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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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Supplementary Methods

(a) Blinded Endpoint Review Committee

The blinded independent Endpoint Review Committee (ERC) consisted of two infectious disease physicians with experience in acute/general medicine (Professor Tim Peto, Oxford; Professor Graham Cooke, Imperial). Potential failures/recurrences were identified through questions regarding signs and symptoms of ongoing or new *S. aureus* infection on routine case record forms, and by electronic searching of new or ongoing foci of infection being reported, and of *S. aureus* isolated from any microbiological specimen. For all such potential failures/recurrences, a structured clinical narrative was completed by the site physician and approved by the site Principal Investigator. All reported failures, recurrences and deaths were then adjudicated using standardised proformas by the blinded ERC without knowledge of randomized allocation.

(b) Statistical methods

Time-to-event analyses measured time from randomization. Analyses of clinical outcomes censored at the earliest of 12 weeks from randomization and the last clinical information. Analyses of mortality censored at the earliest of 12 weeks or last vital status information (including that ascertained at trial closure through the National Health Service records). Analyses of mortality post-recurrence censored at the last vital status information.

To estimate continuously varying cause-specific event rates (hazards) we used flexible parametric models based on the standard Weibull model.[1, 2] The underlying Weibull model has monotonic (i.e. always increasing or always decreasing) hazard, but the flexible parametric models introduce additional terms in the hazard linearisation (via natural cubic splines) which allow event rates to increase and then decrease or vice versa. The Akaike Information Criterion (AIC) was used to identify the number of interior knots for the natural cubic splines (between 0 and 4).[2] For recurrence, *S. aureus*-related mortality and non-*S. aureus*-related mortality, the best fitting model according to AIC was with 1 interior knot at the 50th percentile of the uncensored survival times, plus 2 boundary knots at their minimum and maximum.

Predictors of recurrence

Predictors of recurrence were identified using competing risks methods.[3] A multivariate model was based on backwards elimination with exit $p=0.1$ to identify an exploratory model including non-linearity by fractional polynomials where $p \leq 0.05$, forcing randomized arm, gender, age at randomization, predominant focus of infection and Charlson co-morbidity score into the model. 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, see below), we considered all factors in **Table 1** and **Supplementary Table 1**, excluding physician-determined factors (imaging and primary antibiotics), and excluding any factors where no participants suffered recurrence in one or more categories (e.g. in intensive care at randomization). The sepsis-related organ failure assessment (SOFA) score is the sum of a number of components: as recommended, component scores were set to missing where unknown (1-7% across components). Continuous factors with evidence of outliers were truncated at the 1st and 99th (or 2.5th and 97.5th) percentiles based on the distribution.

690 (91.0%) of the 758 included participants had complete data for all factors. A small number of participants had missing data for binary (e.g. yes/no) factors (numbers given in

Table 1 and **Supplementary Table 1**); these participants were assumed to belong to the modal (i.e. most common) category, except for predominant focus of infection where participants with missing data were assumed to belong to category, "not established"; and portal of entry, where participants with missing data were assumed to belong to category, "not known (absence of any of the above)". With these assumptions, 727 (95.9%) participants had complete data and were used for initial variable selection. A final model was then refitted to all observations with complete data for the selected factors, and the remaining factors were re-checked and included if $p \leq 0.1$.

Interactions with randomized arm were included where $p \leq 0.05$ combining categories with small numbers of recurrences (≤ 3) for model stability; all interactions meeting this threshold when included individually were included together in the final model (as power for interactions may be low, these could have $p > 0.05$ in the final model). As focus of infection had a large number of categories, and was a priori a key variable of interest given the potential for rifampicin to benefit participants with deep-seated infections, interactions with randomized arm were explored by categorising foci as deep-seated or other (including not established as other; main effects for all foci, interaction for deep-seated vs. other only), and deep-seated, other or not established (three categories). A deep-seated focus was pre-defined in the main trial analysis as an infection of an implanted vascular device, native/prosthetic heart value or a native/prosthetic bone/joint, or a deep tissue infection/abscess (including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection). Interactions with randomized arm were also explored for each focus with ≥ 1 recurrence in each randomized arm (i.e. main effects for all foci, interaction for relevant focus only) pooled as follows: native heart valve and native joint / vertebral bone/disc; prosthetic heart valve/joint / implanted vascular device and deep tissue infection/abscess / epidural/intraspinal empyema / infected intravascular thrombus; and skin/soft tissue / surgical wound / pneumonia and central/peripheral venous line.

The recurrence models above deliberately included only factors that were not subject to physician choice, in particular use of imaging and primary antibiotic type, since these could be on the causal pathway between baseline characteristics and outcomes, and hence be mediators of any effect of rifampicin. We therefore considered whether there was any effect of performing imaging or primary antibiotic type only in addition to the factors in the final model above. Imaging performed was defined as transthoracic/transoesophageal echocardiogram at/before day 3 (to allow short delays due to scheduling), or ultrasound/MRI/PET/PET CT recorded on the baseline/day 3 case record form (as specific dates of ultrasound/MRI/PET/PET CT scans were not collected). Primary (active) antibiotic type was defined by antibiotics received between days -1 and 4 from randomization (to match the visit windows for imaging) and was classified as flucloxacillin only, flucloxacillin in combination with other antibiotic(s), any other betalactam, non-betalactam, or MRSA.

