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Predictors of recurrence, early treatment failure and death from *Staphylococcus aureus* bacteraemia: Observational analyses within the ARREST trial

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SUMMARY

Objectives: Adjunctive rifampicin did not reduce failure/recurrence/death as a composite endpoint in the ARREST trial of *Staphylococcus aureus* bacteraemia, but did reduce recurrences. We investigated clinically-defined 14-day treatment failure, and recurrence and *S. aureus*-attributed/unattributed mortality by 12-weeks to further define their predictors.

Methods: A post-hoc exploratory analysis using competing risks models was conducted to identify sub-groups which might benefit from rifampicin. A points-based recurrence risk score was developed and used to compare rifampicin's benefits.

Results: Recurrence was strongly associated with liver and renal failure, diabetes and immune-suppressive drugs ($p < 0.005$); in contrast, failure and *S. aureus*-attributed mortality were associated with older age and higher neutrophil counts. Higher SOFA scores predicted mortality; higher Charlson scores and deep-seated initial infection focus predicted failure. Unexpectedly, recurrence risk increased with increasing BMI in placebo ($p = 0.04$) but not rifampicin ($p = 0.60$) participants ($p_{heterogeneity} = 0.06$). A persistent focus was judged the primary reason for recurrence in 23(74%). A 5-factor risk score based on BMI, Immunosuppression, Renal disease, Diabetes, Liver disease (BIRDL) strongly predicted recurrence ($p < 0.001$).

Conclusions: Rifampicin reduces recurrences overall; those with greatest absolute risk reductions were identified using a simple risk score. Source control and adequate duration of antibiotic therapy remain essential to prevent recurrence and improve outcomes.

Introduction

Bloodstream infection, or bacteraemia, caused by *Staphylococcus aureus* (*S. aureus*) is a common, life-threatening infection worldwide.[1] Numerous observational studies have documented its high associated mortality (20–30%) and the frequent and serious complications that arise from dissemination of bacteria by the bloodstream.[2] These complications include deep-seated infections, such as endocarditis and infections of bones, joints, and medical devices, which can recur if not treated effectively.

Despite the frequency and severity of the complications of *S. aureus* bacteraemia, few randomised controlled trials have been conducted to define optimal antimicrobial therapy.[3] We recently reported the results of the largest trial of antimicrobial treatment ever conducted for *S. aureus* bacteraemia.[4] ARREST randomised 758

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adults with *S. aureus* bacteraemia to receive standard antimicrobial therapy with either 2 weeks' adjunctive rifampicin or placebo to determine whether rifampicin reduced the incidence of treatment failure at 14-days, infection recurrence, and death. After 12 weeks' follow-up, rifampicin had no significant effect on the composite primary, or any secondary, efficacy measures, including mortality, duration of bacteraemia, and the development of rifampicin resistance. Twenty planned and exploratory sub-group analyses of the primary composite endpoint failed to identify a population that unequivocally benefitted from rifampicin. However, rifampicin was associated with a small but significant reduction in composite endpoint components of bacteriologically-defined and clinically-defined recurrence (number-needed-to-treat (NNT) to prevent one recurrence 29 and 26 respectively).

Given these relatively large recurrence NNT, and that rifampicin had no effect on short-term or long-term mortality and substantially complicated other treatment through drug-drug interactions, we concluded that adjunctive rifampicin provided no overall benefit over standard antibiotic therapy in unselected adults with *S. aureus* bacteraemia. Yet the influence of rifampicin on disease recurrence remains intriguing. The trial offers a unique opportunity to characterise the predictors of recurrence, 14-day failure and attributable and non-attributable mortality from *S. aureus* bacteraemia and to identify any sub-groups where the benefits of rifampicin on recurrence might be large enough to support recommending its use.

Materials and methods

As previously described,[4,5] adult inpatients (≥18 years) with *S. aureus* bacteraemia in 29 UK centres were eligible to enter the ARREST trial (ISRCTN37666216). Participants were randomised 1:1 to receive 2-weeks' rifampicin versus placebo, plus standard 'backbone' antibiotic therapy chosen by the attending physician. Participants were followed for 12-weeks. ARREST was approved by the London (Westminster) Research Ethics Committee (12/LO/0637). Participants, or their legal representatives (if incapacitated), gave written informed consent.

Endpoints

Failure was defined as symptoms and signs of infection ongoing for >14-days from randomisation, and recurrence as symptoms and signs of infection after >7-days of apparent clinical improvement. Bacteriologically-defined failure and recurrence required *S. aureus* to be isolated from blood or another sterile site (e.g. joint fluid, pus from tissue). A structured clinical narrative for all potential clinical/bacteriological failures/recurrences was completed by the site physician and all potential failures/recurrences and causes of death were adjudicated by a blinded independent Endpoint Review Committee (ERC) (Supplementary Methods).[4]

Statistical analysis

To maximise statistical power we focussed on clinically-defined failure at 14-days and clinically-defined recurrence by 12-weeks, and separately considered *S. aureus*-attributed mortality (ERC-adjudicated definitely/probably *S. aureus*-related) and non-*S. aureus*-attributed mortality by 12-weeks, regardless of previous failure/recurrence. Models for recurrence counted failure and death without failure/recurrence as competing risks.[6] Mortality models considered death from the other cause a competing risk. To estimate continuously varying cause-specific event rates, we used flexible parametric models for the cause-specific hazards (Supplementary Methods).[7]

Multivariate models[6] were based on backwards elimination with exit $p = 0.1$ to identify an exploratory model (but focussing interpretation on factors with $p < 0.05$), including non-linearity by fractional polynomials where $p \leq 0.05$, forcing randomised arm, gender, age at randomisation, predominant focus of infection and Charlson co-morbidity score into models. Even given the trial's size, the number of events was modest: however, given the lack of evidence to date on predictors of recurrence and failure, we considered all factors in Table 1 and Supplementary Table 1, excluding physician-determined factors (imaging and primary antibiotics). All analyses should therefore be considered exploratory.

