs, thus facilitating haematogenous dissemination. We performed a systematic review to determine whether antimicrobials with intracellular activity improve outcomes in SAB when used as an adjunct to β-lactam or glycopeptide monotherapy. The Pubmed/MEDLINE, Embase and Cochrane databases were systematically searched for eligible studies that reported on the use of first-line antimicrobials plus a single additional antimicrobial of interest in patients with SAB (any cause). Six relevant studies were identified, all reporting on rifampicin use. Four studies (three randomized controlled trials and one cohort) reported on adults with SAB, including 54 patients treated with adjunctive rifampicin and 44 standard-therapy controls. Estimated across all of these studies, adjunctive rifampicin was associated with trends towards reduced all-cause mortality and reduced clinical or bacteriological failure. The fifth study indicated that adjunctive rifampicin accelerates the resolution of persistent SAB in neonates. Data from the sixth study were considered flawed owing to differences in co-morbidities between groups. Limited data suggest that rifampicin-induced hepatitis is not clinically significant but that drug interactions are. In conclusion, adjunctive rifampicin may improve outcomes in SAB when used as an adjunct to β-lactam or glycopeptide monotherapy.

**INTRODUCTION**

*Staphylococcus aureus* is a formidable human pathogen, and an important cause of both nosocomial and community-acquired bacteraemia. Despite the incidence falling due to enhanced infection prevention measures in hospitals, there are still over 9000 cases of *S. aureus* bacteraemia (SAB) per year in England, Wales and Northern Ireland, and in 2012 12.7% of these were due to meticillin-resistant *S. aureus* (MRSA) (Public Health England, 2013). Infection often involves soft tissue, but bacteria can enter and spread through the bloodstream. This can result in various metastatic, deep-seated infections, such as infective endocarditis (IE), prosthetic joint infection, osteomyelitis (especially vertebral) and septic arthritis.

While anti-staphylococcal β-lactamase-resistant penicillins (e.g. cloxacillin, flucloxacillin, dicloxacillin and oxacillin) are the cornerstone of treatment for meticillin-sensitive *S. aureus* (MSSA), vancomycin has been the mainstay for treating MRSA bacteraemia for decades, this despite vancomycin demonstrating slower killing and poorer efficacy compared with β-lactams’ bactericidal activity against MSSA. Furthermore, vancomycin ‘MIC creep’ remains an ongoing concern, with the potential to increase the treatment failure rate (Sakoulas et al., 2004). Disappointingly, early commencement of appropriate antibiotic therapy has demonstrated little effect on clinical outcomes (Ammerlaan et al., 2009).

Through natural selection pressures, *S. aureus* has acquired a diverse array of virulence factors that afford it the ability not only to evade host immune defences, but also to hijack them for its own advantage. Following phagocytosis by macrophages, *S. aureus* survives and persists intracellularly for days, and appears to prolong the life of the cell by
inducing upregulation of anti-apoptotic genes (including bcl2 and mcl1) (Koziel et al., 2009; Kubica et al., 2008). A saer/S knockout S. aureus strain with reduced survival in human neutrophils has an unimpaired ability to cause local infection in mice, but mortality from sepsis is reduced compared with wild-type S. aureus (Voyich et al., 2009). Interestingly, neutropenic patients are less likely to develop SAB than those with a normal neutrophil count (Thwaites & Gant, 2011). These findings have led to the suggestion that S. aureus survival within leukocytes may facilitate its haematogenous dissemination by transporting the bacteria throughout the body, a hypothesis elegantly expounded by Thwaites & Gant (2011).

To date, knowledge of the intracellular presence of S. aureus has not influenced antibiotic recommendations for SAB, despite awareness of the poor intracellular activity of both fluoroquinolines and vancomycin (Qazi et al., 2004; Sandberg et al., 2009). There have been few well-structured clinical trials to examine the effectiveness of antibiotics with better intracellular activity (such as fluoroquinolones and rifampicin; Table 1). This paper systematically reviews the evidence supporting the use of antimicrobials with improved intracellular activity as an adjunct to β-lactam or glycopeptide monotherapy in the treatment of SAB in humans, with respect to effect on mortality or clinical/bacteriological failure.