Points-based risk score

A points-based risk score, where each predictor of recurrence is assigned a number of points, and the higher an individual participant's score the higher their recurrence risk, was developed, first based on the coefficients for each factor in the model. Since this final model included both main effects of rifampicin and interactions with rifampicin, the score (reflecting underlying risk regardless of randomized arm) was based on coefficients for the placebo arm where factors were included with an interaction with randomized arm. Factors were included in the risk score if $p \leq 0.1$ or the absolute value of the coefficient for a categorical factor was ≥ 0.2 or if the absolute value of the coefficient multiplied by the

factor's inter-quartile range for a continuous factor was ≥0.2. Continuous factors were categorised using clinically appropriate cut-offs and the mid-point of each category calculated[4] (for categories with no minimum or maximum value, a clinically appropriate value was chosen). The number of points associated with each category was then based on the difference between the midpoint of that category and the reference category. Charlson and SOFA scores were treated as continuous (i.e. risk score increases/decreases for each Charlson or SOFA point, but with a maximum increase/decrease based on the maximum Charlson and SOFA scores in the data). Coefficients were then divided by the coefficient nearest zero and rounded to the nearest integer giving an initial score value, reflecting a participant's risk of recurrence had they been assigned placebo. The initial score values were then further modified by iteratively dropping factors that added the least predictive ability to the model (age, chronic lung disease), assessed by using the integrated discrimination improvement[5]. This initial score reflects the best performance possible from translating a full continuous linear predictor into a points-based score. However, it is not practical for bedside use (**Supplementary Table 3**). We therefore compared its performance to a simplified score which initially included points only for factors with $p \leq 0.005$ in the final multivariable model (immunosuppression, diabetes and liver or renal disease; area under receiver operating characteristic curve (AUROC)=0.71), then considered the integrated discrimination improvement from adding other factors one at a time. Only BMI significantly improved discrimination and therefore this was added to create a five factor simplified score (AUROC=0.74).

Discriminative ability was measured using the non-parametric area under the receiver operating characteristic curve (AUROC), and calibration using the Hosmer-Lemeshow goodness-of-fit χ^2 test evaluated on arms defined by quintiles; all performance measures were calculated for a binary outcome ignoring competing risks.[6]

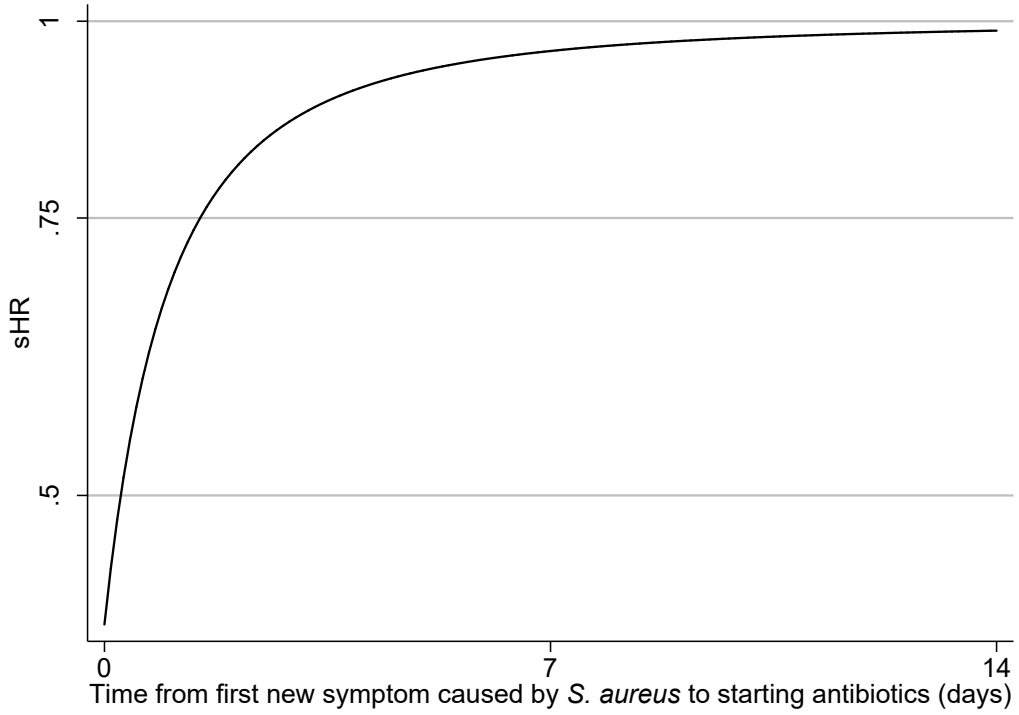
Number needed to treat was calculated based on observed data, and also predicted from a competing risks model. To do this, a model containing only the recurrence score and randomized arm was fitted. Corresponding cumulative incidences of recurrence at 12 weeks was then obtained, separately by arm, by setting the recurrence score to each value of interest and arm to either rifampicin or placebo. The differences in incidence and numbers needed to treat were then calculated.

To explore whether the reduction in recurrence risk with rifampicin differed by initial risk, a model containing the recurrence score, randomized arm and their interaction was fitted.