Initial variable selection was done on complete cases; final models were re-fitted to complete cases for the included factors. Interactions with randomised arm were then considered; all interactions with heterogeneity $p \leq 0.05$ when considered individually were included together in the final model. A points-based risk score, where each predictor of recurrence is assigned a number of points, and the higher an individual's score the higher their recurrence risk, was then developed from model coefficients,[8] and compared to a simplified score considering only factors with strong model support ($p \leq 0.005$) and which substantially improved the area under the receiver operating curve (AUROC). To explore whether relative reductions in recurrence with rifampicin differed by initial predicted risk, a model containing only the risk score, randomised arm and their interaction was fitted (Supplementary Methods). Finally, the additional impact of imaging and primary antibiotic type, both determined by the physician, was evaluated.

Predictors of 14-day failure were identified similarly using logistic regression, excluding participants who died or experienced recurrence by 14-days to match the competing risks analyses of the other outcomes. Predictors of *S. aureus*-attributed mortality and non-*S. aureus* attributed mortality were identified similarly using competing risks methods. Analyses used Stata v15.1.

Results

Between December 2012 and October 2016, 758 eligible participants were randomised to add placebo ($n = 388$) or rifampicin ($n = 370$) to their 'backbone' antibiotic treatment (Table 1, Supplementary Table 1).[4] By 12-weeks, clinically-defined failure/recurrence or death occurred in 162 (21.4%) participants. There were 48 clinically-defined 14-day failures (6.3% participants) and 31 clinically-defined recurrences (4.1%); no participants were reported to have experienced both failure and recurrence. As anticipated, most (90.3%) recurrences occurred after week-2 (Fig. 1). 112

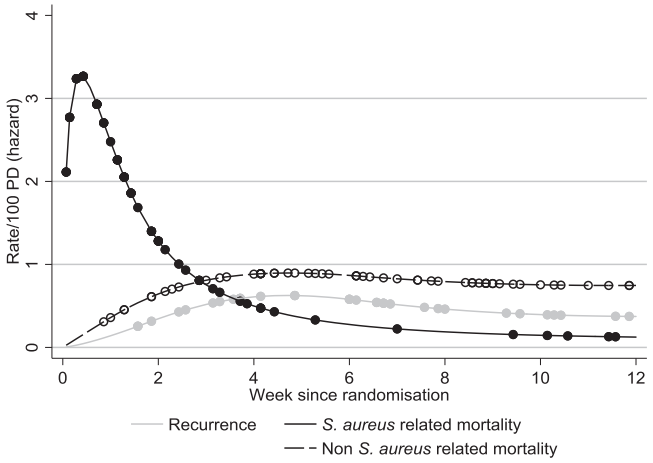

Fig. 1. Event rates over time from randomisation. Note: symbols indicate when events occurred.

Table 1
Characteristics at randomisation of all participants in the trial and all those subsequently suffering recurrence, *S. aureus* attributed mortality, non-*S. aureus* attributed mortality and failure.