METHODS

Information sources and search terms. Using the Pubmed/MEDLINE, Embase and Cochrane databases, a literature search for relevant articles was performed with the following keywords: ‘met(h)icillin-resistant S(taphylococcus) aureus’, ‘met(h)icillin-sensitive S(taphylococcus) aureus’, ‘S(taphylococcus) aureus’, ‘bacteremia’, ‘septicemia’, ‘bloodstream infection’, ‘treatment’, ‘management’ and the names of the antimicrobials being investigated (Table 1). This paper systematically reviews the evidence supporting the use of antimicrobials with improved intracellular activity as an adjunct to β-lactam or glycopeptide monotherapy in the treatment of SAB in humans, irrespective of sample size. Bacteraemia must have been defined as a blood culture that grew S. aureus. In order to generate data specific to the management of bacteraemia due to S. aureus, studies reporting on serious S. aureus infection without bacteraemia were excluded. We required one or more of the following outcomes to be reported by the authors: all-cause mortality; clinical response (resolution of signs and symptoms of infection); and bacteriological response (resolution of bacteraemia defined by negative blood cultures). We selected studies that reported on the use of first-line antimicrobials (β-lactam or glycopeptides) plus additional antimicrobials of interest in patients of any age with SAB of any cause. The antimicrobials had to be used in combination (i.e. synchronously), and salvage therapy involving monotherapy with an agent of interest was not considered acceptable. We did not include in vitro studies or studies reporting on animal models of SAB.

Eligibility criteria. Given the paucity of published data, we chose to perform a quantitative estimate of odds ratios for comparable outcome measures reported in four of the identified studies, using the total number of studied patients across all four of these reports. This included three randomized controlled trials (RCTs) providing dichotomous data and one cohort study.

RESULTS

The search identified a total of 2256 articles. Following review of the title and abstract, 2240 were excluded, and a further 10 were excluded following full-text review to give 6 eligible studies, as shown in Fig. 1 (Levine et al., 1991; Riedel et al., 2008; Tan et al., 1993; Van der Auwera et al., 1983, 1985; Yzerman et al., 1998). All six of the articles that met our inclusion criteria described the use of adjunctive rifampicin in the treatment of SAB.

Clinical and bacteriological efficacy of rifampicin

Van der Auwera et al. (1983) performed an open-label RCT of adjunctive rifampicin in 56 adults with S. aureus infection at a Belgian centre. Patients with any S. aureus infection (e.g. soft tissue infection, bronchopneumonia) were included, but the authors included overview data for the subgroup of patients who were bacteremic (n=19), allowing separate analysis. Patient-level data were not available. Patients in the control group received oxacillin [12 g day⁻¹ intravenously (IV)] or vancomycin [2 g day⁻¹ IV] depending on sensitivity of the strain, and the intervention group received oxacillin or vancomycin plus IV rifampicin (600 mg day⁻¹) for a minimum of 4 days before IV-to-oral switch. The site of primary infection was undetermined in

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Sandberg et al. (2009)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Lemaire et al. (2011)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Thwaites &amp; Gant (2011)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Nielsen et al. (1997)</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Lemaire et al. (2011)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Lemaire et al. (2011)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Sandberg et al. (2009)</td>
</tr>
</tbody>
</table>
eight (42%) of the bacteraemic patients, an infected IV catheter in four (21%) patients, broncho-pulmonary tract infection in three (16%) patients, a post-operative wound in one (5%) patient and ‘other’ in three (16%) patients. No patient had IE. There were no significant differences in site of infection between treatment groups, although the mean age of bacteraemic patients in the intervention group was 48 years versus 58 years for the control group. All patients studied had either cancer or neurosurgical disease, representing significant co-morbidity. The outcomes for bacteraemic patients are shown in Table 2 and, notably, the difference in combined clinical or bacteriological failure between intervention and control groups (0 and 4, respectively) is significant ($P<0.03$) by Fisher’s exact test, favouring combination therapy.