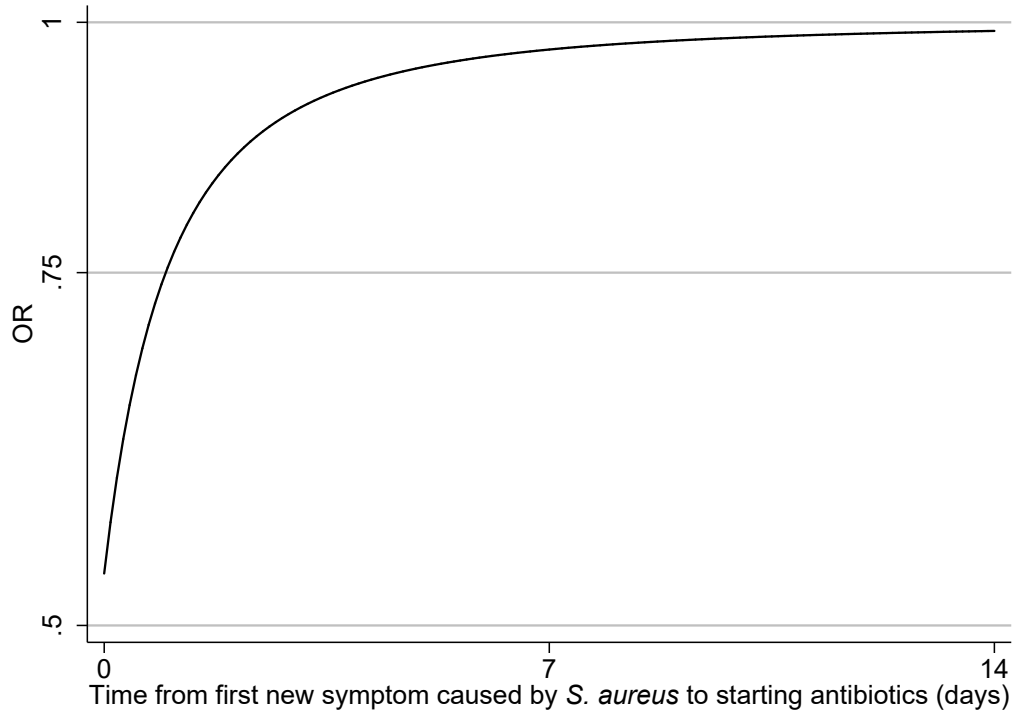
Predictors of S. aureus-related mortality, non-S. aureus related mortality and failure
Predictors of *S. aureus*-related mortality and non-*S. aureus* related mortality were identified similarly to predictors of recurrence, counting the other cause of death as a competing risk (for *S. aureus*-related mortality, interaction with randomized arm was not explored for immunosuppression as only one death was observed in those with immunosuppression). Predictors of failure at 14 days were identified using logistic regression, excluding participants who died or experienced recurrence by this time to match the competing risks analyses of the other outcomes (as, by definition, these participants could not have experienced failure).

Supplementary Figure 1 Effect of time from first new symptom caused by *S. aureus* to starting antibiotics at baseline on risk of (a) recurrence and (b) failure