Factor	All participants $N=758$* n (col%) or median (IQR)	Recurrence $N=31$ (4.1%) n (row%) or median (IQR)	Uni-variable p	*S. aureus*-attributed mortality $N=56$ (7.4%) n (row%) or median (IQR)	Uni-variable p	Non-*S. aureus* attributed mortality $N=56$ (7.4%) n (row%) or median (IQR)	Uni-variable p	Failure $N=48$ (6.3%) n (row%) or median (IQR)	Uni-variable p
Randomised arm			0.01		0.76		0.70		0.95
Rifampicin	370 (48.8%)	8 (2.2%)		28 (7.6%)		28 (7.6%)		23 (6.2%)	
Placebo	388 (51.2%)	23 (5.9%)		28 (7.2%)		28 (7.2%)		25 (6.4%)	
Male	495 (65.3%)	21 (4.2%)	0.77	38 (7.7%)	0.67	35 (7.1%)	0.62	29 (5.9%)	0.50
Age at last birthday (years)	65 (50, 76)	58 (47, 75)	0.27	79 (73, 84)	<0.0001	76 (67, 85)	<0.0001	74 (64, 80)	0.001
BMI (kg/m^2)	26.3 (22.6, 31.1)	28.1 (24.9, 34.9)	0.05	24.7 (21.5, 27.4)	0.006	24.9 (22.1, 30.1)	0.08	25.6 (21.6, 28.9)	0.20
Charlson comorbidity score*	2 (0, 3)	2 (1, 3)	0.27	2 (1, 4)	0.03	3 (1, 6)	<0.0001	2 (1, 4)	0.07
SOFA score*	2 (1, 4)	2 (1, 4)	0.77	3 (2, 6)	0.0002	4 (2, 5)	0.001	3 (1, 4.5)	0.13
MRSA	47 (6.2%)	1 (2.1%)	0.47	4 (8.5%)	0.80	5 (10.6%)	0.43	4 (8.5%)	0.52
Initial infection focus*,†			0.81		0.12		0.94		0.0002
Deep-seated	301 (39.7%)	14 (4.7%)		24 (8.0%)		20 (6.6%)		38 (12.6%)	
Native heart valve	33 (4.4%)	1 (3.0%)		5 (15.2%)		1 (3.0%)		4 (12.1%)	
Osteoarticular**	133 (17.5%)	7 (5.3%)		10 (7.5%)		9 (6.8%)		17 (12.8%)	
Deep tissue infection/abscess (including brain infection)/epidural/intraspinal empyema/infected intravascular thrombus	88 (11.6%)	3 (3.4%)		6 (6.8%)		7 (8.0%)		9 (10.2%)	
Prosthetic heart valve/joint/implanted vascular device	47 (6.2%)	3 (6.4%)		3 (6.4%)		3 (6.4%)		8 (17.0%)	
Superficial	323 (42.6%)	12 (3.7%)		17 (5.3%)		24 (7.4%)		8 (2.5%)	
Central/peripheral venous line	125 (16.5%)	7 (5.6%)		1 (0.8%)		9 (7.2%)		0 (0.0%)	
Skin/soft tissue/surgical wound/pneumonia	198 (26.1%)	5 (2.5%)		16 (8.1%)		15 (7.6%)		8 (4.0%)	
Not established	133 (17.5%)	5 (3.8%)		15 (11.3%)		12 (9.0%)		2 (1.5%)	
Specific comorbidities									
Cancer*	129 (17.0%)	1 (0.8%)	0.07	10 (7.8%)	0.82	16 (12.4%)	0.02	6 (4.7%)	0.43
Immunosuppressed*,‡	62 (8.2%)	6 (9.7%)	0.02	1 (1.6%)	0.11	5 (8.1%)	0.80	5 (8.1%)	0.57
Chronic lung disease ($N=756$)	90 (11.9%)	5 (5.6%)	0.47	10 (11.1%)	0.14	11 (12.2%) ($N=55$)	0.05	10 (11.1%)	0.05
Renal disease*			0.003		0.003		0.32		0.0004
No	612 (80.8%)	19 (3.1%)		43 (7.0%)		41 (6.7%)		34 (5.6%)	
Moderate or severe	70 (9.2%)	3 (4.3%)		12 (17.1%)		8 (11.4%)		12 (17.1%)	
End stage (requiring dialysis)	75 (9.9%)	9 (12.0%)		1 (1.3%)		7 (9.3%)		2 (2.7%)	
Liver disease ($N=755$)*	56 (7.4%)	8 (14.3%)	0.0002	4 (7.1%)	0.91	2 (3.6%)	0.25	4 (7.1%)	0.77
Diabetes*	228 (30.1%)	15 (6.6%)	0.03	17 (7.5%)	0.99	16 (7.0%)	0.74	17 (7.5%)	0.40
Time from first new symptom caused by *S. aureus* to starting antibiotics (days) ($N=754$)	1 (0, 3)	2 (1, 4)	0.22	1 (0, 2.5)	0.30	1 (0, 2)	0.14	2 (0, 5)	0.54
Time from admission to positive blood culture (days)	0 (0, 1)	0 (0, 0)	0.04	0 (0, 1)	0.76	0 (0, 6)	0.12	0 (0, 1)	0.43

Note: showing n(% of row) for categorical factors, or median (IQR) for continuous factors. p-values from competing risks regression (recurrence, *S. aureus*-attributed mortality, non-*S. aureus* attributed mortality) or logistic regression (failure).

* One participant withdrew shortly after randomisation without an enrolment form having been completed: most baseline characteristics (indicated with *) are therefore missing for this one participant. If any other participants had missing data, then denominators are shown.

† Individuals could have multiple foci, in which case the predominant focus is given, defined by the following order: native heart valve > native joint/vertebral bone/disc > deep tissue infection/abscess/epidural/intraspinal empyema/infected intravascular thrombus > prosthetic heart valve/joint/implanted vascular device > central/peripheral venous line > skin/soft tissue/surgical wound/pneumonia.

** Includes any native joint/vertebral bone/disc/other bone infection.

‡ Systemic corticosteroid therapy, neutropenia, currently receiving immune suppressive therapy (excluding anti-neoplastic chemotherapy), organ or marrow transplant, or living with HIV.

Table 2
Characteristics of recurrences.