Van der Auwera et al. (1985) subsequently performed a double-blinded RCT at two Belgian centres to evaluate a regimen using oxacillin (12 g day$^{-1}$ IV) or vancomycin (2 g day$^{-1}$ IV) combined with oral rifampicin at a higher dose (1200 mg day$^{-1}$) in 65 adults with $S. aureus$ infection. The control group received a placebo in addition to conventional first-line therapy. Again, all $S. aureus$ infections were included, but data were provided for the bacteraemic subgroup ($n=29$). The site of primary infection was an infected wound in nine (31%), an infected IV catheter in seven (24%), bone in five (17%), pulmonary in four (14%), IE in one (3%), ‘other’ in one (3%) and unknown in two (7%) patients. The authors reported that no significant differences were found for the sex, age or underlying co-morbidities between groups. Fourteen (48%) patients had either underlying cancers or neurological disease. Table 2 shows the outcomes for the patients in this study. The differences in outcomes between groups did not reach significance. The two clinical failures in the intervention group died. These patients both had leukaemia, and one died due to Escherichia coli bacteraemia plus Candida spp. pneumonia, and the other due to culture-negative bronchopneumonia. Their deaths are, therefore, unlikely to be attributable to SAB, so are unlikely to have been prevented by rifampicin.

The RCT conducted by Levine et al. (1991) in the United States enrolled 42 consecutive patients with MRSA endocarditis and bacteraemia, a number of whom were IV drug users. The median response time to therapy was the primary outcome. Patients were randomized to receive either vancomycin (2 g day$^{-1}$ IV) or the same dose of vancomycin plus IV rifampicin (600 mg day$^{-1}$) for 28 days, with dose adjustment to maintain optimum serum vancomycin concentration. A total of 19 patients in the vancomycin group completed the regimen and 16 patients in the adjuvant rifampicin group did likewise. The mean durations of SAB were presented (6.4 days and 7.6 days, respectively); however, the actual duration of bacteraemia was determined for only 17 subjects owing to patient refusal of investigations or self-discharge. The other 25 patients had positive final blood cultures, leaving insufficient data to allow comment on any effect of adjunctive rifampicin on duration of bacteraemia. There was no difference between groups with respect to duration of fever. Neither regime resulted in an effective early microbiological response in these endocarditis patients – 9/11 patients in the vancomycin group remained bacteraemic after 72 h, as did 5/6...
### Table 2. Pooled retrospective analysis of adults with SAB included in four prospective studies of adjunctive rifampicin