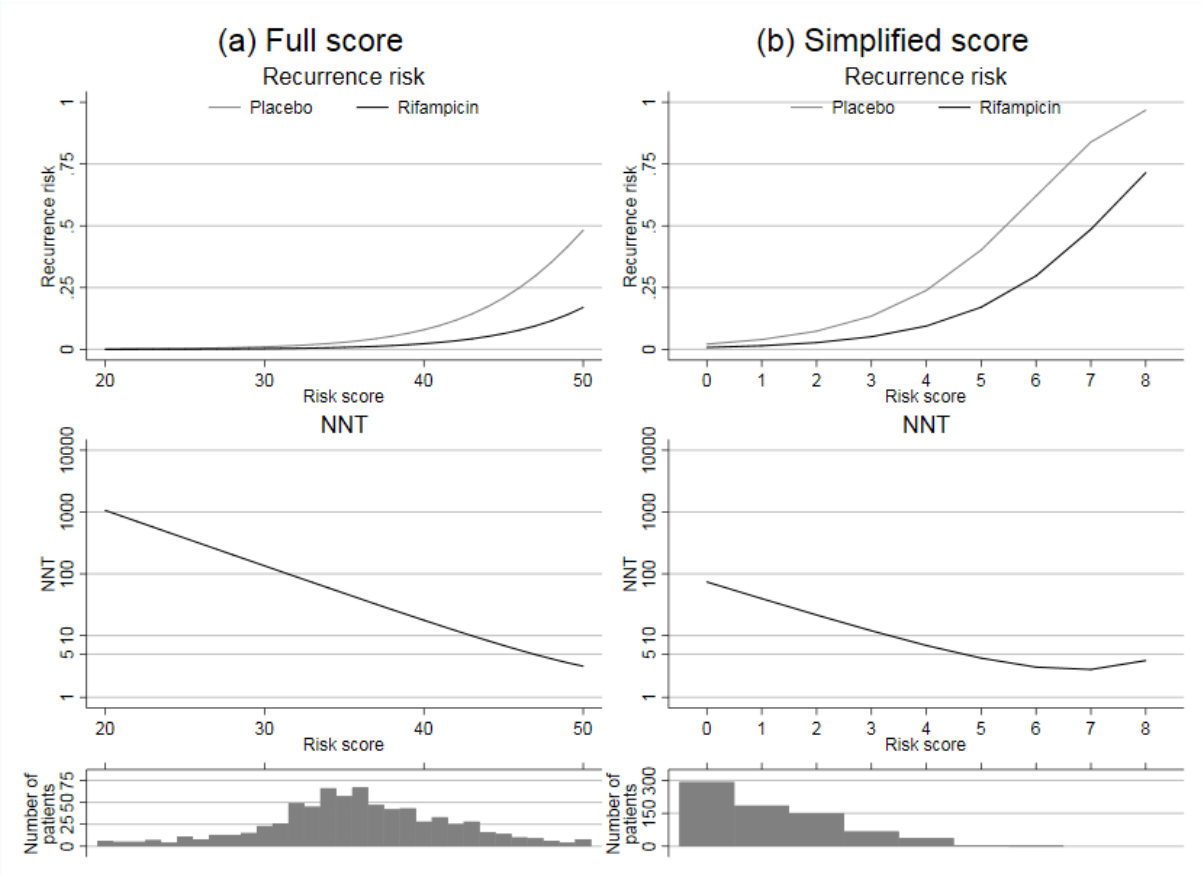
(a) Recurrence



(b) Failure



Supplementary Figure 2 Points-based risk score for recurrence based on (a) full model and (b) simplified model



Supplementary Table 1 Additional characteristics at randomization of all participants in the trial and all those subsequently suffering recurrence, *S. aureus* related mortality, non-*S. aureus* related mortality and failure

Factor	Total N=758* n (col%) or median (IQR)	Recurrence N=31 (4.1%) n (row%) or median (IQR)	Uni-variable p	*S. aureus*-related mortality N=56 (7.4%) n (row%) or median (IQR)	Uni-variable p	Non-*S. aureus* related 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
Mode of acquisition*			0.24		0.46		0.23		0.098
Community acquired	485 (64.0%)	21 (4.3%)		39 (8.0%)		30 (6.2%)		38 (7.8%)	
Nosocomial infection (≥48h post admission)	132 (17.4%)	2 (1.5%)		10 (7.6%)		12 (9.1%)		5 (3.8%)	
Healthcare associated (all other)	140 (18.5%)	8 (5.7%)		7 (5.0%)		14 (10.0%)		5 (3.6%)	
Likely portal of entry of *S. aureus* into the bloodstream			0.85		0.004		0.55		0.14
Genitourinary/fetal (including urological surgery)	21 (2.8%)	0 (0.0%)		1 (4.8%)		3 (14.3%)		2 (9.5%)	
Iatrogenic skin break (surgery, non-urinary catheter)	214 (28.2%)	11 (5.1%)		5 (2.3%)		15 (7.0%)		8 (3.7%)	
Non-iatrogenic skin break (skin or soft tissue infection, IVDU)	173 (22.8%)	9 (5.2%)		25 (14.5%)		16 (9.2%)		16 (9.2%)	
Lung	29 (3.3%)	1 (3.4%)		6 (20.7%)		2 (6.9%)		1 (3.4%)	
Not known (absence of any of the above)	218 (28.8%)	10 (4.6%)		19 (8.7%)		19 (8.7%)		21 (9.6%)	
Not completed (missing data)	3 (0.4%)	0 (0.0%)		0 (0.0%)		1 (33.3%)		0 (0.0%)	
CRP at first positive blood culture (mg/L) (N=756) †	170 (3.9)	188 (17.4) (N=30)	0.13	215 (15.8) (N=55)	0.003	174 (14.5)	0.99	220 (19.1)	0.001
Neutrophil count at first positive blood culture (10^9/L) (N=753)	8.1 (5.3, 12.0)	7.3 (4.4, 9.9) (N=30)	0.24	11.6 (8.2, 15.6)	<0.0001	9.0 (5.6, 15.6)	0.04	10.6 (7.4, 15.9)	0.001
Lymphocyte count at first positive blood culture (10^9/L) (N=752)	0.9 (0.6, 1.4)	0.9 (0.7, 1.2) (N=30)	0.64	0.8 (0.5, 1.2)	0.32	0.8 (0.5, 1.2) (N=55)	0.04	0.8 (0.4, 1.3)	0.17
Active injecting drug use (N=751)	83 (10.9%)	3 (3.6%)	0.93	2 (2.4%)	0.09	3 (3.6%)	0.23	2 (2.4%) (N=47)	0.12
Vascular catheter in situ at screening ** (N=744)	191 (25.7%)	10 (5.2%)	0.40	5 (2.6%) (N=54)	0.008	15 (7.9%)	0.86	3 (1.6%) (N=47)	0.004
Surgery in the last 30 days (N=756)	90 (11.9%)	3 (3.3%)	0.68	4 (4.4%)	0.24	7 (7.8%)	0.87	6 (6.7%)	0.90
Peripheral-/cerebro-vascular/peptic ulcer disease / congestive heart failure / history of MI / dementia*	224 (29.6%)	10 (4.5%)	0.78	29 (12.9%)	0.0003	27 (12.1%)	0.003	20 (8.9%)	0.04