		Placebo $N=23$	Rifampicin $N=8$	Total $N=31$
Focus at initial episode*	Central venous line (including picc line)	5 (22%)	2 (25%)	7 (23%)
	Implanted vascular device	4 (17%)	0 (0%)	4 (13%)
	Native heart valve	1 (4%)	0 (0%)	1 (3%)
	Native joint	1 (4%)	1 (13%)	2 (6%)
	Vertebral bone/disc	3 (13%)	3 (38%)	6 (19%)
	Epidural or intraspinal empyema	1 (4%)	0 (0%)	1 (3%)
	Deep tissue infection or abscess	1 (4%)	3 (38%)	4 (13%)
	Surgical wound	2 (9%)	0 (0%)	2 (6%)
	Skin/soft tissue (excluding wounds)	6 (26%)	1 (13%)	7 (23%)
	Pneumonia	1 (4%)	0 (0%)	1 (3%)
	Not established	4 (17%)	1 (13%)	5 (16%)
Focus at recurrence*	Central venous line (including picc line)	3 (13%)	1 (13%)	4 (13%)
	Implanted vascular device	5 (22%)	0 (0%)	5 (16%)
	Native heart valve	1 (4%)	0 (0%)	1 (3%)
	Native joint	0 (0%)	2 (25%)	2 (6%)
	Vertebral bone/disc	5 (22%)	5 (63%)	10 (32%)
	Epidural or intraspinal empyema	1 (4%)	0 (0%)	1 (3%)
	Other bone	2 (9%)	0 (0%)	2 (6%)
	Deep tissue infection or abscess	3 (13%)	3 (38%)	6 (19%)
	Skin/soft tissue (excluding wounds)	4 (17%)	1 (13%)	5 (16%)
	Not established	4 (17%)	0 (0%)	4 (13%)
Median days between symptoms relating to first bacteraemia and starting antibiotics (IQR)		1.0 (2.0, 3.0)	1.0 (3.0, 6.5)	2.0 (1.0, 4.0)
Median days between first positive culture and recurrence (IQR)		46 (29, 58)	48 (33, 67)	46 (29, 58)
Median BMI (IQR) kg/m^2		28.1 (25.1, 40.1)	27.2 (23.1, 29.5)	28.1 (24.9, 34.9)
Source control during initial episode?	Complete	5 (22%)	1 (13%)	6 (19%)
	Partial	2 (9%)	0 (0%)	2 (6%)
	No	13 (57%)	7 (88%)	20 (65%)
	Unknown source	3 (13%)	0 (0%)	3 (10%)
If complete/partial source control, median days from first positive culture to source removal (IQR) ($N=6$†)		3 (1, 3)	2 (2, 2)	3 (1, 3)
On antibiotics at recurrence?		5 (22%)	6 (75%)	11 (35%)
If no, median days between stopping antibiotics and recurrence (IQR)		25.5 (9.0, 35.0)	31.0 (30.0, 32.0)	29.5 (11.0, 34.5)
Backbone antibiotic prescribed during initial episode until date of recurrence**	Cefazolin	1 (4%)	0 (0%)	1 (3%)
	Ceftriaxone	2 (9%)	1 (13%)	3 (10%)
	Clindamycin	0 (0%)	1 (13%)	1 (3%)
	Co-amoxiclavulante	1 (4%)	0 (0%)	1 (3%)
	Daptomycin	2 (9%)	0 (0%)	2 (6%)
	Flucloxacillin	19 (83%)	6 (75%)	25 (81%)
	Levofloxacin	1 (4%)	0 (0%)	1 (3%)
	Meropenem	1 (4%)	0 (0%)	1 (3%)
	Teicoplanin	1 (4%)	1 (12%)	2 (6%)
	Vancomycin	1 (4%)	2 (25%)	3 (10%)
Median total days‡ on backbone antibiotic (IQR)		18.0 (15.0, 29.0)	30.5 (18.5, 45.0)	19.0 (15.0, 31.0)
Focus identified and confirmed during initial episode?	Yes	13 (57%)	6 (75%)	19 (61%)
	Partially	1 (4%)	0 (0%)	1 (3%)
	No	9 (39%)	2 (25%)	11 (35%)
Focus changed between initial episode and recurrence?	Yes	6 (26%)	2 (25%)	8 (26%)
	Partially	2 (9%)	3 (38%)	5 (16%)
	No	8 (35%)	2 (25%)	10 (32%)
	Not established on one or both episodes	7 (30%)	1 (13%)	8 (26%)
Recurrence confirmed bacteriologically?		15 (65%)	3 (38%)	18 (58%)
Level of certainty of recurrence	Definite	18 (78%)	6 (75%)	24 (77%)
	Probable	2 (9%)	2 (25%)	4 (13%)
	Possible	3 (13%)	0 (0%)	3 (10%)
Factors leading to recurrence	Probably failure of antibiotic treatment	2 (9%)	1 (13%)	3 (10%)
	Probably failure of source management (source not recognised)	10 (43%)	2 (25%)	12 (39%)
	Probably failure of source management (source recognised, not actively managed)	4 (17%)	3 (38%)	7 (23%)
	Probably failure of source management (source recognised, actively managed)	3 (13%)	1 (13%)	4 (13%)
	Not possible to distinguish whether antibiotic or source management failure	4 (17%)	1 (13%)	5 (16%)

Note: showing n(%) or median (IQR).

* % of participants with focus. Some participants have multiple foci so totals are >100%.

† The other one participant with complete/partial source control had a focus of infection of skin/soft tissue. Therefore source removal not applicable.

** % of participants prescribed antibiotic. Some participants had different backbone antibiotics at different times and therefore more than one backbone antibiotic overall, so totals are >100%.

‡ Median days on backbone antibiotic, or for participants who had multiple sequential backbone antibiotics, median of the sum of days on all backbone antibiotics.

(14.8%) participants died by 12-weeks. *S. aureus*-attributed mortality was more common than non-*S. aureus* attributed mortality until day-21, with only six non-*S. aureus* attributed-deaths before day-14 (Fig. 1).

Recurrence descriptions and predictors

Of 31 participants experiencing recurrences (8 rifampicin versus 23 placebo; $p=0.01$), 5(63%) rifampicin versus 9(39%) placebo had a deep focus at the initial infection episode ($p=0.41$; 40% deep focus overall), but 7(88%) versus 13(57%) respectively had a deep focus at recurrence (Table 2; Supplementary Table 2). The recurrence infection focus was vertebral bone/disc in 10(32%) recurrences, compared with 69/758 (9%) initial episodes, and differed from the initial episode in 8(26%) recurrences, with similar proportions in the randomised arms. Recurrence was confirmed bacteriologically in 15(65%) placebo versus 3(38%) rifampicin participants ($p=0.23$). The choice of initial backbone antibiotic treatment was similar between the arms, with most (81%) receiving flucloxacillin. However, 6(75%) rifampicin versus 5(22%) placebo remained on antibiotics at recurrence ($p=0.01$). The median time on antibiotics pre-recurrence was 31 versus 18 days respectively ($p=0.11$) and between first positive culture and recurrence 48 versus 46 days respectively ($p=0.64$).

Overall, only 8(26%) participants with recurrence achieved complete/partial source control of the initial infection (1(13%) rifampicin versus 7(30%) placebo; $p=0.64$). Recurrence was adjudicated by the ERC to result from antibiotic treatment failure alone in just 3(10%) participants (one rifampicin, two placebo). The main factor leading to recurrence for 23(74%) of participants was considered a failure of source management, including 12(39%) where the source was not recognised.

Of the 31 participants with recurrences, nine (29%) died post-recurrence (1/8 (13%) rifampicin versus 8/23 (35%) placebo; log-rank $p=0.19$). Six deaths occurred by 12-weeks; of these, five were *S. aureus*-attributed (one rifampicin, four placebo) and one non-*S. aureus* attributed (placebo; pneumonia and renal failure).