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Group (n)</th>
<th>Standard therapy</th>
<th>Daily rifampicin dose</th>
<th>Duration of rifampicin therapy</th>
<th>Outcome measure</th>
<th>All-cause mortality [n (%)]</th>
<th>Clinical or bacteriological failure [n (%)]</th>
<th>Bacteriological failure alone [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Auwera et al. (1983)</td>
<td>RCT</td>
<td>Rifampicin (10)</td>
<td>Oxacillin or</td>
<td>600 mg IV</td>
<td>Unknown</td>
<td></td>
<td>3 (30.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Van der Auwera et al. (1985)</td>
<td>RCT</td>
<td>Standard (9)</td>
<td>Vancomycin IV*</td>
<td>–</td>
<td>–</td>
<td></td>
<td>6 (66.7)</td>
<td>4 (44.4)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Van der Auwera et al. (1985)</td>
<td>RCT</td>
<td>Rifampicin (13)</td>
<td>Oxacillin or</td>
<td>1200 mg PO</td>
<td>18.9 days†</td>
<td></td>
<td>2 (15.4)</td>
<td>2 (15.4)</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (16)</td>
<td></td>
<td></td>
<td>Vancomycin IV*</td>
<td>–</td>
<td>–</td>
<td></td>
<td>2 (12.5)</td>
<td>3 (18.8)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Levine et al. (1991)</td>
<td>RCT</td>
<td>Rifampicin (16)‡</td>
<td>Vancomycin IV§</td>
<td>600 mg IV</td>
<td>28 days</td>
<td></td>
<td>1 (6.3)</td>
<td>2 (12.5)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Standard (19)‡</td>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td></td>
<td>2 (10.5)</td>
<td>4 (21.1)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Yzerman et al. (1998)</td>
<td>Cohort study</td>
<td>Rifampicin (15)</td>
<td>Teicoplanin IV</td>
<td>1200 mg IV</td>
<td>15 days†</td>
<td></td>
<td>1 (6.7)</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Pooled analysis of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 (13.0)</td>
<td>6 (11.1)</td>
<td>1/38 (2.6)</td>
</tr>
<tr>
<td>across all reports</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 (22.7)</td>
<td>11 (25.0)</td>
<td>4/25 (16)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>0.38</td>
<td>0.14</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18–1.46</td>
<td>0.13–1.11</td>
<td>0.01–1.35</td>
</tr>
<tr>
<td>z statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.256</td>
<td>1.765</td>
<td>1.697</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2091</td>
<td>0.0775</td>
<td>0.0898</td>
</tr>
</tbody>
</table>

CI, confidence interval; PO, oral.

* Determined by sensitivity of *S. aureus* strain and allergies of patient.
† Mean duration of rifampicin therapy.
‡ Excluding bacteraemic patients included in the original study who were not fully followed up (either refused further cultures or left hospital against medical advice).
§ All strains were MRSA.
patients in the vancomycin-and-rifampicin group. There was no significant difference between groups in terms of the cure rate, the need to undergo surgery or death. Long-term follow-up of these patients was not possible, but none were readmitted for relapse of endocarditis. A summary of the outcomes is shown in Table 2.

Yzerman et al. (1998) performed a single-centre cohort study in the Netherlands exploring the impact of rifampicin as an adjunct to teicoplanin therapy in the treatment of nosocomial SAB. A total of 15 patients received treatment and were included in their analysis. These patients received teicoplanin (400 mg day\(^{-1}\) IV) for a mean duration of 15 days (range 5–45 days), plus IV rifampicin (600 mg day\(^{-1}\)) from the onset of treatment. A total of 13/15 patients achieved clinical cure (disappearance of clinical signs of bacteremia and return of APACHE II scores to pre-infection levels). Two patients failed to improve on dual therapy, but one of these cases was unrelated to bacteremia as blood cultures became negative after commencement of therapy – this patient died during the follow-up period. In the other patient, the source of SAB was sternal osteomyelitis following coronary artery bypass grafting, and despite initial improvement the bacteremia relapsed after 11 days as sternal cultures remained positive. Importantly, the same \textit{S. aureus} strain was responsible for the relapse and had become rifampicin-resistant. The primary site of infection for most patients studied (seven, 46.7\%) was an intravascular device. Wound infections accounted for three cases (20\%), pneumonia for one (7\%), urinary tract infection for one (7\%) and the primary site was unknown for the remaining three cases (20\%).

Data for all-cause mortality and clinical and bacteriological failure were pooled for these four prospective studies of adults with SAB. Odds ratios for the pooled patient groups (intervention and control) are presented in Table 2. Rifampicin was given at a dose of either 1200 (\(n=28\)) or 600 (\(n=26\)) mg day\(^{-1}\). Not all studies reported duration of therapy, but the range of reported durations was from a mean of 15 days to a fixed duration of 28 days.