Factor	Total N=758* n (col%) or median (IQR)	Recurrence N=31 (4.1%) n (row%) or median (IQR)	Uni-variable p	*S. aureus*-related mortality N=56 (7.4%) n (row%) or median (IQR)	Uni-variable p	Non-*S. aureus* related 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
Time from positive blood culture to starting antibiotics (days)	0 (0, 1)	0 (0, 1)	0.31	0 (0, 0)	0.04	0 (0, 1)	0.85	0 (0, 0)	0.02
In intensive care unit*	70 (9.2%)	0 (0.0%)	-	11 (15.7%)	0.008	4 (5.7%)	0.53	6 (8.6%)	0.33
Transferred from another hospital	57 (7.5%)	1 (1.8%)	0.36	4 (7.0%)	0.86	5 (8.8%)	0.70	5 (8.8%)	0.46
Imaging performed	522 (68.9%)	26 (5.0%)	0.08	34 (6.5%)	0.15	35 (6.7%)	0.25	39 (7.5%)	0.08
Backbone antibiotic therapy‡			0.72		0.51		0.16		0.52
MSSA: flucloxacillin alone	174 (23.0%)	10 (5.7%)		10 (5.7%)		8 (4.6%)		7 (4.0%)	
MSSA: flucloxacillin in combination with other antibiotic(s)	398 (52.5%)	15 (3.8%)		29 (7.3%)		34 (8.5%)		28 (7.0%)	
MSSA: other beta-lactam(s)	77 (10.2%)	3 (3.9%)		9 (11.7%)		8 (10.4%)		6 (7.8%)	
MSSA: other	62 (8.2%)	2 (3.2%)		4 (6.5%)		1 (1.6%)		3 (4.8%)	
MRSA	47 (6.2%)	1 (2.1%)		4 (8.5%)		5 (10.6%)		4 (8.5%)	

* One participant withdrew shortly after randomization 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.

† Mean (SE) estimated using normal interval regression to account for values above limit of quantification in one centre.

** Vast majority of vascular catheters had been removed by randomization.

‡ Defined by antibiotics received between days -1 and 4.

Note: showing n(% of row) for categorical factors, or median (IQR) for continuous factors other than CRP where mean(SE) is shown. p-values from competing risks regression (recurrence, *S. aureus*-related mortality, non-*S. aureus* related mortality) or logistic regression (failure).

Supplementary Table 2 Further details of recurrences

	Participant given placebo or rifampicin?	Focus at initial episode	Focus at recurrence	Days between onset of symptoms relating to first bacteraemia and start of antibiotics	Days between first positive blood culture and recurrence	BMI (kg/m^2)	Achieved source control of initial episode?	Days from first positive blood culture to removal of source	On antibiotics at time of recurrence?	Days between stopping antibiotics and recurrence	Antibiotic(s) prescribed during initial episode up until date of recurrence (total number of days on antibiotic)[1]	Imaging performed (days from first positive blood culture to imaging)	Focus identified and confirmed during initial episode?	Did the focus change between the initial episode and recurrence? (If so, was focus on recurrence a local or distant new focus?)	Was the recurrence confirmed bacteriologically?	Level of certainty of recurrence	Interpretation	Has the participant died? (Weeks since randomization)[2]
1	Placebo	Skin/soft tissue (excluding wounds)	Other bone; deep tissue infection or abscess	0	13	28.1	No	Source not removed	Yes	Not applicable	Co-amoxiclavulante (3); **Flucloxacillin** (12)	TTE (4); SPECT/CT (9)$^+$; CT (12)$^+$; MRI (16)$^+$; US (30)$^+$	Yes	Yes (distant)	No	Definite	Probably Failure Of Antibiotic Treatment	Died (20.0)
2	Placebo	Central venous line (including picc line)	Not established	1	74	34.9	Yes	3	No	30	Linezolid (3); Daptomycin (1); **Flucloxacillin** (41)	PET/CT (2)$^+$; TTE (4); PET/CT (8)$^+$	Yes	Focus not established on one or both episodes	No	Possible	Not Possible To Distinguish Whether Antibiotic Or Source Management Failure	Died (10.3)
3	Placebo	Implanted vascular device	Implanted vascular device	0	69	28.1	No	Source not removed	No	40	**Flucloxacillin** (29)	TOE (5); US (date not reported)	Yes	No	Yes	Definite	Probably Failure Of Source Management - Source Recognised, Not Actively Managed*	Died (150.3)

4	Placebo	Not established	Vertebral bone/disc	1	51	41.2	No	Source not removed	No	34	Co-amoxiclavulante (2); Doxycycline (3); **Flucloxacillin** (14)	MRI (4)[+]; TOE (5); US (11)[+]; TTE (11); MRI (89)[+]	No	Focus not established on one or both episodes	No**	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (82.7)
5	Placebo	Surgical wound	Not established	2	68	24.9	Unknown source	Source not removed	No	50	Gentamicin (1); **Flucloxacillin** (18)	US (2); TTE (4); US (6)[+]; TTE (70)	No	Focus not established on one or both episodes	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Died (11.4)
6	Placebo	Skin/soft tissue (excluding wounds)	Skin/soft tissue (excluding wounds)	2	46	45.0	Partial	9	No	31	Gentamicin (1); Co-amoxiclavulante (3); **Flucloxacillin** (13)	TTE (3); MRI (6); XR (48)	Yes	No	No	Possible	Probably Failure Of Source Management - Source Recognised, Actively Managed, But Still Recurred	Not known to have died (24.1)
7	Placebo	Implanted vascular device	Implanted vascular device	2	29	28.1	Yes	1	Yes	Not applicable	Vancomycin (5); Gentamicin (2); **Flucloxacillin** (6); **Daptomycin** (18)	TTE (3)	Yes	No	Yes	Definite	Probably Failure Of Source Management - Source Recognised, Actively Managed, But Still Recurred	Not known to have died (96.1)
8	Placebo	Skin/soft tissue (excluding wounds)	Skin/soft tissue (excluding wounds)	1	51	27.7	Yes	Source not removed	No	29	**Flucloxacillin** (21)	TTE (2); CT (5)[+]; XR (54)[+]	Yes	No	Yes	Definite	Not Possible To Distinguish Whether Antibiotic Or Source Management Failure	Died (7.0)