Final multivariable models included 733 participants of whom 31(4.2%) experienced recurrence. Recurrence was less common with adjunctive rifampicin (overall rifampicin vs placebo $p=0.001$; Table 3) (as in[4]). Most striking was that recurrence was independently more common in participants with specific comorbidities (namely liver and renal disease, diabetes and those with immunosuppression/receiving immune suppressive drugs, all $p<0.005$). Charlson and SOFA scores were modestly higher in participants with any of these specific co-morbidities (median (IQR) 3 (2–4) and 3 (1–5) respectively, versus 0 (0–2) and 2 (1–3) respectively in those without any of them, $p<0.0001$ and $p=0.0001$ respectively). However, whilst univariably neither Charlson ($p=0.27$) nor SOFA ($p=0.77$) scores were associated with recurrence, after adjusting for other factors, higher Charlson ($p=0.009$) and SOFA ($p=0.02$) scores independently reduced recurrence risk, whether participants had these specific co-morbidities or not ($p_{heterogeneity}>0.6$). This adjusted association with Charlson was driven by inclusion of renal disease and diabetes; and with SOFA by renal disease.

14-day failure predictors

14-day failure was independently more common in older participants ($p=0.006$) and those with higher neutrophil counts ($p=0.02$) or Charlson scores ($p=0.02$) (Table 3). Initial predominant focus was also associated with failure ($p=0.001$), which was lowest in those with central/peripheral lines or unestablished foci, and highest in those with deep foci. Failure was independently more common in those with a longer time between first new symptom caused by *S. aureus* and starting antibiotics ($p=0.05$; Supplementary Fig. 1(b)) or shorter time between positive blood culture and starting antibiotics at baseline ($p=0.01$). There was no effect of rifampicin ($p=0.68$), gender ($p=0.41$) or any other factor ($p>0.1$) and no interactions with randomised arm ($p_{heterogeneity}>0.1$). A model containing C-reactive protein (CRP) instead of neutrophils was similarly predictive (Akaike Information Criterion (AIC) = 309 vs original 306), but neutrophils was more predictive than CRP in a model containing both ($p=0.03$ and $p=0.23$ respectively).

Mortality predictors

Overall, *S. aureus*-attributed mortality was independently higher in participants who were older ($p<0.0001$), with higher neutrophil counts ($p=0.001$) or SOFA score ($p=0.005$) (Table 3). Similarly *S. aureus* unattributed mortality was independently more common in participants who were older ($p<0.0001$), with higher Charlson ($p=0.003$) or SOFA ($p=0.01$) scores. There was no effect of rifampicin, focus of infection, gender or any other factor ($p>0.1$) and no interactions with randomised arm ($p_{heterogeneity}>0.05$) for either *S. aureus*-attributed or unattributed mortality.

Exploratory sub-group analysis of rifampicin effect on recurrence and points-based recurrence risk score

Overall, there was no evidence that the overall significant relative effect of rifampicin upon recurrence differed by focus of infection categorised as deep-seated vs. other/not established ($p_{heterogeneity}=0.16$), or deep-seated vs. other vs. not established ($p_{heterogeneity}=0.37$). However, considering focus separately, after adjusting for other factors, there was some evidence that, in contrast to other participants, rifampicin did not reduce recurrences in those with an initial native joint/vertebral bone/disc focus ($p_{heterogeneity}=0.03$, Table 3) (unadjusted results in Table 4). Interestingly, there was also some evidence that recurrence risk increased with increasing BMI in placebo ($p=0.04$), but did not depend on BMI in rifampicin ($p=0.60$; $p_{heterogeneity}=0.06$) (Table 3, Fig. 2).

To identify patients who might benefit most from rifampicin in terms of absolute recurrence risks, we developed a points-based risk score for recurrence from the competing-risks regression model in Table 3. The full linear predictor had AUROC = 0.84

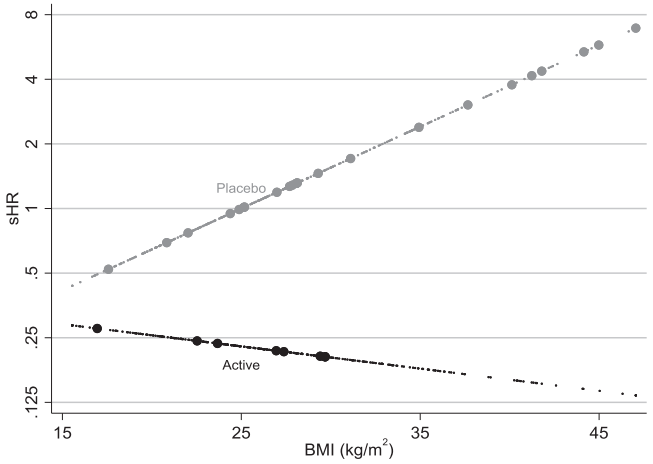

Fig. 2. Effect of BMI on recurrence by randomised arm. Note: sHR=subhazard ratio. Filled circles show BMI values where recurrences occurred; points show other BMI values where recurrence did not occur.

Table 3
Independent baseline predictors of recurrence, *S. aureus*-attributed mortality, non-*S. aureus* attributed mortality and failure.