Tan et al. (1993) performed a retrospective chart review to identify very low-birth weight infants with persistent SAB (bacteremic for 5 or more days despite therapy), treated with vancomycin (or meticillin) and rifampicin combination therapy. Seven persistent SAB cases were identified. The mean age of the neonates studied was 21.6 days (range 6 to 64). Five isolates were of MRSA, and two were of MSSA. Six children received vancomycin and one meticillin, and all received concurrent treatment with the aminoglycoside amikacin. Only two neonates had a potential focus of infection: one child also grew MRSA from cerebrospinal fluid, and another also grew MSSA from a joint aspirate. The children had been bacteremic for a mean of 9 days (range 5 to 15) before addition of IV rifampicin (10 mg kg\(^{-1}\)) to their treatment regimen. Blood cultures became negative in all neonates following the addition of rifampicin, after a mean duration of 1.7 days (range 1 to 5). Blood cultures became negative within 1 day in five out of the seven neonates. Three neonates died, although significant co-morbidities were present in all patients (bronchopulmonary dysplasia, intraventricular haemorrhage, necrotizing enterocolitis and periventricular leukomalacia). The patients studied were atypical: they were (i) very low-birth weight infants, (ii) who all had significant co-morbidity and (iii) who had been unable to clear their SAB following conventional therapy. However, this study is significant as the data are indicative that addition of rifampicin accelerates the clearance of \textit{S. aureus} from the blood of compromised patients who have had a prolonged duration of bacteremia.

Riedel et al. (2008) performed a single-centre retrospective cohort analysis in the United States to assess the impact of the addition of rifampicin to standard therapy for cases of definite native valve \textit{S. aureus} IE with positive blood cultures. The authors identified 42 cases of \textit{S. aureus} IE treated with rifampicin and 42 controls without rifampicin. Rifampicin was added to the treatment regimen after a median of 3 days (range 0–19 days), and continued for a median of 20 days (range 14–48 days). All-cause mortality in the rifampicin group was 21\%, and 5\% in the control group (follow-up period undefined). Patients who received rifampicin tended to be more severely ill in comparison with controls, as evidenced by longer durations of bacteremia prior to the addition of rifampicin (median duration 3.1 days longer, \(P<0.001\)), a greater need for surgery (seven more patients in the rifampicin group, \(P=0.03\)) and reduced survival (79\% vs 95\%, \(P=0.048\)). Significantly, when outcomes were analysed by APACHE II score, no difference was found in mortality between groups. Due to this limitation of the study, we did not consider the data further.

### Side effects and drug interactions of rifampicin

Riedel et al. (2008) reported on the potential hepatotoxic side effects of rifampicin. They found that patients receiving rifampicin were significantly more likely to have elevated (\(\geq 5\times\) baseline) aspartate aminotransferase and alanine aminotransferase levels than patients not receiving rifampicin (nine vs one, \(P=0.014\)). This finding is confounded by the fact that all patients with elevated transaminases were also infected with hepatitis C virus. Levine et al. (1991) found that only 1 of 16 rifampicin-treated patients developed elevated transaminases (compared with no patients in the control group). In their first trial, Van der Auwera et al. (1983) simply reported that ‘tolerance to treatment was similar and satisfactory in both groups’, with no further details given. In their second trial, Van der Auwera et al. (1985) found equivalent rates of drug side effects in the rifampicin-treated and control groups (40 and 44\%, respectively) for all patients with \textit{S. aureus} infection included in the study. Insufficient data were available to determine whether there was a difference if patients were bacteremic, but this seems unlikely. These side effects included vomiting, diarrhoea, rash, transient
eosinophilia, elevation of serum bilirubin, alkaline phosphatase and glutamic pyruvic transaminase. In their study of very low-birth weight neonates with persistent SAB, Tan et al. (1993) found no adverse effects of rifampicin (specifically abnormal liver function tests, rash or thrombocytopenia). In their cohort of 15 cases of SAB treated with teicoplanin plus rifampicin, Yzerman et al. (1998) reported no ‘serious adverse effects’, but did find that most patients experienced a slight elevation of alkaline phosphatase and γ-glutamyl transpeptidase, though aminotransferases were within normal limits. Although hepatotoxicity is a side effect of rifampicin, it was not found to be a clinical problem in the cohorts of patients described here. Indeed, rifampicin is a commonly used drug in the treatment of *Mycobacterium tuberculosis* infection.