9	Placebo	Implanted vascular device; vertebral bone/disc; skin/soft tissue (excluding wounds)	Implanted vascular device; deep tissue infection or abscess	1	25	29.3	No	Source not removed	No	8	Piperacillin/tazobactam (3); **Flucloxacillin** (14)	TTE (3); MRI (3)[+]; MRI (10)[+] TOE (23); CT (30); CT angiogram (37); TTE (46); CT (57); MRI (133)[+]; TTE (133)	No	Partially (local)	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (18.6)
10	Placebo	Not established	Vertebral bone/disc; other bone	2	33	27.9	No	Source not removed	Yes	Not applicable	Vancomycin (1); Ciprofloxacin (2); **Ceftriaxone** (31)	XR (1); TTE (4); MRI (31); MRI (33); XR (33); XR (60); CT (88)[+]	No	Focus not established on one or both episodes	No	Probable	Probably Failure Of Source Management - Source Not Recognised	Died (53.3)
11	Placebo	Epidural or intraspinal empyema	Vertebral bone/disc; epidural or intraspinal empyema	4	57	20.8	No	Source not removed	No	9	Clarithromycin (2); **Flucloxacillin** (20); **Ceftriaxone** (26)	US (4)[+]; TTE (4); MRI (6); TTE (7); US (11)[+]; TOE (12); MRI (58); MRI (209)	Yes	Partially (local)	Yes	Definite	Probably Failure Of Source Management - Source Recognised, Not Actively Managed	Not known to have died (59.4)
12	Placebo	Not established	Implanted vascular device	2	48	22.0	No	Source not removed	No	3	Piperacillin/tazobactam (3); **Flucloxacillin** (43)	TTE (2); US (2)[+]; CT (9)[+]; TOE (11); PET/CT (15); US (23)[+]; XR (48)[+]; TTE (51);	No	Focus not established on one or both episodes	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (60.6)

												TOE (63); TTE (97); TTE (134)						
13	Placebo	Central venous line (including picc line)	Central venous line (including picc line)	2	37	27.0	Yes	3	No	21	Vancomycin (1); Gentamicin (1); Co-amoxiclavulante (1) **Flucloxacillin** (15)	TTE (39); TTE (45); US doppler (50)	Yes	Yes (distant)	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (87.0)
14	Placebo	Native joint	Vertebral bone/disc	6	58	37.7	No	Source not removed	No	35	**Flucloxacillin** (23); Fusidic Acid (1)	MRI (0); CT (2)+; TTE (4); MRI (17); MRI (59); TTE (60); MRI (92); MRI (103); CT (219)+	No	Yes (distant)	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (53.9)
15	Placebo	Not established	Not established	15	27	25.2	Unknown source	Source not removed	No	8	Piperacillin/tazobactam (1); **Flucloxacillin** (17)	TOE (3); MRI (5)+; TTE (6); MRI (9)+; XR (25)	No	Focus not established on one or both episodes	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (87.7)
16	Placebo	Vertebral bone/disc	Vertebral bone/disc	3	29	40.1	No	Source not removed	Yes	Not applicable	Co-amoxiclavulante (1); Benzylpenicillin (1); **Flucloxacillin** (12); **Teicoplanin** (18)	TOE (3); MRI (6); CT (10)+; MRI (31);	Yes	No	No	Definite	Probably Failure Of Antibiotic Treatment	Not known to have died (30.6)

17	Placebo	Implanted vascular device; surgical wound	Implanted vascular device	3	14	31.1	No	Source not removed	Yes	Not applicable	**Flucloxacillin** (9); **Daptomycin** (7); Rifampicin (9)	US (3)$^{+}$; TTE (6); US doppler (7); TOE (9)	Yes	No	No	Definite	Probably Failure Of Source Management - Source Recognised, Not Actively Managed	Not known to have died (19.6)
18	Placebo	Central venous line (including picc line)	Central venous line (including picc line)	2	41	24.4	Partial	3	No	22	**Vancomycin** (7); Doxycycline (7); **Cefazolin** (11); Teicoplanin (1)	US (14)$^{+}$; PET/CT (44); TTE (45)	Partially	No	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (13.9)
19	Placebo	Central venous line (including picc line)	Central venous line (including picc line)	3	51	25.1	No	Source not removed	No	20	Vancomycin (2); Piperacillin/tazobactam (3); **Flucloxacillin** (29)	US (3)$^{+}$; TTE (3)	Yes	Yes (distant)	Yes	Definite	Probably Failure Of Source Management - Source Recognised, Not Actively Managed	Not known to have died (19.7)
20	Placebo	Native heart valve; vertebral bone/disc	Native heart valve	0	20	44.1	No	Source not removed	No	3	Co-amoxiclavulante (2); **Flucloxacillin** (16)	TTE (-3); TTE (3); MRI (23); TTE (24); CT (28)$^{+}$; TTE (32); CT (35)$^{+}$; MRI (35)$^{+}$	No	No	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Died (4.4)
21	Placebo	Central venous line (including picc line); skin/soft tissue (excluding	Skin/soft tissue (excluding wounds)	1	84	58.5	Yes	1	No	67	Vancomycin (1); Clarithromycin (2); **Meropenem** (15); **Levofloxacin** (12)	US (3)$^{+}$; CT (3)$^{+}$; US (5)$^{+}$; CT (5)$^{+}$; TTE (8); US (23)$^{+}$; TTE (85); CT (122)$^{+}$	Yes	Yes (uncertain location)	No	Possible	Probably Failure Of Source Management - Source Recognised, Actively Managed, But Still Recurred	Not known to have died (17.0)