	Recurrence ($N=733$)		*S. aureus*-attributed mortality ($N=731$)		Non-*S. aureus* attributed mortality ($N=757$)		Failure ($N=707$)	
	sHR [95% CI]	*P*	sHR [95% CI]	*P*	sHR [95% CI]	*p*	OR [95% CI]	*P*
Rifampicin vs placebo where no interaction effects	–	–	1.21 [0.66–2.19]	0.54	1.26 [0.73–2.19]	0.41	1.14 [0.61–2.15]	0.68
Rifampicin vs placebo if BMI 25 kg/m^2 and focus of infection not native joint/vertebral bone/disc/other bone	0.23 [0.07–0.71]	0.01	–	–	–	–	–	–
BMI: overall per kg/m^2 higher	–	–	0.95 [0.89–1.01]	0.08	–	–	–	–
Per kg/m^2 higher in rifampicin	0.98 [0.89–1.07]	0.60	–	–	–	–	–	–
Per kg/m^2 higher in placebo	1.09 [1.00–1.19]	0.04	–	–	–	–	–	–
Heterogeneity		0.06		–		–		–
Overall rifampicin vs placebo (incorporating interaction effects)		0.001		–		–		–
Gender, female vs male	0.87 [0.37–2.03]	0.74	0.68 [0.36–1.31]	0.25	1.23 [0.70–2.16]	0.46	1.33 [0.68–2.60]	0.41
Age (per 10 years older)	1.18 [0.88–1.57]	0.27	1.72 [1.33–2.23]	<0.0001	1.55 [1.28–1.89]	<0.0001	1.35 [1.09–1.68]	0.006
Charlson score (per unit higher)	0.56 [0.36–0.87]	0.009	1.12 [0.99–1.28]	0.08	1.19 [1.06–1.34]	0.003	1.17 [1.02–1.35]	0.02
SOFA score (per unit higher)	0.76 [0.61–0.96]	0.02	1.17 [1.05–1.31]	0.005	1.13 [1.03–1.24]	0.01	–	–
Neutrophil count (per 10^9/L higher)	–	–	1.08 [1.03–1.13]	0.001	–	–	1.07 [1.01–1.12]	0.02
Predominant focus of infection, vs. skin/soft tissue/surgical wound/pneumonia		–		0.25		0.90		0.001
Native heart valve	1.85 [0.16–20.9]	0.62	2.15 [0.59–7.80]	0.24	0.48 [0.06–3.63]	0.48	3.76 [1.00–14.1]	0.05
Native joint/vertebral bone/disc/other bone	0.64 [0.15–2.76]*	0.55	1.14 [0.46–2.85]	0.77	1.12 [0.49–2.56]	0.79	3.25 [1.30–8.14]	0.01
Deep tissue infection/abscess (including brain infection)/ epidural/intraspinal empyema/infected intravascular thrombus	0.83 [0.18–3.97]	0.82	1.29 [0.47–3.54]	0.62	1.42 [0.59–3.44]	0.44	2.69 [0.95–7.62]	0.06
Prosthetic heart valve/joint/ Implanted vascular device	1.15 [0.22–5.95]	0.87	0.57 [0.16–2.01]	0.38	0.62 [0.17–2.21]	0.46	3.72 [1.23–11.2]	0.02
Central/peripheral venous line	1.75 [0.48–6.47]	0.40	0.15 [0.02–1.18]	0.07	0.97 [0.40–2.32]	0.94	0.19 [0.04–0.93]***	0.04
Not established	1.38 [0.34–5.56]	0.65	1.49 [0.67–3.31]	0.32	1.19 [0.54–2.61]	0.67	0.19 [0.04–0.93]***	0.04
Renal disease, vs. no		<0.0001	–	–	–	–		–
Moderate or severe	6.52 [0.70–60.9]	0.1002	–	–	–	–	–	–
End stage (requiring dialysis)	25.2 [5.89–107.4]	<0.0001	–	–	–	–	–	–
Liver disease, yes vs no	14.2 [4.08–49.7]	<0.0001	–	–	–	–	–	–
Chronic lung disease, yes vs no	2.43 [0.65–9.05]	0.19**	–	–	–	–	–	–
Diabetes, yes vs no	5.06 [1.77–14.5]	0.002	–	–	–	–	–	–
Immunosuppressed, yes vs no	4.78 [1.97–11.6]	0.001	–	–	–	–	–	–
Time from first new symptom caused by *S. aureus* to starting antibiotics (per day longer)	Suppl. Fig. 1(a)	0.007	–	–	–	–	Suppl. Fig. 1(b)	0.05
Time from admission to positive blood culture (per day longer)	0.86 [0.75–0.98]	0.02	–	–	–	–	–	–
Time from positive blood culture to starting antibiotics (per day longer)	–	–	–	–	–	–	0.55 [0.35–0.89]	0.01

Note: sHR=subhazard ratio. OR=odds ratio. Adjusted for other factors in column.
* Effect in placebo. Effect in rifampicin: sHR=4.76 [1.12, 20.34] $p=0.04$. Heterogeneity $p=0.03$.
** $p=0.094$ before interactions added; $p=0.19$ in final model including interactions.
*** Central/peripheral venous line and not established combined as no participants with a focus of central/peripheral venous line experienced failure therefore combined with category with next lowest risk (Table 1).

[95% CI 0.77–0.92] for predicting recurrence in the placebo arm. A score based on all factors in this model (Supplementary Table 3) ranged from 1–80, had AUROC = 0.81 [0.72–0.91], good calibration (Hosmer–Lemeshow $p=0.70$), and strongly predicted recurrence (unadjusted sHR = 1.20 per point higher [1.14–1.27] $p < 0.001$). There was no evidence that rifampicin's relative benefits differed by initial risk score ($p_{heterogeneity}=0.30$), but absolute benefits varied substantially (Supplementary Table 4, Supplementary Fig. 2).