Riedel et al. (2008) found that significant drug interactions occurred unrecognized in 22 of 42 rifampicin-treated patients (52%). These interactions occurred with methadone (n=9), warfarin (n=4), human immunodeficiency virus protease inhibitors (n=3), antifungals [fluconazole (n=3) and voriconazole (n=1)] and phenytoin (n=2). Unfortunately, the authors did not define what they meant by ‘significant drug interactions’. None of the other studies commented on rifampicin drug interactions.

**Development of rifampicin resistance during therapy**

In the cohort of patients with IE and SAB in the study by Riedel et al. (2008), rifampicin resistance developed in nine (21%) patients (all were bacteraemic at initiation of rifampicin) after a median of 16 days of rifampicin therapy (range 11 to 26 days). This figure could be an underestimate because follow-up blood cultures were only drawn as clinically indicated, not systematically. Interestingly, rifampicin-resistant isolates were not recovered from any patients who had negative blood cultures at the time of rifampicin initiation. Unfortunately, this was the only study to systematically evaluate the emergence of rifampicin resistance. In the study by Yzerman et al. (1998), a rifampicin-resistant *S. aureus* strain was responsible for SAB relapse in one patient. None of these studies commented on the risk of selecting rifampicin-resistant *M. tuberculosis*, which may be a concern in some instances, especially in higher-incidence countries and where longer courses might be used.

**DISCUSSION**

We have systematically identified six studies describing the use of rifampicin as an adjunct to standard β-lactam or glycopeptide therapy in patients with SAB of any cause. Overall, there is a trend towards lower all-cause mortality and reduced rates of clinical and bacteriological failure in adults receiving combination therapy, based on a quantitative estimate of odds ratios where sufficient data were provided by the authors for analysis (Table 2). Due to the small cumulative sample (54 cases, 44 controls), statistical significance at the P=0.05 level was not reached. However, odds ratios showed moderate to strong benefits for adjunctive rifampicin reducing clinical or bacteriological failure in cases (odds ratio 0.38, P=0.0775) and reducing bacteriological failure alone (odds ratio 0.14, P=0.0898). We recognize the limitations of this form of quantitative analysis, but believe that owing to the paucity of data it is reasonable to include all relevant studies in the analysis.

Rifampicin has been studied in mouse models of SAB. Following intraperitoneal inoculation of *S. aureus*, mice treated with meticillin alone suffered a mortality rate of 70%, whereas those treated with rifampicin (monotherapy) had a mortality rate of only 27.1% (P<0.0005) (Mandell & Vest, 1972). The authors also demonstrated that, while high concentrations of metcillin and vancomycin had poor activity against intraleukocytic *S. aureus*, low concentrations of rifampicin were able to completely eradicate intraleukocytic bacteria. In a randomized open-label study of patients with nosocomial MRSA pneumonia, the combination of vancomycin (2 g day⁻¹ IV) plus rifampicin (600 mg day⁻¹ oral) increased the rate of clinical cure (P=0.047) and decreased 60-day mortality (P=0.042) in comparison with vancomycin monotherapy (Jung et al., 2010).

The theoretical advantage of rifampicin in the treatment of SAB relates to its better intracellular anti-staphyloccocal activity in comparison with fluclouxillin and vancomycin. Rifampicin, fluclouxillin and vancomycin all reach efficacious concentrations in heart valve tissue and therefore rifampicin offers no theoretical pharmacokinetic advantage in treating the heart valve vegetations found in IE (Kropec & Daschner, 1991). However, adjunctive rifampicin may still benefit patients with *S. aureus* IE through its activity against intraleukocytic bacteria in the bloodstream. Of the 105 patients included in our pooled analysis, 43 (41%) had IE but there were insufficient patient-level data to allow a subgroup analysis to explore this further.