		wounds)																
22	Placebo	Skin/soft tissue (excluding wounds)	Skin/soft tissue (excluding wounds; deep tissue infection or abscess	4	31	17.6	No	Source not removed	No	13	**Flucloxacillin** (15)	US doppler (3); TTE (3); XR (28); XR (28); CT (28); XR (28);	Yes	Yes (distant)	Yes	Probable	Not Possible To Distinguish Whether Antibiotic Or Source Management Failure	Died (3.7)
23	Placebo	Deep tissue infection or abscess; pneumonia	Not established	0	73	41.8	Unknown source	Source not removed	No	59	**Co-amoxiclavulante** (14)	TTE (4); TTE (75); CT (78)⁺	No	Focus not established on one or both episodes	Yes	Definite	Not Possible To Distinguish Whether Antibiotic Or Source Management Failure	Not known to have died (10.9)
24	Rifampicin	Central venous line (including picc line)	Native joint	1	44	27.0	Yes	2	Yes	Not applicable	Vancomycin (1); Gentamicin (1); **Flucloxacillin** (42)	XR (9); US (11)⁺ MRI (11)	Yes	Yes (distant)	No	Definite	Not Possible To Distinguish Whether Antibiotic Or Source Management Failure	Not known to have died (148.6)
25	Rifampicin	Vertebral bone/disc	Vertebral bone/disc	23	78	16.9	No	Source not removed	No	30	**Flucloxacillin** (4); **Ceftriaxone** (43)	MRI (4)⁺; TTE (4)	Yes	No	No	Definite	Probably Failure Of Antibiotic Treatment	Not known to have died (144.9)
26	Rifampicin	Vertebral bone/disc; deep tissue infection or	Vertebral bone/disc; deep tissue infection or	8	16	23.7	No	Source not removed	Yes	Not applicable	Meropenem (2); **Vancomycin** (8); **Teicoplanin** (6);	CT (1); MRI (1); TTE (7); MRI (15)⁺; MRI (96)⁺	Yes	Partially (local)	No	Definite	Probably Failure Of Source Management - Source Recognised, Not	Not known to have died (22.4)

		abscess	abscess														Actively Managed	
27	Rifampicin	Central venous line (including picc line)	Central venous line (including picc line)	1	51	22.5	No	Source not removed	No	32	**Vancomycin** (18)	TTE (9); CT (54); TTE (65)	Yes	No	Yes	Definite	Probably Failure Of Source Management - Source Recognised, Not Actively Managed	Not known to have died (86.0)
28	Rifampicin	Native joint; skin/soft tissue (excluding wounds)	Vertebral bone/disc	4	45	29.7	No	Source not removed	Yes	Not applicable	Amoxicillin (3); Gentamicin (1); **Flucloxacillin** (43); Clindamycin (43)	US (3)[+]; TTE (3); MRI (46); TTE (46)	No	Yes (distant)	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Died (10.6)
29	Rifampicin	Not established	Vertebral bone/disc	2	22	27.4	No	Source not removed	Yes	Not applicable	Piperacillin/tazobactam (2); **Flucloxacillin** (19); Vancomycin (5); Ciprofloxacin (4)	TTE (4); MRI (7)[+]; MRI (10)[+]; MRI (32); MRI (42); MRI (46)	No	Focus not established on one or both episodes	Yes	Definite	Probably Failure Of Source Management - Source Not Recognised	Not known to have died (40.9)
30	Rifampicin	Vertebral bone/disc; deep tissue infection or abscess	Vertebral bone/disc; deep tissue infection or abscess; skin/soft tissue (excluding wounds)	5	56	29.4	No	Source not removed	Yes	Not applicable	**Flucloxacillin** (19); Vancomycin (4); Clindamycin (9)	XR (0); XR (0); MRI (1); US doppler (4); MRI (19); TTE (21)	Yes	Partially (local)	No	Probable	Probably Failure Of Source Management - Source Recognised, Actively Managed, But Still Recurred	Not known to have died (34.7)

31	Rifampicin	Deep tissue infection or abscess	Deep tissue infection or abscess; native joint	0	86	29.7	No	Source not removed	Yes	Not applicable	**Flucloxacillin** (25); Vancomycin (3); **Clindamycin** (61)	XR (3)[+]; CT (3)[+]; MRI (11); MRI (14)[+]; MRI (66)	Yes	Partially (local)	No	Probable	Probably Failure Of Source Management - Source Recognised, Not Actively Managed	Not known to have died (14.1)