A simplified risk score based on five key factors (**B**MI, **I**mmunosuppression, **R**enal disease, **D**iabetes, **L**iver disease (**BIRDL**), Table 5) ranged from 0–8, with AUROC=0.74 [95% CI 0.63–0.85], good calibration (Hosmer–Lemeshow $p=0.95$), and also strongly predicted recurrence (unadjusted sHR = 1.84 per point higher [1.49–2.26] $p < 0.001$) with no evidence of heterogeneity in rifampicin's relative benefits ($p_{heterogeneity} = 0.76$). However, because the absolute recurrence risk varied strongly by the BIRDL risk score (Fig. 3, Supplementary Table 5), number-needed-to-treat (NNT) with rifampicin to prevent one recurrence was under 12 for the 109/737 (14.8%) participants with BIRDL scores ≥3. In those with BIRDL ≥3, rifampicin was not associated with increased SAEs ($p=0.57$) or grade 3/4 AEs ($p=0.42$).

Discussion

S. aureus bacteraemia is a serious and difficult to treat infection, primarily because the bacteria can disseminate to form deep infection foci that are easily missed and often require surgical drainage and prolonged antimicrobial therapy to cure. Early treatment failure, recurrence, and death are common and reported respectively in around 10%, 5%, and 20% of those affected.[2,9–12] Previous stud-

Table 4
Recurrences, *S. aureus*-attributed deaths, non-*S. aureus* attributed deaths and failures by randomised arm and predominant focus of infection.

Predominant infection focus	Recurrence		*S. aureus*-attributed death		Non-*S. aureus* attributed death		Failure	
	Placebo $N=388$	Rifampicin $N=370$	Placebo $N=388$	Rifampicin $N=370$	Placebo $N=388$	Rifampicin $N=370$	Placebo $N=388$	Rifampicin $N=370$
Native heart valve	1/16 (6%)	0/17 (0%)	4/16 (25%)	1/17 (6%)	1/16 (7%)	0/17 (0%)	4/16 (25%)	0/17 (0%)
Native joint/vertebral bone/disc/other bone	3/71 (4%)	4/62 (6%)	5/71 (7%)	5/62 (8%)	5/71 (7%)	4/62 (6%)	7/71 (10%)	10/62 (16%)
Deep tissue infection/abscess (including brain infection)/epidural/intraspinal empyema/infected intravascular thrombus	2/46 (4%)	1/42 (2%)	3/46 (7%)	3/42 (7%)	4/46 (9%)	3/42 (7%)	6/46 (13%)	3/42 (7%)
Prosthetic heart valve/joint/implanted vascular device	3/26 (12%)	0/21 (0%)	0/26 (0%)	3/21 (14%)	3/26 (12%)	0/21 (0%)	4/26 (15%)	4/21 (19%)
Central/peripheral venous line	5/65 (8%)	2/60 (3%)	0/65 (0%)	1/60 (2%)	4/65 (6%)	5/60 (8%)	0/65 (0%)	0/60 (0%)
Skin/soft tissue/surgical wound/pneumonia	5/98 (5%)	0/100 (0%)	8/98 (8%)	8/100 (8%)	8/98 (8%)	7/100 (7%)	3/98 (3%)	5/100 (5%)
Not established	4/66 (6%)	1/68 (1%)	8/66 (12%)	7/68 (10%)	3/66 (5%)	9/68 (13%)	1/66 (2%)	1/68 (2%)

Note: showing n events/n with focus (%), unadjusted, i.e. not accounting for associations in Table 3. Individuals could have multiple foci, in which case they are included under the predominant category (native heart valve > native joint/vertebral bone/disc > deep tissue infection/abscess/epidural/intraspinal empyema/infected intravascular thrombus > prosthetic heart valve/joint/implanted vascular device > central/peripheral venous line > skin/soft tissue/surgical wound/pneumonia).

Table 5
Simplified recurrence risk score (BIRDL).

Factor	Score value given if present	Minimum possible value for score	Maximum possible value for score
BMI (kg/m^2)		0	2
≤30	0		
>30–40	1		
>40	2		
Immunosuppressed*	1	0	1
Renal disease†		0	2
No	0		
Moderate or severe	1		
End stage (requiring dialysis)	2		
Diabetes†	1	0	1
Liver disease†	2	0	2
Total		0	8

For example, a patient with BMI 22, end stage renal disease and diabetes would have recurrence risk score = 0 + 0 + 2 + 1 + 0 = 3.

* Systemic corticosteroid therapy, neutropenia, currently receiving immune suppressive therapy (excluding anti-neoplastic chemotherapy), organ or marrow transplant, or living with HIV.

† Renal disease and mild (including chronic hepatitis), moderate or severe liver disease defined as for the Charlson comorbidity index. Diabetes includes that with (as per Charlson) or without end-organ damage. End stage renal disease defined as requiring either peritoneal dialysis or haemodialysis.

ies have concluded that these outcomes are more common in the elderly with comorbidities, if initial antimicrobial therapy is inadequate, if bacteraemia is prolonged, and if the focus of infection is either not established or is deep-seated and not drained or removed.[2,9–12] However, there are limited high-quality data that can be used to investigate the individual predictors of these outcomes and almost none from large, randomised trials of antimicrobial interventions hypothesised to reduce them.

The ARREST trial provides a unique opportunity to better understand the determinants of poor outcome from *S. aureus* bacteraemia.[4] Further characterisation of the 31 recurrences revealed that 32% were associated with vertebral bone/disc infection when recurrence occurred. Numbers were small, but preceding the recurrence, placebo participants were somewhat less likely to have an initial deep infection focus, were less likely to be on antibiotics at the time of recurrence, and had recurrences that were more likely to be bacteriologically-confirmed than rifampicin participants. These findings suggest rifampicin may enhance bacterial killing and sterilisation of less complicated infections,[13] rather than those with deep foci, and that short antibiotic courses may increase recurrence risk. However, the blinded ERC adjudicated that failure to identify and control the initial focus, rather than inadequate antibiotic treatment, was the main factor behind 75% of recurrences, regardless of whether or not rifampicin was given.