It is striking that the three high-quality RCTs assessing adjunctive rifampicin in SAB were all performed between 22 and 30 years ago. Despite data that provide preliminary support for adjunctive rifampicin, no further RCTs have been reported to date. This is likely to change with the ARREST trial currently being conducted by Thwaites et al. (2012). ARREST is a randomized, double-blind, placebo-controlled trial of adjunctive rifampicin for SAB, and represents a welcome step forward in the pursuit of improved outcomes for patients with SAB.

The development of resistance to rifampicin by *S. aureus* is a well-recognized problem. In a study of clinical isolates, rifampicin resistance was found to occur spontaneously at a level of between 1.75 and 5.11 rifampicin-resistant c.f.u. per 10⁸ *S. aureus* c.f.u. (Moorman & Mandell, 1981). This occurs due to single bp changes in the β-subunit of the rpoB-encoded RNA polymerase, resulting in amino acid changes that impair the ability of rifampicin to bind and exert its bactericidal effect. It appears that multiple rpoB mutations may be present in clinical isolates of rifampicin-resistant *S.
S. aureus, and resistance to high rifampicin levels arises in a single-step fashion (Aubry-Damon et al., 1998; Wichelhaus et al., 1999). Only one of the studies we identified reported systematically on the development of rifampicin resistance, finding a rate of 21% after a median of 16 days’ rifampicin therapy. Of note, these isolates were from patients with SAB due to IE, not a group of patients with SAB of any cause. No individual data were provided to determine whether the development of rifampicin resistance was associated with a poorer outcome. Although it is possible for significant rpoB mutations to arise after one dose of rifampicin (Mwangi et al., 2007), the finding of 21% resistance after a median of 16 days by Riedel et al. (2008) suggests that further work could determine an optimal duration of rifampicin therapy to minimize development of resistance. Given the low rate of bacteriological failure (2.6%) in patients with SAB treated with rifampicin, it seems unlikely that significant rifampicin resistance could have occurred, although this was not specifically reported in the studies from which this figure is generated (Table 2). Rifampicin monotherapy can lead to the development of resistance during treatment of tuberculosis. Based on the above discussion it seems equally inappropriate to consider rifampicin monotherapy in S. aureus infection.

Rifampicin therapy can produce a number of side effects, including rashes, hepatitis, thrombocytopenia and gastrointestinal symptoms. Encouragingly, these side effects did not appear to be a major problem in the groups of patients in the included studies. Only one study reported on drug interactions with rifampicin, finding that these occurred unrecognized in a worrying 52% of patients (Riedel et al., 2008). This emphasizes that caution is required when using rifampicin in complex cases such as those of SAB, where polypharmacy is likely to be an issue.

In summary, we have found preliminary evidence for the use of rifampicin as an adjunctive agent in the treatment of SAB. Given the overall low rate of bacteriological failure, it is possible that when used in combination with other agents the rate of rifampicin resistance is not clinically significant, suggesting that the evolution of antimicrobial resistance is reduced compared with monotherapy. Still, further work is required to understand the dynamics of rifampicin resistance in patients with SAB. Side effects do not appear to be a major problem, though vigilance is required to minimize drug interactions. Only high-quality RCT data from a large cohort of patients can determine whether adjunctive rifampicin is indeed beneficial in SAB; therefore, we eagerly await the results of the ongoing ARREST trial. Disappointingly, no other antimicrobials with in vitro anti-staphylococcal intracellular activity have been investigated in well-structured clinical trials as an adjunct to first-line therapy in managing SAB. Given the potential benefits of adjunctive rifampicin, we hope this paper will stimulate interest in the role of other antimicrobials with intracellular activity that may have the potential to improve outcomes for patients with SAB.

REFERENCES