CT = computed tomography scan; MRI = magnetic resonance imaging; PET/CT = positron emission tomography/computed tomography; SPECT/CT = single photon emission computed tomography/computed tomography; TOE = transoesophageal echocardiogram; TTE = transthoracic echocardiogram; US = ultrasound scan; XR = plain radiograph

[1]Backbone antibiotic(s) in bold; Listed in chronological order of initial prescription of each antibiotic; Antibiotics and number of days documented only up until date of recurrence

[2]Includes information obtained at trial closure, relating to the time after 12 weeks

[+]Date recorded by study team rather than date of imaging (as date of imaging not collected)

*Adjudicated as failure of antibiotic treatment in original report[7], however after further blinded review considered failure of source management

**Adjudicated as bacteriologically confirmed in original report[7], however after further blinded review considered clinically confirmed only

Supplementary Table 3 Points-based recurrence score based on full final multivariable model

Factor	Score value given if present	Minimum possible value for score	Maximum possible value for score
Starting value (constant)	35	35	35
Chronic patient factors			
Charlson score (per point)	-2 (minimum -20)	-20	0
Liver disease*	10	0	10
Diabetes*	6	0	6
Immunosuppressed‡	6	0	6
Renal disease*		0	12
No	0		
Moderate or severe	7		
End stage (requiring dialysis)	12		
BMI (kg/m^2)		0	7
≤25	0		
>25-30	2		
>30-35	3		
>35-40	5		
>40	7		
Infection related factors			
SOFA score (per point)	-1 (minimum -10)	-10	0
Prolonged time from first new symptom caused by *S. aureus* to starting antibiotics (≥1 days)	2	0	2
Prolonged time from admission to positive blood culture (≥2 days)	-2	-2	0
Predominant focus of infection†		-2	2
Native heart valve	2		
Native joint / vertebral bone/disc / other bone	-2		
Deep tissue infection/abscess (including brain infection) / epidural/intraspinal empyema / infected intravascular thrombus	0		
Prosthetic heart valve/joint / Implanted vascular device	0		
Central/peripheral venous line	2		
Skin/soft tissue / surgical wound / pneumonia	0		
Not established	1		
Total		**1**	**80**

For example, a patient with Charlson score 2, 0 days from admission to positive blood culture, focus of infection skin/soft tissue / surgical wound / pneumonia, 1 day from first new symptom caused by *S. aureus* to starting antibiotics, end stage renal disease, SOFA score 4 and BMI 22 would have recurrence risk score = 35 – (2*2) + 0 + 0 + 2 + 12 – (4*1) + 0 = 41.

* 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.

† Individuals can 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).

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

Supplementary Table 4. Observed risk of recurrence by full points-based recurrence score

Score	Total participants (% of N=733 with complete data)	Observed recurrences in placebo (%) [predicted % recurrences*]	Recurrences in rifampicin (%) [predicted % recurrences*]	NNT observed	NNT predicted*
1-10	0	- [0.0%]	- [0.0%]	-	-
11-30	110 (15.0%)	0 (0.0%) [0.2%]	0 (0.0%) [0.0%]	-	863
31-33	120 (16.4%)	1 (1.6%) [1.6%]	0 (0.0%) [0.4%]	63	89
34-36	190 (25.9%)	3 (3.0%) [2.9%]	0 (0.0%) [0.8%]	33	48
37-40	160 (21.8%)	4 (5.1%) [6.5%]	3 (3.7%) [1.9%]	68	22
41-60	153 (20.9%)	15 (18.1%) [55.5%]	5 (7.1%) [20.5%]	9	3
61-80	0	- [100.0%]	- [100.0%]	-	-

* Predicted % recurrences and NNT are from the model for the mid-point score (rounded to nearest whole number) in each category
Note: presented graphically in Supplementary Figure 2.

Supplementary Table 5. Observed risk of recurrence by simplified BIRDL recurrence score

Score	Total participants (% of N=737 with complete data)	Observed recurrences in placebo (%) [predicted % recurrences]	Recurrences in rifampicin (%) [predicted % recurrences]	NNT observed	NNT predicted
0	292 (40.1%)	3 (2.0%) [2.1%]	0 (0.0%) [0.8%]	49	74
1	185 (25.1%)	3 (3.6%) [4.0%]	2 (2.0%) [1.5%]	63	40
2	151 (20.3%)	6 (6.8%) [7.4%]	3 (4.8%) [2.8%]	49	22
3	67 (9.0%)	6 (17.1%) [13.5%]	1 (3.1%) [5.1%]	7	12
4	37 (4.9%)	4 (21.1%) [23.9%]	2 (11.1%) [9.5%]	10	7
5	3 (0.4%)	1 (33.3%) [40.2%]	0 (0.0%) [17.1%]	3	4
6	2 (0.3%)	0 (0.0%) [62.1%]	0 (0.0%) [29.7%]	-	3
7	0	- [83.9%]	- [48.6%]	-	3
8	0	- [96.8%]	- [71.5%]	-	4

Note: presented graphically in main Figure 3 and Supplementary Figure 2.
NNT: number needed to treat
Note: presented graphically in Supplementary Figure 2.

Supplementary References

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