Comparing the baseline predictors of recurrence, failure and death suggests there may be biological and clinical differences between these outcomes. Unlike 14-day failure and *S. aureus*-attributed/unattributed mortality, recurrence was not associated with age, total Charlson score or initial disease severity (assessed by SOFA score or blood neutrophils), but was strongly associated with specific comorbidities associated with immune dysfunction (liver and renal failure, diabetes and immunosuppression/receiving immune suppressive drugs). Other case-series have reported a similar increased risk of recurrence following *S. aureus* bacteraemia in those with impaired immunity.[11,14,15] 14-day failure was associated with initial infection focus, being less likely in those whose focus was not established or was an infected intravenous catheter, and more likely in those with endocarditis, or osteoarticular or medical device infections.

Initial infection focus had relatively little influence on rifampicin's effect on recurrence. In particular, a deep infection focus did not predict recurrence and there was no evidence rifampicin benefitted the treatment of these infections, especially if the focus was not controlled by drainage or removal. Intriguingly, high

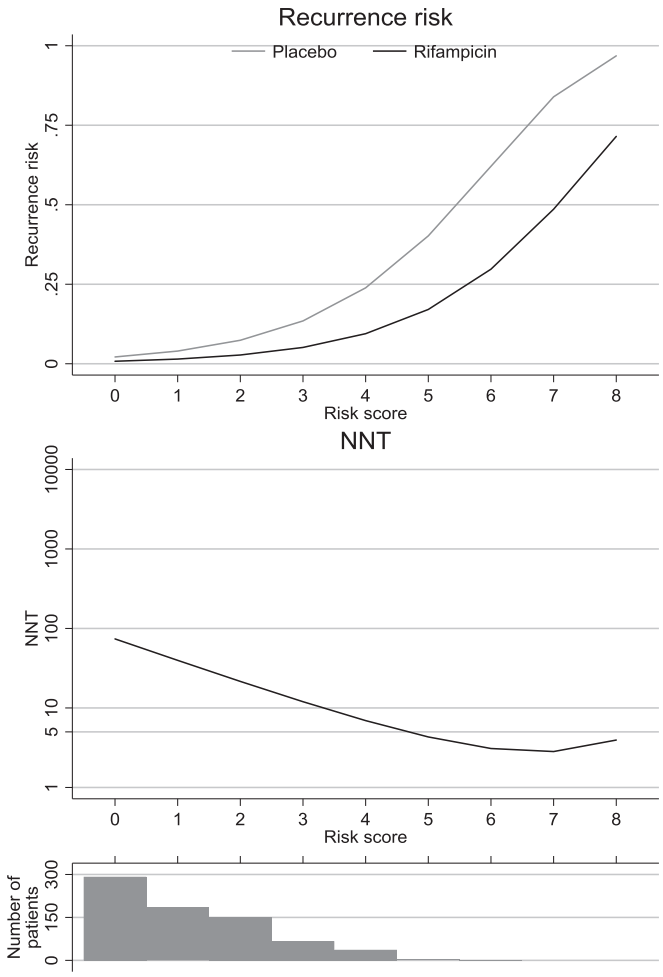

Fig. 3. Distribution of BIRDL score and associated recurrence risk and NNT.

BMI appeared to predict recurrence in the placebo but not the rifampicin arm (Fig. 2), which might be explained by differences in the ability to identify and drain/remove infection foci, or possible under-dosing, in those with high BMI. Additional pharmacokinetic studies are planned to address the latter hypothesis.

Given the importance of recurrence as an outcome from *S. aureus* bacteraemia we created a simple points-based risk score (**BIRDL**: **B**MI, **I**mmunosuppression, **R**enal disease, **D**iabetes, **L**iver disease) which was highly predictive of recurrence. The score requires validation in different populations, but could form the basis for better identifying high-risk patients. Whilst we were unable to identify a sub-group with greater or lesser relative benefits from rifampicin, absolute recurrence risk varied markedly according to this risk score, leading to NNT with rifampicin <12 for those with BIRDL≥3, 15% of trial participants, compared with 26 in the whole population. If validated, this score could therefore be used to target rifampicin to a sub-group most likely to benefit, and also pinpoint those in whom every effort should be made to identify and remove the infection focus. The score could also, for example, allow the targeted, cost-effective use of positron emission tomography (PET) to identify occult deep infection foci.[16]

Our study has several limitations. First, the trial excluded 232 patients in whom rifampicin was considered mandatory many of whom had infected deep prosthetic devices (e.g. arterial grafts, heart valves, joint replacements). Patients with infected devices were not formally excluded, but the relatively small numbers of such patients enrolled mean our findings cannot be generalised to those with bacteraemia associated with infected devices.[17] Second, the relatively low mortality (15%) compared to observational cohorts suggest those with the most severe disease may not have entered the trial, which may reduce the generalisability of the findings. Third, the small numbers of outcomes mean the multivariable models should be considered exploratory given the numbers of predictors examined and further validation is essential to inform clinical practice.

In summary, the predictors of recurrence may be different from those predicting early treatment failure and death following *S. aureus* bacteraemia. This suggests these outcomes may arise from different biological mechanisms and that combining them in a composite endpoint in future trials is unlikely to be informative.[18] Rifampicin reduces recurrences overall; but its impact in unselected patients appears small compared with unmodifiable patient factors and interventions such as source control. Whilst those at highest risk of recurrence had similar relative benefits from rifampicin, this translated into much greater absolute benefits and hence lower NNT (<12). The BIRDL score might thus be able to identify those at highest risk of recurrence and who might benefit most from rifampicin, but should be tested and validated prospectively in different populations. Source control and adequate antibiotic treatment durations remain essential to prevent recurrence and improve outcomes from *S. aureus* bacteraemia.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.08.001.

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